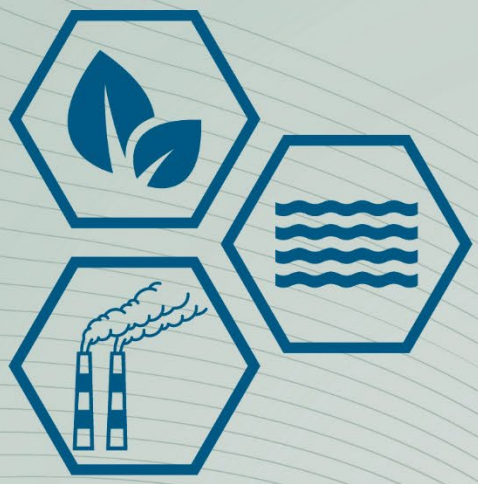

Toxicological Profile for Chlorinated Dibenzo-*p*-Dioxins

Draft for Public Comment

October 2024

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute-, intermediate-, and chronic-duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Office of Innovation and Analytics
Toxicology Section
1600 Clifton Road, N.E.
Mail Stop S106-5
Atlanta, Georgia 30329-4027

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA Section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health-related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under Section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Christopher M. Reh, Ph.D.
Associate Director
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

VERSION HISTORY

Date	Description
October 2024	Draft for public comment toxicological profile released
November 2012	Addendum to the toxicological profile released
December 1998	Final toxicological profile released

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Hana R. Pohl, M.D., Ph.D. (Lead)
Brittany Szafran, D.V.M., Ph.D.
Gaston Casillas, Ph.D.
Fahim Atif, Ph.D.

ATSDR, Office of Innovation and Analytics, Toxicology Section, Atlanta, GA

Lisa Ingerman, Ph.D., D.A.B.T.
Gary L. Diamond, Ph.D.
Heather Carlson-Lynch, M.S., D.A.B.T.
Mario Citra, Ph.D.
Deborah Herber, Ph.D.
Connor McGuire, Ph.D.

SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:

Includes ATSDR; National Center for Environmental Health (NCEH); National Institute for Occupational Safety and Health (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

Additional reviews for science and/or policy:

ATSDR, Office of Community Health Hazard Assessment; ATSDR, Office of Capacity Development and Applied Prevention Science; ATSDR, Office of Science; NCEH, Division of Laboratory Sciences; NCEH, Division of Environmental Health Science and Practice; EPA, Office of Research and Development; EPA, Office of Water.

PEER REVIEWERS

1. Diane B. Re, Ph.D.; Associate Professor; EHS Department, Columbia University; New York, New York

2. Slawo Lomnicki, Ph.D.; Associate Professor; Department of Environmental Sciences; Louisiana State University; Baton Rouge, Louisiana

3. Stuart Harrad, Ph.D.; Professor of Environmental Chemistry; School of Geography, Earth & Environmental Sciences; University of Birmingham; Birmingham, United Kingdom

These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Chlorinated dibenzo-*p*-dioxins (CDDs) are a class of related chlorinated aromatic hydrocarbons that are structurally similar. The basic structure is a dibenzo-*p*-dioxin (DD) molecule comprised of two benzene rings joined via two oxygen bridges at adjacent carbons on each of the benzene rings. There are eight homologues of CDDs, monochlorinated through octachlorinated. Each homologous class contains one or more isomers or congeners. The family of CDDs contains 75 congeners—2 monochlorodibenzo-*p*-dioxins (MCDD), 10 dichlorodibenzo-*p*-dioxins (DCDD), 14 trichlorodibenzo-*p*-dioxins (TrCDD), 22 tetrachlorodibenzo-*p*-dioxins (TCDD), 14 pentachlorodibenzo-*p*-dioxins (PeCDD), 10 hexachlorodibenzo-*p*-dioxins (HxCDD), 2 heptachlorodibenzo-*p*-dioxins (HpCDD), and a single octachlorodibenzo-*p*-dioxin (OCDD). The seven 2,3,7,8-chlorine substituted congeners are the most toxic CDD congeners, with 2,3,7,8-TCDD being the most toxic and most extensively studied. This compound is often called “TCDD” or merely "dioxin" in the popular literature. Chlorinated dibenzofurans (CDFs) are structurally and toxicologically related chemicals as are certain “dioxin-like” polychlorinated biphenyls (PCBs); the reader is encouraged to consult the toxicological profile for chlorodibenzofurans (CDFs) (ATSDR 2023) and the toxicological profile for polychlorinated biphenyls (PCBs) (ATSDR 2000) for information on the health effects associated with exposure to these groups of chemicals.

The primary route of exposure to CDDs for the general population is ingestion of food, particularly animal products. This type of exposure is the main contributor to the background exposure. Background exposure refers to exposure of the general population who are not exposed to readily identifiable point-sources of CDDs that result in widespread, low-level circulation of CDDs in the environment. It is generally accepted that the contribution of inhalation and direct contact with CDDs to the body burden of the general population is not more than a few percent of the total exposure. Inhalation exposure is a major route for populations near the facilities utilizing thermal processes (waste incinerations, forest fires, trash burning, uncontrolled landfill fires, smelting industry, titanium dioxide production). It should be also noted that the background levels of dioxins are different in urban versus rural areas (Urban et al. 2014). Inhalation and direct contact represent major exposure routes in cases of occupational or accidental exposures. A background exposure level of approximately 0.7 pg 2,3,7,8-TCDD/kg/day (assuming a 70-kg reference body weight) ($7x10^{-7}$ µg/kg/day) has been estimated for the general population in the United States (Travis and Hattemer-Frey 1987). If other CDD and CDF congeners are

included, then the background exposure level increases to approximately 18–192.3 pg toxic equivalency (TEQ)/day (0.26–2.75 pg/kg/day [$2.6x10^{-7}$–$2.75x10^{-6}$ µg/kg/day] using a 70-kg reference body weight) (Schecter et al. 1994b) (for additional information on TEQs, see Section 2.1). The inclusion of dioxin-like PCBs further raises the estimate to 3–6 pg TEQ/kg/day ($3x10^{-6}$–$6x10^{-6}$ µg/kg/day) (Beck et al. 1989a; WHO 1991). More recent data on the levels of CDDs/CDFs in the U.S. food supply suggest that levels of CDDs/CDFs have declined. Based on data from a 2001–2004 Total Dietary Study, dietary intake from CDDs/CDFs was 0.32 pg TEQ/kg/day ($3.2x10^{-7}$ µg/kg/day) (FDA 2006). The average concentration of 2,3,7,8-TCDD in the adipose tissue of the U.S. population is 5.8 pg/g lipid (Orban et al. 1994). For all TEQ congeners, excluding dioxin-like PCBs, the national average was approximately 28 pg TEQ/g lipid.

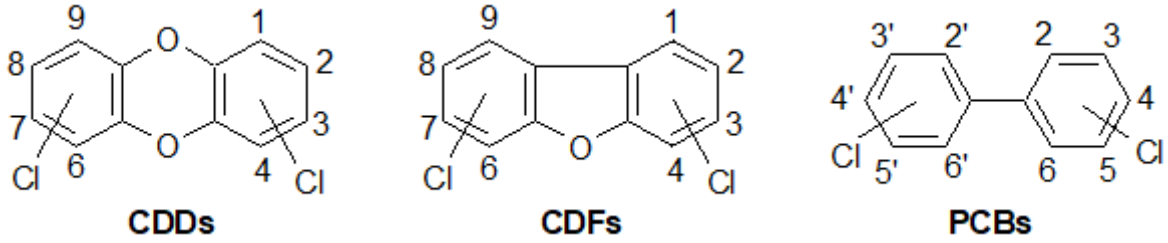
The U.S. Environmental Protection Agency (EPA) 2004 Dioxin Reassessment characterized background exposures to dioxin-like compounds, including an estimate of an average background intake dose and an average background body burden (Lorber et al. 2009). These quantities were derived from data generated in the mid-1990s but have been updated using data from a decade later. The average background intake from the 1990s was 61.0 pg TEQ/day, and was made using 17 CDD/CDFs. Using more current data, the average background intake was 40.6 pg TEQ/day.

In humans, the partitioning ratio of 2,3,7,8-TCDD between adipose tissue lipid and serum lipid is approximately 1 and remains near unity over at least a 1,000-fold concentration range over background levels (Patterson et al. 1988; Schecter et al. 1991c). This makes serum lipid an accurate and more practical measure of body burden than adipose tissue lipid.

1.2 SUMMARY OF HEALTH EFFECTS

The general population is most likely to be exposed to CDDs by the oral route. In the environment, humans are exposed to a mixture of three closely related compounds: CDDs, CDFs, and PCBs. CDDs, CDFs, and some PCB congeners are often referred to as dioxin-like chemicals or dioxins. The chemical structures of CDDs, CDFs, and PCBs are presented in Figure 1-1.

Figure 1-1. Basic Chemical Structure of Chlorinated Dibenzo-*p*-Dioxins (CDDs), Chlorodibenzofurans (CDFs), and Polychlorinated Biphenyls (PCBs)



The dioxin-like compounds share a common mechanism of action that involves binding to the aryl hydrocarbon (Ah) receptor, which is an intracellular protein. Epidemiological studies and experimental animal toxicological studies demonstrate that exposure to dioxin-like compounds can result in a wide range of adverse health outcomes including developmental toxicity, reproductive toxicity, liver toxicity, immunotoxicity, damage to teeth, wasting syndrome, lethality, cancer, and chloracne. The potencies of the different dioxin-like compounds vary with the substitution pattern, with 2,3,7,8-substituted CDDs and CDFs being more toxic than other congeners. Among the 2,3,7,8-substituted compounds, 2,3,7,8-TCDD and 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin (1,2,3,7,8-PeCDD) are the most toxic and OCDD and octachlorodibenzofuran (octaCDF) are the least toxic; 2,3,4,7,8-pentachlorodibenzofuran (2,3,4,7,8-PeCDF) is the most toxic CDF congener (Van den Berg et al. 2006). Toxic Equivalency Factors (TEFs) have been developed, which use 2,3,7,8-TCDD, the most toxic CDD, as the reference chemical (see Section 2.1 for additional information). The TEFs allow for a comparison of the toxicity of the different dioxin-like compounds, and can also be used to estimate the overall toxicity of an environmental mixture of dioxin-like compounds. Using the TEFs (see Section 2.1 for additional information), risk assessors can sum the risks associated with the individual dioxin-like compounds to derive an overall risk.

The toxicity of CDDs, particularly 2,3,7,8-TCDD, has been extensively investigated in epidemiological and animal experimental studies. The types of populations examined in CDD epidemiological studies include workers, Vietnam War veterans exposed to Agent Orange, communities living near point sources, communities exposed to accidental releases, and the general population. Many of the epidemiological studies involve exposure to a mixture of CDDs and other dioxin-like compounds. There are some populations that are primarily exposed to elevated levels of 2,3,7,8-TCDD; these include some producers and users of chemicals in which 2,3,7,8-TCDD might have occurred as impurities, residents of Seveso

Italy who were exposed to an accidental release of high levels of 2,3,7,8-TCDD, and populations exposed to the herbicide, Agent Orange.

Animal experimental studies have evaluated the toxicity of 12 CDD congeners: 2-MCDD, 2,3-DCDD, 2,7-DCDD, 2,3,7-TrCDD, 1,2,3,4-TCDD, 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,4,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, HxCDD mixtures, 1,2,3,4,6,7,8-HpCDD, and OCDD; the majority (>60%) of the animal studies are acute-duration oral studies of 2,3,7,8-TCDD. Studies of 2,3,7,8-TCDD have examined most endpoints following acute-, intermediate-, or chronic-duration oral exposure or acute-duration dermal exposure; there are more limited data for the other CDD congeners.

Adverse health effects have been reported in most major systems. The health effects of 2,3,7,8-TCDD and other CDD congeners observed in orally exposed animals are summarized in Figures 1-2 and 1-3, respectively. These figures do not include epidemiological studies because most studies did not report exposure levels or doses; rather, exposure is typically reported as blood CDD levels (cumulative or for a specific congener) or TEQ levels for CDD congeners, CDD and CDF congeners, or CDD, CDF, and PCB congeners. Effects observed at the lowest doses in animal studies include developmental toxicity, immunotoxicity, hepatotoxicity, reproductive toxicity, and cancer.

Developmental Effects. The developmental toxicity of CDDs has been extensively evaluated in epidemiological and animal experimental studies. Epidemiological studies provide suggestive evidence of an association between CDD body burden and developmental effects, particularly for impaired development of the reproductive system. Animal studies provide strong evidence of the developmental toxicity of 2,3,7,8-TCDD; effects included increased fetal/newborn mortality, structural anomalies such as cleft palate and hydronephrosis, decreased birth weight and growth, impaired development of the lungs and heart, impaired mandible and tooth development, gastrointestinal hemorrhages, immunotoxicity, and impaired neurodevelopment. The most sensitive developmental effects are neurodevelopmental (delays in neurodevelopmental milestones, altered social behaviors, altered motor activity, hyperactivity) and immunological (decreased thymus weight and atrophy and decreased immune response). Developmental effects have also been observed in animals exposed to 2,7-DCDD, 1,2,3,7,8-PeCDD, and mixed HxCDD congeners.

Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

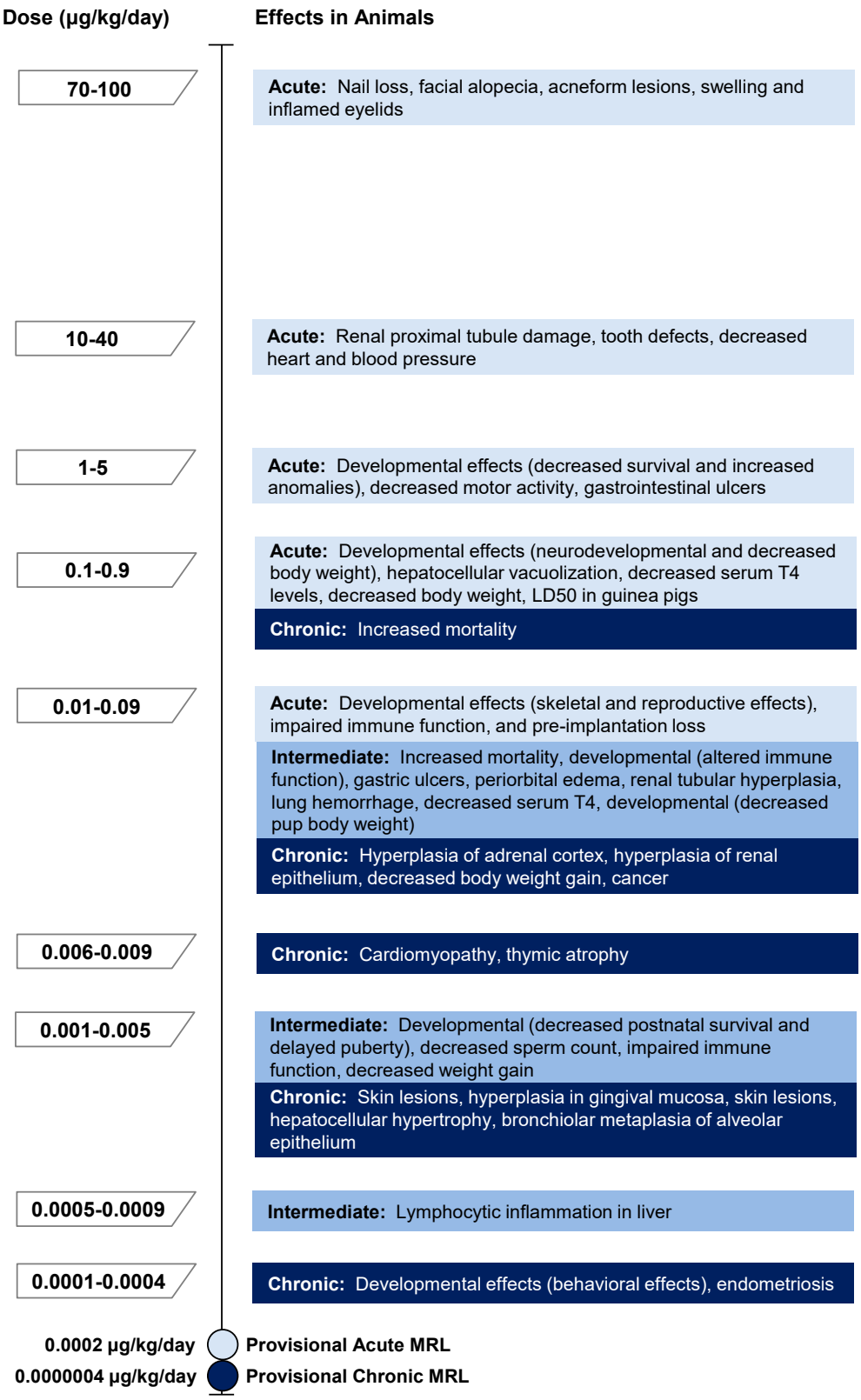
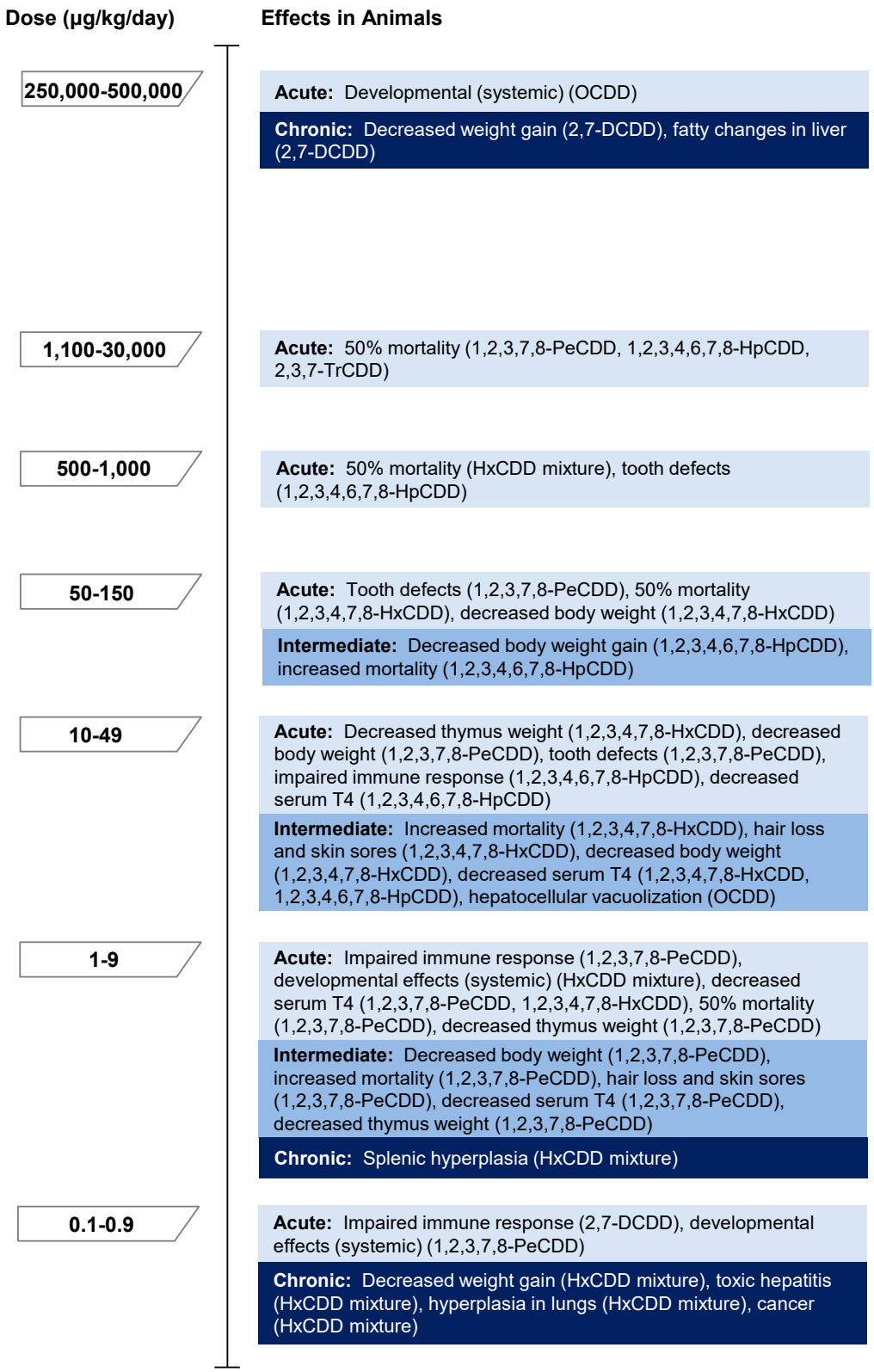


Figure 1-3. Health Effects Found in Animals Following Oral Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs)



Immune Effects. Epidemiological studies provide suggestive evidence of an association between exposure to high levels of CDDs and adverse immunological effects; however, the findings are not consistent across studies and populations. Animal studies provide strong evidence that immunotoxicity is a sensitive target of CDD toxicity. Studies with 2,3,7,8-TCDD have found decreases in thymus weight and atrophy and impaired immune function (decreased response to antigens and impaired host resistance) following acute-, intermediate-, and chronic-duration oral exposure. Decreases in thymus weight have also been observed following oral exposure to 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, or 1,2,3,4,6,7,8-HpCDD and impaired immune function has been observed in animals orally exposed to 2,7-DCDD, 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, and 1,2,3,4,6,7,8-HpCDD.

Hepatic Effects. Epidemiological studies have not yielded consistent results on the hepatotoxicity of CDDs. However, studies in a number of animal species provide strong evidence that the liver is a sensitive target of toxicity. The observed effects include increases in liver weight, increases in serum liver enzymes, alterations in serum lipid levels, and histopathological alterations such as cytoplasmic vacuolization, hypertrophy, necrosis, inflammation, and biliary hyperplasia. Liver effects have also been observed in animals following long-term oral exposure to 2,7-DCDD, a mixture of HxCDD congeners, and OCDD.

Reproductive Effects. Some reproductive effects have been observed in the Seveso cohort including increased time to pregnancy and alterations in sperm parameters in men exposed as boys. Animal studies provide strong evidence of the reproductive toxicity of CDDs. The observed effects following oral exposure to 2,3,7,8-TCDD include decreased serum testosterone levels; decreased sperm production, viability, and motility; impaired uterine function; altered estrus cycle; endometriosis; decreased fertility; increased pre-implantation loss; and altered maternal behavior.

Cancer. Meta-analyses of occupational exposure studies have found increased risk of associations between serum CDD levels and cancer risk. Increases in the incidence of hepatocellular carcinoma, thyroid follicular cell adenoma, squamous cell carcinoma in the lungs, hard palate, tongue, and gingival cells in the oral mucosa have been found in animals orally exposed to 2,3,7,8-TCDD. Hepatocellular carcinomas have also been observed in animals exposed to HxCDD and 2,7-DCDD. The Department of Health and Human Services (HHS) has classified 2,3,7,8-TCDD as a known human carcinogen (NTP 2021) and the International Agency for Research on Cancer (IARC) has determined that 2,3,7,8-TCDD is carcinogenic to humans (IARC 2012). The EPA categorized the mixture of 1,2,3,6,7,8-HxCDD and

1,2,3,7,8,9-HxCDD as a probable human carcinogen (EPA 1987a). IARC (1997) concluded that other CDDs are not classifiable as to their carcinogenicity in humans.

1.3 MINIMAL RISK LEVELS (MRLs)

Sensitive targets of CDDs are summarized in Figures 1-4–1-12. Due to the absence of inhalation studies, data were not available for deriving inhalation MRLs for 2,3,7,8-TCDD or other CDD congeners. The oral database for 2,3,7,8-TCDD was considered adequate for derivation of acute-duration and chronic-duration oral MRLs. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A. The oral databases for 2-MCDD, 2,3-DCDD, 2,7-DCDD, 2,3,7-TrCDD, 1,2,3,4-TCDD, 1,2,3,7,8-PeCDD, 1,2,4,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD were not considered adequate for deriving oral MRLs, as summarized in Table 1-2.

Figure 1-4. Summary of Sensitive Targets of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral

Available data indicate that developmental, immunological, reproductive, and hepatic toxicity are the most sensitive targets of 2,3,7,8-TCDD oral exposure.

Numbers in circles are the lowest LOAELs (µg/kg/day) among health effects in animals; no quantitative human data were identified.

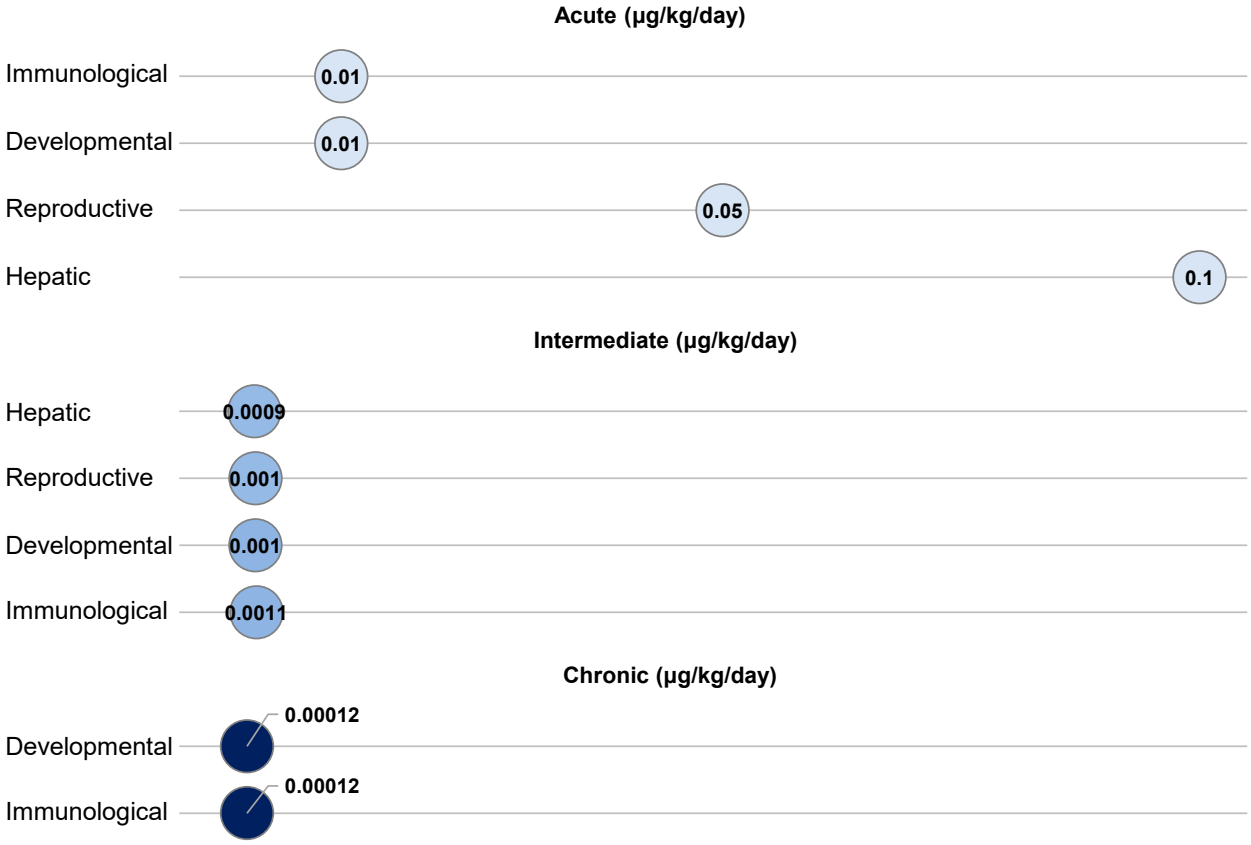


Figure 1-5. Summary of Sensitive Targets of 2,7-Dichlorodibenzo-*p*-Dioxin (2,7-DCDD) – Oral

Available data indicate that body weight and hepatic developmental, immunological, and endocrine toxicity are the most sensitive targets of 2,7-DCDD oral exposure.
Numbers in circles are the lowest LOAELs (µg/kg/day) among health effects in animals; no quantitative human data were identified.

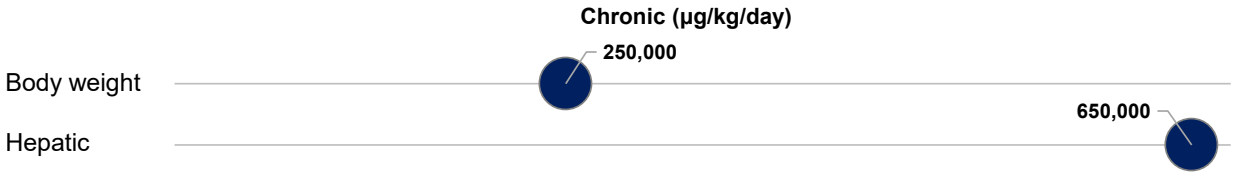


Figure 1-6. Summary of Sensitive Targets of 2,3,7-Trichlorodibenzo-*p*-Dioxin (2,3,7-TrCDD) – Oral

Available data indicate that death is a sensitive target of 2,3,7-TrCDD oral exposure.
Numbers in circles are the lowest LOAELs (µg/kg/day) among health effects in animals; no quantitative human data were identified.

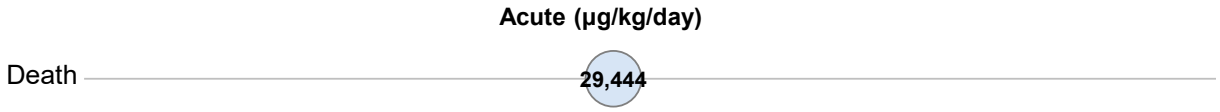


Figure 1-7. Summary of Sensitive Targets of 1,2,3,7,8-Pentachlorodibenzo-*p*-Dioxin (1,2,3,7,8-PeCDD) – Oral

Available data indicate that developmental, immunological, and endocrine toxicity are the most sensitive targets of 1,2,3,7,8-PeCDD oral exposure.
Numbers in circles are the lowest LOAELs (µg/kg/day) among health effects in animals; no quantitative human data were identified.

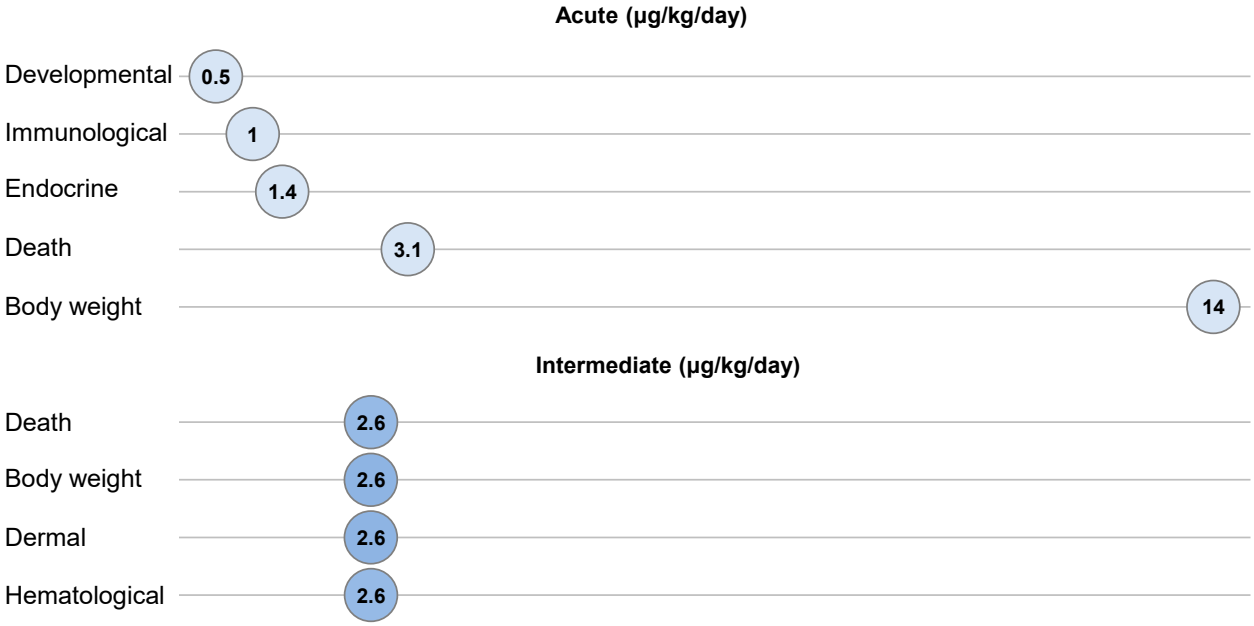


Figure 1-8. Summary of Sensitive Targets of 1,2,4,7,8-Pentachlorodibenzo-*p*-Dioxin (1,2,4,7,8-PeCDD) – Oral

Available data indicate that death is a sensitive target of 1,2,4,7,8-PeCDD oral exposure.
Numbers in circles are the lowest LOAELs (µg/kg/day) among health effects in animals; no quantitative human data were identified.

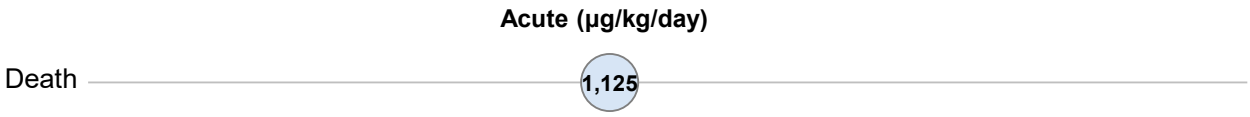


Figure 1-9. Summary of Sensitive Targets of 1,2,3,4,7,8-Hexachlorodibenzo-*p*-Dioxin (1,2,3,4,7,8-HxCDD) – Oral

Available data indicate that endocrine, immunological, death, and hematological toxicity are the most sensitive targets of 1,2,3,4,7,8-HxCDD oral exposure.

Numbers in circles are the lowest LOAELs (µg/kg/day) among health effects in animals; no quantitative human data were identified.

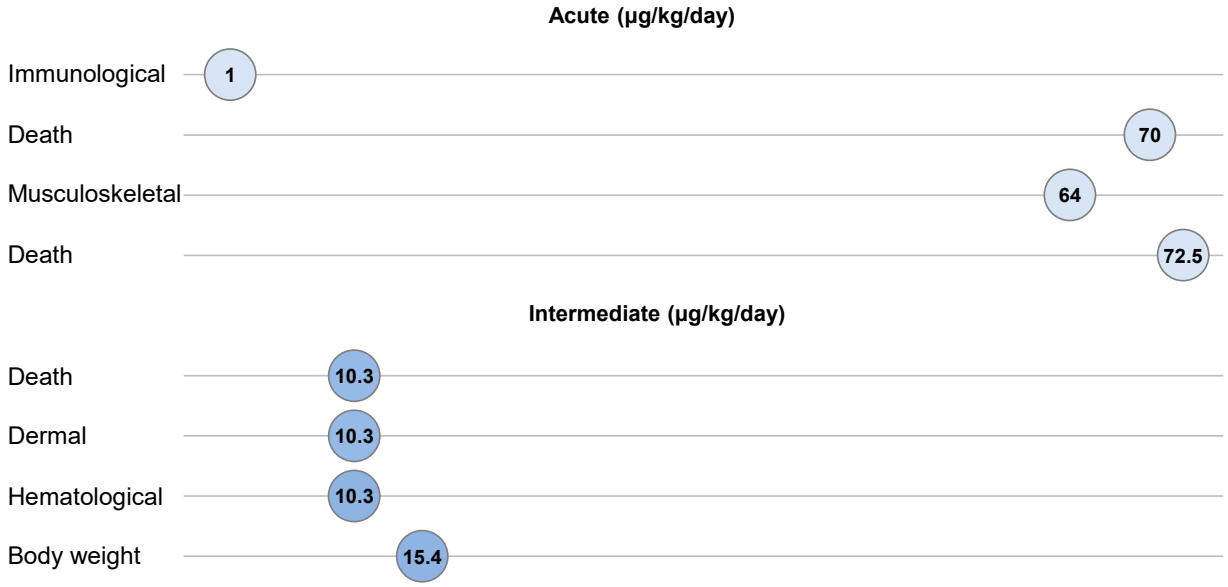


Figure 1-10. Summary of Sensitive Targets of 1,2,3,6,7,8-Hexachlorodibenzo-*p*-Dioxin (1,2,3,6,7,8-HxCDD) – Oral

Available data indicate that immunological toxicity and death are the most sensitive targets of 1,2,3,6,7,8-HxCDD oral exposure.

Numbers in circles are the lowest LOAELs (µg/kg/day) among health effects in animals; no quantitative human data were identified.

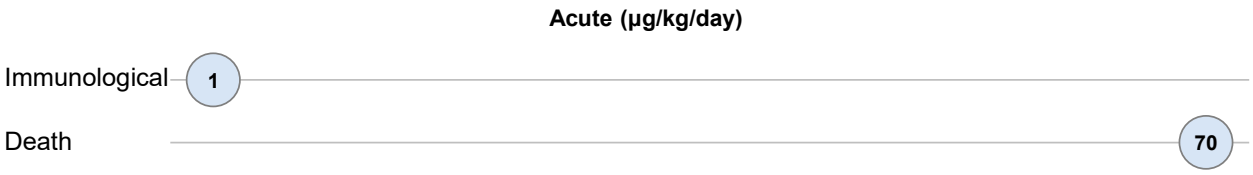


Figure 1-11. Summary of Sensitive Targets of 1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-Dioxin (HpCDD) – Oral

Available data indicate that hepatic, immunological, endocrine, and hematological toxicity are the most sensitive targets of 1,2,3,4,6,7,8-HpCDD oral exposure.

Numbers in circles are the lowest LOAELs (µg/kg/day) among health effects in animals; no quantitative human data were identified.

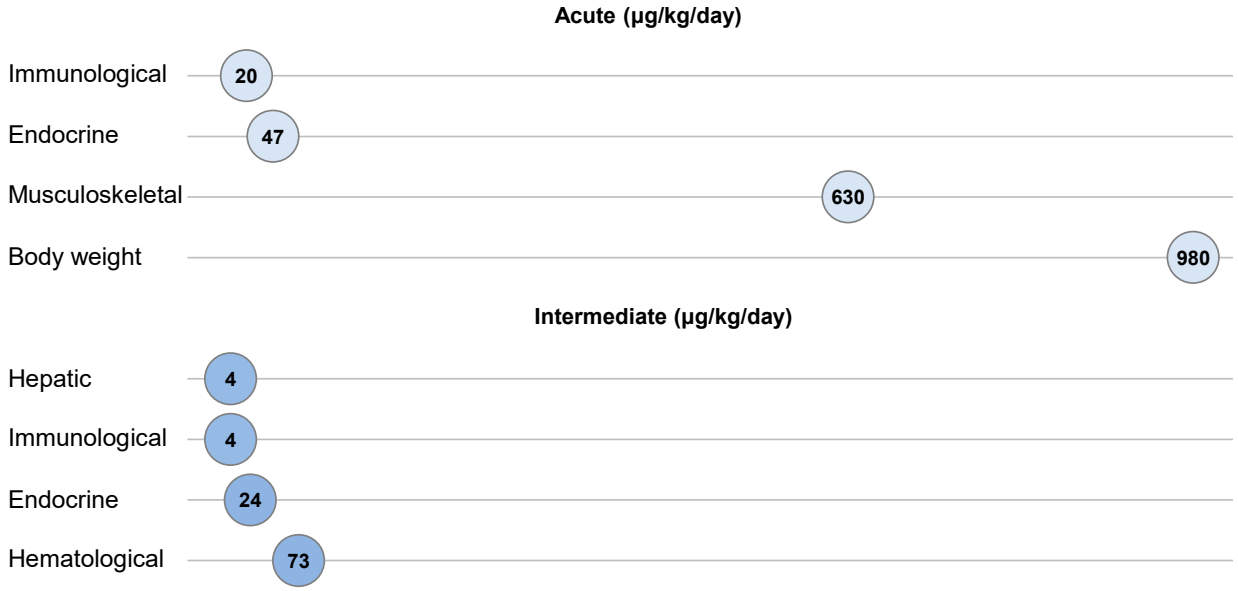


Figure 1-12. Summary of Sensitive Targets of Octachlorodibenzo-*p*-Dioxin (OCDD) – Oral

Available data indicate that hepatic, hematological and developmental toxicity are the most sensitive targets of OCDD oral exposure.

Numbers in circles are the lowest LOAELs (µg/kg/day) among health effects in animals; no quantitative human data were identified.

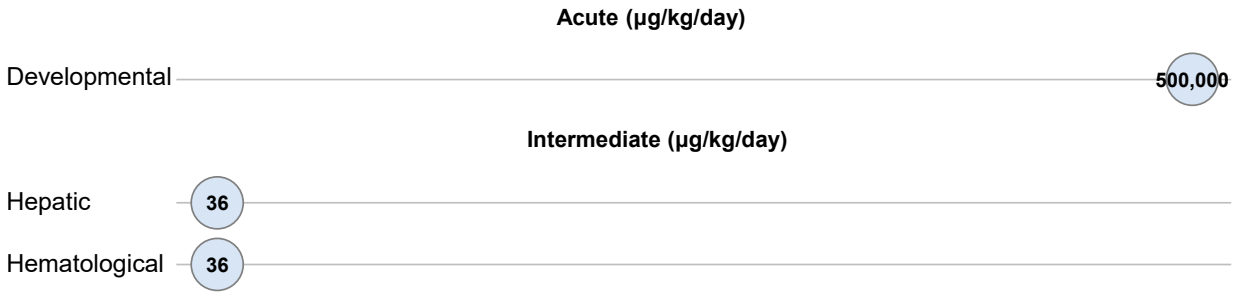


Table 1-1. Minimal Risk Levels (MRLs) for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)[a]

Exposure route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	**No inhalation MRLs were derived for any duration.**						
Oral	Acute	**$2x10^{-4}$ µg/kg/day**	Impaired immune function in mice	NOAEL	0.005 µg/kg/day	UF: 30 MF: 0.7	Burleson et al. 1996
	Intermediate	**None**	–	–	–	–	–
	Chronic	**$4x10^{-7}$ µg/kg/day**	Neurodevelopmental and impaired immune function in monkeys	LOAEL	0.00012 µg/kg/day	UF: 300	Bowman et al. 1989a, 1989b; Hong et al. 1989; Rier et al. 2001a; Schantz and Bowman 1989; Schantz et al. 1986, 1992

[a]See Appendix A for additional information.

LOAEL = lowest observed adverse effect level; MF = modifying factor; NOAEL = no observed adverse effect level; POD = point of departure; UF = uncertainty factor

Table 1-2. Minimal Risk Levels (MRLs) for Other CDD Congeners[a]

No MRLs were derived for any exposure route or duration for 2-MCDD.
No MRLs were derived for any exposure route or duration for 2,3-DCDD.
No MRLs were derived for any exposure route or duration for 2,7-DCDD.
No MRLs were derived for any exposure route or duration for 2,3,7-TrCDD.
No MRLs were derived for any exposure route or duration for 1,2,3,4-TCDD.
No MRLs were derived for any exposure route or duration for 1,2,3,7,8-PeCDD.
No MRLs were derived for any exposure route or duration for 1,2,4,7,8-PeCDD.
No MRLs were derived for any exposure route or duration for 1,2,3,4,7,8-HxCDD.
No MRLs were derived for any exposure route or duration for 1,2,3,6,7,8-HxCDD.
No MRLs were derived for any exposure route or duration for 1,2,3,4,6,7,8-HpCDD.
No MRLs were derived for any exposure route or duration for OCDD.

[a]See Appendix A for additional information

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of CDDs. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix C, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans for CDDs included in this chapter of the profile. Figures 2-2 and 2-3 provide an overview of the database of studies in experimental animals for 2,3,7,8-TCDD and other CDDs, respectively, included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to CDDs, but may not be inclusive of the entire body of literature.

Animal oral studies are presented in Table 2-2 and Figure 2-4 for 2,3,7,8-TCDD and Table 2-3 and Figure 2-5 for other CDDs. Animal dermal studies are presented in Tables 2-4 and 2-5; no inhalation data were identified for CDDs.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. Effects have been classified into "less serious LOAELs" or "serious LOAELs (SLOAELs)." "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or

mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of CDDs are indicated in Tables 2-2, 2-3, and 2-4 and Figures 2-4 and 2-5.

A User's Guide has been provided at the end of this profile (see Appendix E). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

As illustrated in Figures 2-1, 2-2, and 2-3, the health effects of CDDs have been extensively evaluated in epidemiological and animal studies. Over 250 epidemiological studies have been identified (Figure 2-1), with developmental outcomes being the most frequently examined endpoint. Many of the epidemiological studies provided limited information on the exposure route and duration. Exposure likely involved multiple exposure routes, particularly inhalation and oral routes. Humans are exposed to a variety of CDD congeners; 2,3,7,8-TCDD is the predominant congener for a number of populations, including phenoxy herbicide workers and Seveso residents exposed to an accidental release of 2,3,7,8-TCDD. As presented in Figure 2-2, the toxicity of 2,3,7,8-TCDD has been investigated in over 350 animal studies. Most of these studies (approximately 75%) involved acute-duration oral exposure. The most well-studied health outcome was developmental toxicity, with approximately 100 more studies than the second most investigated endpoint, immune effects; other well-investigated endpoints include body weight, hepatic, and reproductive endpoints. A much smaller number of studies (approximately 60 studies) have examined the toxicity of 11 other CDD congeners: 2-MCDD, 2,3-DCDD, 2,7-DCDD, 2,3,7-TrCDD, 1,2,3,4-TCDD, 1,2,3,7,8-PeCDD, 1,2,4,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD. The most studied other CDD congener was HxCDD (administered as a single congener or as mixed HxCDD congeners) (22%), followed by 1,2,3,7,8-PeCDD (19%), 2,7-DCDD (14%), OCDD (12%), and 1,2,3,4,6,7,8-HpCDD (11%). As with

2,3,7,8-TCDD, the majority of the studies (79%) were acute-duration oral exposure studies. The most investigated endpoints include acute lethality, body weight, liver, and immune endpoints.

Toxic Equivalency Factors. The general population is not typically exposed to single CDD congeners; rather, they are environmentally exposed to mixtures of halogenated aromatic hydrocarbons, of which various CDDs are constituents. CDFs and PCBs frequently occur with CDDs in the environment. The toxic effects of CDDs, CDFs, and some non-ortho-substituted PCBs (collectively referred to as dioxin-like compounds or dioxins) share a common mechanism of action in that they are mediated through the aryl hydrocarbon receptor (AhR), resulting in similar adverse health outcomes. Although they share toxic endpoints, there are congener-specific differences in toxic potency. Experimental data evaluating the toxicity of mixtures of dioxin-like compounds provide strong evidence of additivity (van den Berg et al. 2006). To provide an estimate of the toxic potency of mixtures of these compounds while accounting for the toxic potency differences between them, a TEF approach was developed.

In the TEF approach for dioxin-like compounds, the relative effect potency of individual CDD, CDF, and PCB congeners for producing toxic or biological effects is estimated and expressed relative to that of the reference compound, 2,3,7,8-TCDD (TEF=1). The TEFs can be used, assuming additivity of the toxic response, for estimating the toxicity of an environmental mixture containing a known distribution of CDDs, CDFs, and/or PCBs. Given the assumption of additivity of the toxic responses, the total TEQ of a mixture is defined as the sum of the products of the concentration of each mixture component multiplied by its respective TEF. The resulting TEQ value is an estimate of the total 2,3,7,8-TCDD-like activity of the mixture (van den Berg et al. 2006).

An expert panel organized by the World Health Organization (WHO) initially developed TEFs for all 2,3,7,8-substituted CDDs and CDFs and several PCBs in 1993, and subsequent WHO expert panels updated these TEFs in 1998, 2005, and 2022. In the 2005 TEFs, PCB compounds were included if they met the following criteria: (1) they show a structural relationship to CDDs and CDFs; (2) they bind to the AhR; (3) they elicit AhR-mediated biochemical and toxic responses; and (4) they are persistent and accumulate in the food chain (van den Berg et al. 2006). For additional information on the development of the TEFs, see Haws et al. (2006), van den Berg et al. (2006), and DeVito et al. (2024). The 1998, 2005, and 2022 WHO TEFs are presented in Table 2-1; it is noted that most epidemiological studies reported in this toxicological profile used the 2005 WHO TEFs.

Table 2-1. Summary of World Health Organization (WHO) 1998, 2005, and 2022 Toxic Equivalency Factors (TEFs)

Compound	1998 TEF[a]	2005 TEF[a]	2022 TEF[a]
Chlorinated dibenzo-*p*-dioxins (CDDs)			
2,3,7,8-TCDD	1	1	1
1,2,3,7,8-PeCDD	1	1	0.4
1,2,3,4,7,8-HxCDD	0.1	0.1	0.09
1,2,3,6,7,8-HxCDD	0.1	0.1	0.07
1,2,3,7,8,9-HxCDD	0.1	0.1	0.05
1,2,3,4,6,7,8-HpCDD	0.01	0.01	0.05
OctaCDD	0.0001	0.0003	0.001
Chlorodibenzofurans (CDFs)			
2,3,7,8-TCDF	0.1	0.1	0.07
1,2,3,7,8-PeCDF	0.05	0.03	0.01
2,3,4,7,8-PeCDF	0.5	0.3	0.1
1,2,3,4,7,8-HxCDF	0.1	0.1	0.3
1,2,3,6,7,8-HxCDF	0.1	0.1	0.09
1,2,3,7,8,9-HxCDF	0.1	0.1	0.2
2,3,4,6,7,8-HxCDF	0.1	0.1	0.1
1,2,3,4,6,7,8-HpCDF	0.01	0.01	0.02
1,2,3,4,7,8,9-HpCDF	0.01	0.01	0.1
OctaCDF	0.0001	0.0003	0.002
Non-*ortho*-substituted polychlorinated biphenyls (PCBs)			
3,3′,4,4′-tetraCB (PCB 77)	0.0001	0.0001	0.0003
2,3,4,4′,5-tetraCB (PCB 81)	0.0001	0.0003	0.006
3,3′,4,4′,5-pentaCB (PCB 126)	0.1	0.1	0.05
3,3′,4,4′,5,5′-hexaCB (PCB 169)	0.01	0.03	0.005
Mono-*ortho*-substituted PCBs			
2,3,3′,4,4′-pentaCB (PCB 105)	0.0001	0.00003	0.00003
2,3, 4,4′,5-pentaCB (PCB 114)	0.0005	0.00003	0.00003
2,3′,4,4′,5-pentaCB (PCB 118)	0.0001	0.00003	0.00003
2′,3,4,4′,5-pentaCB (PCB 123)	0.0001	0.00003	0.00003
2,3,3′,4,4′,5-hexaCB (PCB 156)	0.0005	0.00003	0.00003
2,3,3′,4,4′,5′-hexaCB (PCB 157)	0.0005	0.00003	0.00003
2,3′,4,4′,5,5′-hexaCB (PCB 167)	0.000001	0.00003	0.00003
2,3,3′,4,4′,5,5′-heptaCB (PCB 189)	0.0001	0.00003	0.00003

[a]TEFs are relative to the toxicity of 2,3,7,8-TCDD.

Sources: DeVito et al. 2024; Van den Berg et al. 2006

Epidemiological Studies. The epidemiological database evaluating the toxicity of CDDs, CDFs, and/or PCBs is extensive. The database consists of occupational exposure studies, studies of communities living

near point sources, communities affected by accidental releases, and the general population exposed to background levels, primarily from CDDs, CDFs, and/or PCBs in the food supply. This profile will focus on the toxicity of CDDs and greater emphasis is placed on epidemiological studies with known exposure to CDDs, or a specific congener; for additional information on the toxicity of CDFs and PCBs, the reader is referred to the toxicological profiles on these compounds (ATSDR 2000, 2023).

With the exception of some occupational exposure and community exposure studies, exposure levels were not measured; most studies used serum lipid CDD, CDF, and/or PCB levels as a biomarker for exposure. Studies reported serum levels as individual congener levels; total CDD, CDF, and/or PCB levels; total CDD/CDF levels; TEFs for individual congeners; and total CDD, total CDD/CDF, or CDD/CDF/PCB TEQs. In many studies, serum 2,3,7,8-TCDD levels were measured a number of years after exposure termination. CDDs are highly persistent lipophilic compounds that are resistant to biodegradation and have a great potential to bioaccumulate. Thus, a single chemical analysis of blood or adipose tissue represents a measure of past cumulative exposure to CDDs. With the assumptions of first-order kinetics for the elimination of 2,3,7,8-TCDD and an elimination half-life of 7–12 years, it is possible to extrapolate or adjust the serum or adipose tissue lipid concentration of 2,3,7,8-TCDD back to the time of the original excess exposure, which may have occurred many years earlier, if the time of original exposure is known. Body burden or total dioxin amount can then be calculated from the serum 2,3,7,8-TCDD levels using the assumption that the concentration of 2,3,7,8-TCDD in serum lipids is in equilibrium with total body lipid 2,3,7,8-TCDD concentrations and that in an average adult, 22% of the body weight is lipid. Some of the studies on health outcomes following exposure to 2,3,7,8-TCDD and related compounds did not monitor exposure levels or internal dose. Surrogates of exposure were used to identify potentially exposed populations and the level of exposure; some of the more commonly used surrogates include chloracne (a dermal condition generally indicative of appreciable exposure), potential exposure to phenoxy herbicides known to be contaminated with 2,3,7,8-TCDD, living in the vicinity of an accidental release of substances containing CDDs and related compounds, or living an area with CDD-contaminated soil.

As noted previously, epidemiological data come from a number of sources, and several cohorts have been followed for a number of years; brief descriptions of some of these cohorts are provided below.

Occupational Exposure. The first reported cases of industrial poisoning were in 1949 at a factory producing 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) in Nitro, West Virginia. 2,3,7,8-TCDD formation resulted from uncontrolled conditions in the reactor producing 2,4,5-trichlorophenol (2,4,5-TCP) from

tetrachlorobenzene in methanol and sodium hydroxide (Moses et al. 1984). Approximately 228 workers (including production workers, laboratory personnel, and medical personnel) were affected. Between 1949 and 1968, three other explosive releases were reported: one involved 254 workers at the BASF AG facility in Ludwigshafen, Germany, in 1953 (Goldman 1972; Thiess et al. 1982; Zober et al. 1990, 1993); a second, similar accident in 1963 involved 106 workers at Philips-Duphar facility in Amsterdam, Netherlands (Holmstedt 1980); and the third was an explosion in a 2,4,5-TCP manufacturing facility in Coalite, England, involving 90 workers (May 1973). The accident at the Philips-Duphar facility involved both facility workers and cleanup workers (Holmstedt 1980). Exposure data on most of these incidents were limited; various numbers of workers were affected, and many of the published reports are anecdotal. Ott et al. (1994) measured serum 2,3,7,8-TCDD levels in 138 of the 254 exposed workers several decades after the explosion at the BASF facility. More than 35 years after the explosion, serum 2,3,7,8-TCDD levels of <1–553 pg/g lipid were found; these correspond to serum levels of 3.3–12,000 pg/g lipid (calculated using a 7-year half-life) at the time of the accident.

Some of the most comprehensive studies on occupational exposure were conducted by the National Institute for Occupational Safety and Health (NIOSH). They are cross-sectional studies of workers at U.S. chemical facilities involved in the manufacture of 2,3,7,8-TCDD-contaminated products between 1942 and 1984 (Calvert et al. 1991, 1992; Egeland et al. 1994; Fingerhut et al. 1991; Sweeney et al. 1993). Serum 2,3,7,8-TCDD levels were measured in the workers at two of the plants. The mean 2,3,7,8-TCDD serum lipid level in 281 production workers in the Newark, New Jersey, and Verona, Missouri, plants was 220 ppt (range, 2–3,390 ppt) 18–33 years after exposure termination; the referent group of 260 people who had no self-reported occupational exposure and were matched by neighborhood, age, race, and sex had a mean serum 2,3,7,8-TCDD level of 7 ppt (Calvert et al. 1992; Sweeney et al. 1993). Sweeney et al. (1990) estimated current mean lipid-adjusted 2,3,7,8-TCDD levels of 293.4 ppt (range, 2–3,390 ppt) in 103 production workers at the New Jersey facility and 177.3 ppt (range, 3–1,290 ppt) in 32 workers at the Missouri facility; the mean half-life extrapolated levels (using a half-life of 7 years) were 2,664.7 ppt (range, 2–30,900 ppt) and 872.3 ppt (range, 3–6,100 ppt) in the two facilities, respectively. It should be noted that serum 2,3,7,8-TCDD levels were only measured in workers at these 2 facilities, and it is not known if the levels in these workers are reflective of serum 2,3,7,8-TCDD levels in workers at the other 10 facilities.

There are also a number of studies of chlorophenol and phenoxy herbicide applicators. Some of these studies used job histories, questionnaires, and interviews to determine which phenoxy herbicides the workers had used. Many of the studies did not measure exposure levels or internal doses; rather,

2,3,7,8-TCDD exposure was assumed if the worker was exposed to a phenoxy herbicide known to be contaminated with 2,3,7,8-TCDD, such as 2,4,5-T. However, the level of exposure to these 2,3,7,8-TCDD-contaminated products was generally not determined.

Residential/Environmental Exposures. Several incidents in which populations were exposed to potentially high levels of 2,3,7,8-TCDD include an industrial accident that occurred during the production of 2,4,5-TCP at the ICMESA plant in Seveso, Italy and the spraying of roads and other places with a mixture of waste oil, including chemical waste generated during the manufacture of 2,4,5-TCP in Missouri. Studies have also been conducted in residents living near a municipal incinerator or near a former pentachlorophenol (PCP) production facility in Taiwan.

The most widely studied release of 2,3,7,8-TCDD primarily involving residential exposures occurred in Seveso, Italy in 1976 (Mastroiacovo et al. 1988). The ICMESA factory produced trichlorophenol by hydrolysis of 1,2,4,5-tetrachlorobenzene with alkali in ethylene glycol. The reactor overheated and the safety valve ruptured, releasing a cloud containing primarily sodium trichlorophenate but also 2,3,7,8-TCDD. It was estimated that >1.3 kg of 2,3,7,8-TCDD was released into the atmosphere and that >17,000 people in a 2.8-km^2 area adjacent to the facility were exposed. To investigate this accident, the contaminated area was separated into regions A, B, and R based on soil levels of 2,3,7,8-TCDD. The population sizes were 736, 4,737, and 31,800 in areas A, B, and R, respectively. The respective mean (and maximum) surface soil levels of 2,3,7,8-TCDD were 230 (447) $\mu g/m^2$, 3 (43.8) $\mu g/m^2$, and 0.9 (9.7) $\mu g/m^2$. Dividing the populations into different zones based on soil levels has been criticized because it does not take into consideration actual exposure levels or differences in within-zone 2,3,7,8-TCDD exposure (Mastroiacovo et al. 1988). Blood and tissue samples from exposed individuals have been saved and 2,3,7,8-TCDD levels in some of the original samples and in follow-up blood samples have been analyzed. Serum 2,3,7,8-TCDD levels were 828–56,000 ppt (lipid adjusted) in 19 residents of zone A (Mocarelli et al. 1991).

Various populations in Missouri were exposed to 2,3,7,8-TCDD in 1971 and 1972 as a result of spraying approximately 29 kg of 2,3,7,8-TCDD-contaminated waste oil on horse arenas, parking lots, and residential roads for dust control (Andrews et al. 1989). The oils originated from an industrial waste residue contaminated with 2,3,7,8-TCDD at levels of 305 ppm (Needham et al. 1991). An exposed group of 51 adults have been the subject of several studies. Adipose tissue levels, as well as paired human serum levels, were measured for 36 of these persons. Sixteen of the individuals were residents of areas where roadways had been sprayed and had mean 2,3,7,8-TCDD adipose tissue levels of 21.1 ppt (range,

1.28–59.1 ppt) in 1985 (Andrews et al. 1989). Eight persons exposed to 2,3,7,8-TCDD at the horse arenas had a mean adipose 2,3,7,8-TCDD concentration of 90.8 ppt (5–577 ppt). In a comparison population of 57 people with no known 2,3,7,8-TCDD exposure, 2,3,7,8-TCDD levels in the adipose tissue ranged from 1.4 to 20.2 ppt, with a mean of 7.4 ppt. Although the population of study was not large, the subjects were evaluated in depth for medical effects (Hoffman et al. 1986; Stehr et al. 1986; Webb et al. 1984).

Exposures in Vietnam. During the Vietnam War, a program of aerial spraying of herbicides, code name Ranch Hand, was conducted in 10–20% of the Republic of Vietnam. During the 9 years of the program (1962–1970), 19 million gallons of herbicides were dispersed. Six herbicides were used, with Agent Orange being the primary herbicide used (11 million gallons dispersed) (Wolfe et al. 1985). Agent Orange was a 1:1 mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-T in diesel oil and contained <1–20 ppm 2,3,7,8-TCDD as a contaminant. A number of studies have examined the possible association between Agent Orange exposure and adverse health effects in Vietnam War veterans and Vietnamese residents living in the area of spraying. The results of a study comparing blood 2,3,7,8-TCDD levels in Vietnam veterans and the general U.S. population found that, on average, there was no significant difference between blood 2,3,7,8-TCDD levels between Vietnam veterans and comparison populations (CDC 1987). Thus, "service in Vietnam" or self-reported exposure to Agent Orange is not a reliable index of 2,4,5-T or 2,3,7,8-TCDD exposure. Studies of Air Force personnel participating in Operation Ranch Hand have found increased serum 2,3,7,8-TCDD levels in some of the persons (CDC 1987; USAF 1991). The median level in serum lipids for 888 Ranch Hand personnel was 12.4 ppt (range, 0 to 617.7 ppt), in contrast to 4.2 ppt (0–54.8 ppt) in a comparison group of 856 matched Air Force personnel (Wolfe et al. 1995). The median and high serum 2,3,7,8-TCDD levels would extrapolate to original serum levels of 43 and 3135 ppt, respectively, based on 20 years of elapsed time and a half-life of 8.5 years. Since the tour of duty in Vietnam for the majority of U.S. veterans was generally <1 year, the military exposure was considered to be of intermediate duration if not stated otherwise in the original study. In addition to the studies of Vietnam War veterans and the Operation Ranch Hand cohort, a number of studies have been conducted in residents living in areas with heavy Agent Orange exposure. High levels of CDDs, particularly 2,3,7,8-TCDD, have been measured in soil and food from areas in Vietnam that were sprayed with Agent Orange. A study published in 2006 (Schecter et al. 2006) reported a median serum 2,3,7,8-TCDD level of 30.9 ppt lipid (range of 13.6–180 ppt lipid) in a small group of residents of Can Tho province. The medians in other Agent Orange sprayed areas ranged from 1.5 to 7.3 ppt lipid.

Animal Studies. The literature on the health effects of CDDs, especially 2,3,7,8-TCDD, following oral exposure is extensive; thus, it is not practical or realistic to cite all, or even most, of the 2,3,7,8-TCDD oral animal studies. Therefore, the discussion of 2,3,7,8-TCDD in this chapter emphasizes low dose studies that could help construct dose-response relationships and determine points of departure (PODs) for the various specific effects. As summarized in Figure 2-2, there are 350 papers evaluating the oral toxicity of 2,3,7,8-TCDD in animals cited in Chapter 2; however, not all of the studies are included in the LSE table and figure (Table 2-2 and Figure 2-4); for a particular endpoint, higher dose studies were excluded from the LSE table and figure. No exclusion criteria were used for the other CDD congeners due to the small number of studies for a specific congener.

Overview of Health Effects of CDDs. Although a large number of epidemiological studies have evaluated the toxicity of CDDs, the results are not consistent across studies. There are several contributing factors to this inconsistency including:

- Exposures to different mixes of CDD congeners
- Differences in CDD exposure levels
- Insensitive biomarker of exposure
- Exposure to low levels of CDDs
- Time elapsed between exposure and when health outcomes are assessed

Adverse health outcomes have been observed in animals for all health endpoints discussed in this chapter. Effects observed at the lowest doses include developmental toxicity, immunotoxicity, reproductive toxicity, and hepatotoxicity; cancer has also been observed.

- ***Developmental Effects***
  - *Epidemiological Studies.* Studies in highly exposed populations have found associations between 2,3,7,8-TCDD exposure and impaired development of the male reproductive system (decreased sperm concentrations and delayed puberty) when males were exposed as boys and between maternal 2,3,7,8-TCDD levels and neonatal thyroid-stimulating hormone (TSH) levels. Mixed results for neurodevelopmental effects have been observed in highly exposed populations. General population studies have not found consistent associations with birth outcome parameters or immune function.
  - *Animal Studies on 2,3,7,8-TCDD*. Oral exposure animal studies provide strong evidence of the developmental toxicity of 2,3,7,8-TCDD in several animal species (e.g., monkeys, rats, mice, hamsters). The observed effects include increases in fetal/newborn mortality; structural anomalies, such as cleft palate and hydronephrosis; decreased birth weight and growth; gastrointestinal hemorrhage; impaired development of the immune system; and

neurodevelopmental effects such as hyperactivity, altered social behaviors, and impaired learning.
  - *Animal Studies on Other CDD congeners.* A small number of oral animal studies evaluated the developmental toxicity of other CDD congeners. Observed effects include heart damage (2,7-DCDD), decreased thymus weight (1,2,3,7,8-PeCDD), and decreased growth (mixed HxCDD congeners). No developmental effects have been observed in the small number of studies evaluating 2-MCDD, 2,3-DCDD, 1,2,3,4-TCDD, or OCDD.

- ***Immunological Effects***
  - *Epidemiological Studies.* A small number of epidemiological studies evaluating immune competence have found suggestive, but inconsistent, evidence of immunotoxicity.
  - *Animal Studies on 2,3,7,8-TCDD.* A number of immune effects have been observed in animals following oral exposure to 2,3,7,8-TCDD. The observed effects include decreased thymus weight, thymic atrophy, and impaired immune function on tests of host resistance and response to antigens.
  - *Animal Studies on Other CDD congeners.* Decreases in thymus weights (1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, and 1,2,3,4,6,7,8-HpCDD) and impaired immune function (2,7-DCDD, 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, and 1,2,3,4,6,7,8-HpCDD) have also been observed in animals exposed to other CDD congeners.

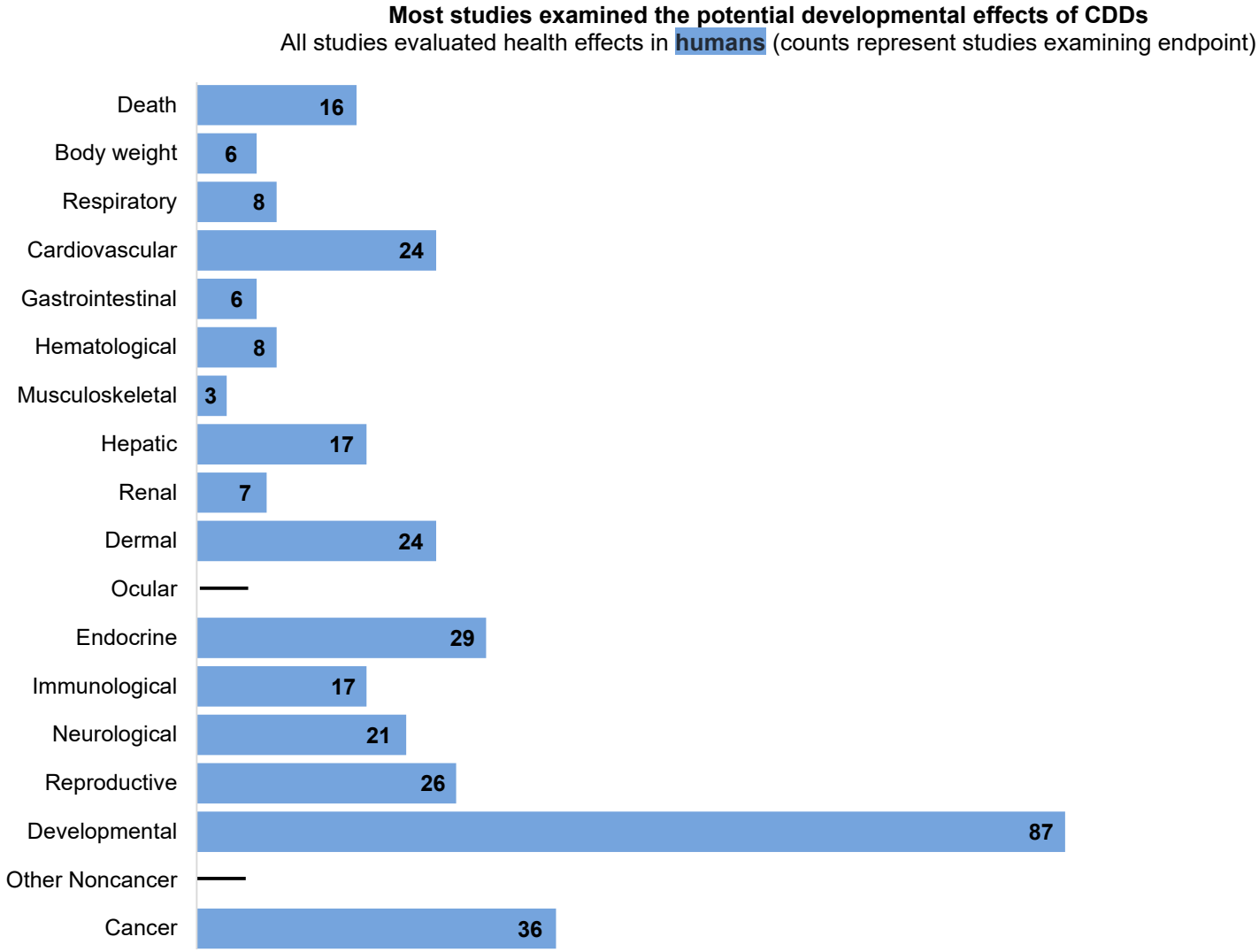
- ***Reproductive Effects***
  - *Epidemiological Studies.* Overall studies evaluating reproductive parameters in men have not found associations with CDD exposure. An increased time to pregnancy was observed in highly exposed women.
  - *Animals Studies on 2,3,7,8-TCDD.* Oral exposure studies in animals provide strong evidence of the reproductive toxicity of 2,3,7,8-TCDD. Effects include alterations in sperm parameters, decreased female fertility, and altered nursing behavior.
  - *Animal Studies on Other CDD Congeners.* The reproductive toxicity of other CDD congeners has not been evaluated.

- ***Hepatic Effects***
  - *Epidemiological Studies.* Inconsistent results of the hepatoxicity of CDDs in humans have been reported, with some studies reporting small alterations in serum liver enzyme lipid levels and others reporting no associations.
  - *Animal Studies on 2,3,7,8-TCDD.* Animal studies provide consistent strong evidence on the hepatoxicity of 2,3,7,8-TCDD. Observed liver effects include increases in liver weight, increases in serum alanine aminotransferase (ALT) levels, altered serum lipid levels, alterations in vitamin A storage, and histopathological alterations such as hepatocellular hypertrophy and necrosis and biliary hyperplasia.
  - *Animal Studies on Other CDD Congeners.* Hepatocellular damage has also been observed in animals exposed to 2,7-DCDD, a mixture of HxCDD congeners, and OCDD.

- ***Cancer Effects***
  - *Epidemiological Studies.* Studies of highly exposed populations have found associations between CDDs and lung cancer, soft tissue sarcomas, and non-Hodgkin lymphoma.
  - *Animal Studies on 2,3,7,8-TCDD.* Several types of tumors have been observed in animal studies including hepatocellular carcinoma, thyroid follicular cell adenoma, squamous cell carcinomas in the lung, hard palate, tongue, and oral mucosa.
  - *Animal Studies of Other CDD Congeners.* Hepatocellular carcinomas have been observed in mice exposed to a mixture of HxCDD congeners and to 2,7-DCDD.

- *Cancer Classifications.* HHS has classified 2,3,7,8-TCDD as known to be a human carcinogen. IARC has determined that 2,3,7,8-TCDD is carcinogenic to humans. EPA has categorized the mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD as a probable human carcinogen.

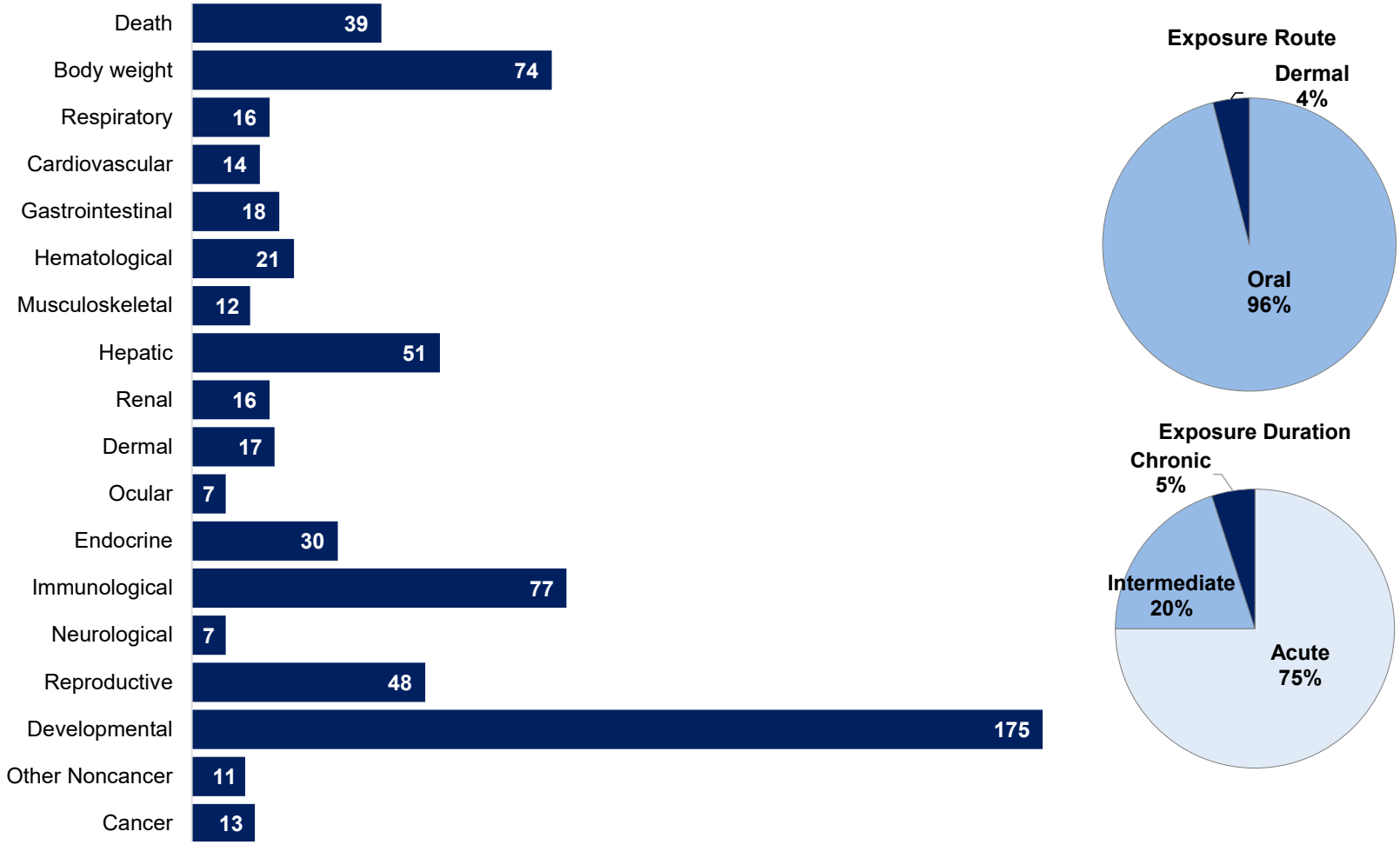
Figure 2-1. Overview of the Number of Studies Examining Chlorinated Dibenzo-*p*-Dioxins (CDDs) Human Health Effects*



*Includes studies discussed in Chapter 2. A total of 258 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

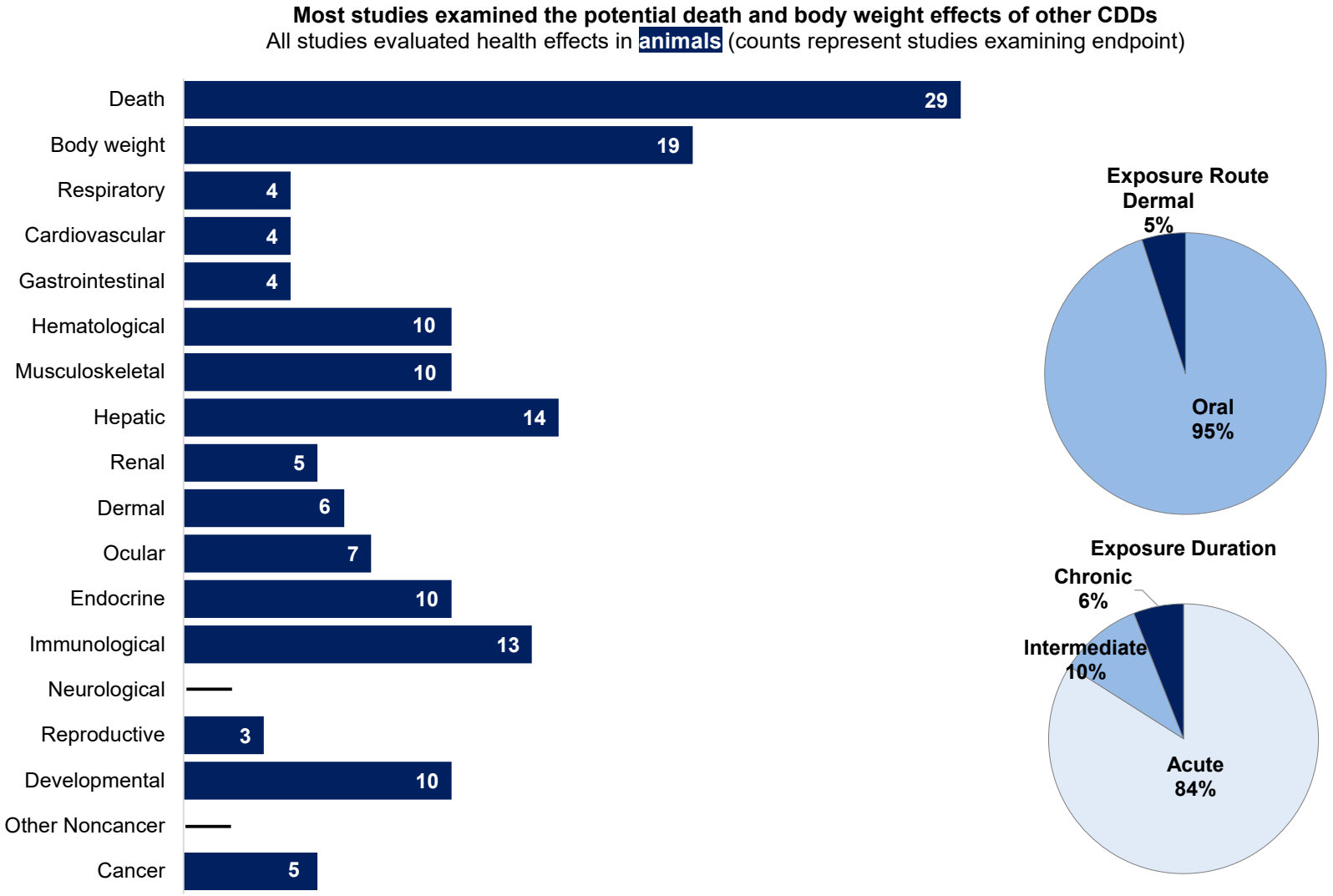
Figure 2-2. Overview of the Number of Animal Studies Examining 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) Health Effects*

Most studies examined the potential developmental effects of 2,3,7,8-TCDD
All studies evaluated health effects in animals (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 393 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Figure 2-3. Overview of the Number of Animal Studies Examining Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) Health Effects*



*Includes studies discussed in Chapter 2. A total of 62 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Guo et al. 2000									**2,3,7,8-TCDD**
1	Monkey (Cynomolgus) 4–7 F	GD 12 (GO)	0, 1, 2, 4	CS, OF	Develop			1	Early fetal loss
McConnell et al. 1978a									**2,3,7,8-TCDD**
2	Monkey (Rhesus) 3 F	Once (GO)	0, 70, 350	BW, GN, HP, BC, CS	Death			70	Increased mortality; 1/3 died
					Bd wt			70	28% lower terminal body weight
					Dermal		70		Nail loss and facial alopecia with acneiform lesions
					Ocular		70		Swelling and inflamed eyelids
					Immuno		70		Severe atrophy of the thymus
McNulty 1984									**2,3,7,8-TCDD**
3	Monkey (Rhesus) 3 F	GD 25, 30, 35, or 40 (GO)	0, 1	RX, DX, LE	Death			1	3/12 mothers died
					Develop			1	Increased occurrence of abortions
Moran et al. 2001									**2,3,7,8-TCDD**
4	Monkey (Cynomolgus) 10 F	Once (GO)	0, 1, 2, 4	RX, HP, BI	Repro	2		4	Decreased serum progesterone; histological evidence of anovulation
Scott et al. 2001									**2,3,7,8-TCDD**
5	Monkey (Cynomolgus) 11 F	Once (GO)	0, 1, 2, 4	HP	Repro		1		Squamous metaplasia in endocervix
Adamsson et al. 2008									**2,3,7,8-TCDD**
6	Rat (Sprague-Dawley) 6–8 F	GD 11 (GO)	0, 0.3, 1	DX, BI, BW, OW	Develop		0.3		Decreased testicular testosterone in 19-day male fetus

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Balk and Piper 1984									**2,3,7,8-TCDD**
7	Rat (Sprague-Dawley) 3-8 M	Once (GO)	0, 25	BI	Endocr		25		Decreased corticosterone levels on days 14 and 21 after dosing
Ball and Chhabra 1981									**2,3,7,8-TCDD**
8	Rat (Sprague-Dawley) 6 M	Once (GO)	0, 5, 100	BW, BI	Bd wt	5		100	25% decrease body weight
Bell et al. 2007a									**2,3,7,8-TCDD**
9	Rat (Wistar) 55–75 F	GD 15 (GO)	0, 0.05, 0.2, 1	RX, DX, HP, OW	Develop	0.2		1	Increased neonatal deaths during lactation (11% fewer pups/litter on PND 21); delayed puberty
Bestervelt et al. 1993									**2,3,7,8-TCDD**
10	Rat (Sprague-Dawley) 14–24 M	Once (GO)	0, 50	BI	Endocr		50		Increased serum ACTH; increased serum corticosterone on days 1 and 5 but decreased on days 10 and 14
Bjerke and Peterson 1994									**2,3,7,8-TCDD**
11	Rat (Holtzman) 10–12 F	GD 15 (GO)	0, 1.0	DX	Develop			1	Decreased percentage of pups born alive (30%), decreased pup body weight (12–14.5%), delayed preputial separation, decreased ventral prostate and seminal vesicle weights, decreased sperm production, feminization of sexual behavior
Bjerke et al. 1994a									**2,3,7,8-TCDD**
12	Rat (Holtzman) 10–12 F	GD 15 (GO)	0, 0.7	DX	Develop			0.7	Impaired development of reproductive system; decreased pup body weight (8–11%)

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Bjerke et al. 1994b									**2,3,7,8-TCDD**
13	Rat (Holtzman) 10–12 F	GD 15 (GO)	0, 0.7	DX	Develop		0.7		Demasculinization and feminization of sexual behavior
Bookstaff et al. 1990									**2,3,7,8-TCDD**
14	Rat (Sprague-Dawley) 4–6 M	Once (GO)	0, 50, 100	BI	Repro		10		ED_{50} altered regulation of LH secretion
Boverhof et al. 2006									**2,3,7,8-TCDD**
15	Rat (Sprague-Dawley) 5 F	Once (GO)	0, 0.001, 0.01, 0.1, 1, 10, 30, 100	BW, OW, HP	Hepatic	10	30		Increased relative liver weight, hepatocellular hypertrophy
Boverhof et al. 2006									**2,3,7,8-TCDD**
16	Rat (Sprague-Dawley) 5 F	Once (GO)	0, 10	BW, BC, OW, HP	Hepatic		10		Minimal to moderate hepatocellular hypertrophy, increased relative liver weight; increased serum cholesterol, triglycerides, and FFA
Brown et al. 1998									**2,3,7,8-TCDD**
17	Rat (Sprague-Dawley) 8 F	GD 15 (GO)	0, 1	HP, DX	Develop			1	Alteration in mammary gland differentiation; increased number of chemically-induced mammary adenocarcinomas in pups; delayed vaginal opening, disruption of estrous cycle
Chaffin et al. 1996									**2,3,7,8-TCDD**
18	Rat (Holtzman) 9 F	GD 15 (GO)	0, 1	DX	Develop		1		Decreased serum estrogen levels in female offspring

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Christian et al. 1986									**2,3,7,8-TCDD**
19	Rat (Sprague-Dawley) 19 M	Once (GO)	0, 25, 37, 50, 75	BW, FI, HP, CS, LE	Bd wt			25	36–48% body weight loss
					Cardio	75			
					Gastro	75			
					Renal		25		Dilated convoluted tubules
Courtney et al. 1978									**2,3,7,8-TCDD**
20	Rat (Wistar) 4–6 F	Once (GO)	0, 100	BW, FI, WI	Bd wt			100	15–30% decreased weight
Crofton et al. 2005									**2,3,7,8-TCDD**
21	Rat (Long-Evans) 4–14 F	Once (GO)	0, 0.0001–10	BW, OF	Endocr		0.15		30% decrease in serum T4 (ED_{30})
De Heer et al. 1994a									**2,3,7,8-TCDD**
22	Rat (Wistar) 4 M	10 days (GO)	0, 1, 5, 25, 50, 150	BW, HP, OW	Immuno	1	5		Reduced relative thymus weight
De Heer et al. 1994b									**2,3,7,8-TCDD**
23	Rat (Wistar) 3 M	Once (GO)	0, 25	BW, OW, HP	Immuno		25		Reversible thymic atrophy starting on day 13
De Heer et al. 1994b									**2,3,7,8-TCDD**
24	Rat (Wistar) 4 M	4 days (GO)	0, 1, 5, 25	BI, OW	Immuno		1		Reduced number of immature CD4CD8 double positive thymocytes; decreased absolute and relative thymus weight
Dienhart et al. 2000									**2,3,7,8-TCDD**
25	Rat (Holtzman) 4–5 F	GD 15 (GO)	0, 1	DX, HP	Develop		1		Altered vaginal morphogenesis in pups

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Fan et al. 1996									**2,3,7,8-TCDD**
26	Rat (Sprague-Dawley) 3–10 M	Once (GO)	0, 1, 3, 10, 20, 30, 40, 90	IX, BW	Immuno	3	10		Impaired delayed-type hypersensitivity reaction
Fenton et al. 2002									**2,3,7,8-TCDD**
27	Rat (Long-Evans) 10 F	GD 15 (GO)	0, 1	RX, DX, HP	Develop		1		Delayed development of mammary gland in pups
Fenton et al. 2002									**2,3,7,8-TCDD**
28	Rat (Long-Evans) 5 F	GD 15, GD 20, PND 1, PND 3, PND 5, or PND 10 (GO)	0, 1	BC	Develop		1		Decreased serum TSH levels in 25- and 60-day offspring; decreased serum T4 levels in 60-day old offspring
Fernandez et al. 2010									**2,3,7,8-TCDD**
29	Rat Dark-Agouti NS F	Once GD 18 (GO)	0, 0.7	DX, BI	Develop		0.7		Delayed myelination in brain areas
Filgo et al. 2016									**2,3,7,8-TCDD**
30	Rat (Sprague-Dawley) 9 F	GDs 15 and 18 (G)	0, 0.5	DX	Develop		0.5		Delayed mammary gland development in male and female offspring
Finnila et al. 2010									**2,3,7,8-TCDD**
31	Rat (Sprague-Dawley) NS F	GD 11 (GO)	0, 1	DX, OF, HP	Develop		1		Reduced bone strength in offspring

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Flaws et al. 1997									**2,3,7,8-TCDD**
32	Rat (Holtzman) 8–48 F	GD 11, 15, or 18 (GO)	0, 1	DX	Develop		1		Cleft clitoris and vaginal thread in female offspring
Fletcher et al. 2001									**2,3,7,8-TCDD**
33	Rat (Sprague-Dawley) 5 M	Once (GO)	0, 0.12, 0.66, 3.5, 19, 100	LE, BW, OW, OF	Bd wt	3.5	19	100	SLOAEL: Decreased mean body weight gain (55%) LOAEL: Decreased mean body weight gain (10%)
					Hepatic		0.12		Increased relative liver weight; decreased hepatic vitamin A content
					Immuno	0.12	0.66		Decreased relative thymus weights
					Other noncancer		0.12		Decreased vitamin A content
Gehrs et al. 1997a									**2,3,7,8-TCDD**
34	Rat (Fischer-344) 6–7 F	GD 14 (GO)	0, 1, 3	DX	Develop		1		Alterations in lymphocyte phenotypes
Gehrs et al. 1997b									**2,3,7,8-TCDD**
35	Rat (Fischer-344) 13 F	GD 14 (GO)	0, 3	DX	Develop		3		Alterations in lymphocyte phenotypes
Gehrs et al. 1997b									**2,3,7,8-TCDD**
36	Rat (Fischer-344) 5 F	GD 14 (GO)	0, 1	DX	Develop		1		Alterations in lymphocyte phenotypes and decreased DTH response

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Giavini et al. 1983									**2,3,7,8-TCDD**
37	Rat (CRCD) 15 F	2 weeks (GO)	0, 0.125, 0.5, 2	RX, DX	Bd wt	0.125	0.5		Reduced maternal weight gain (12.8%)
					Neuro	0.5	2		Decreased activity in dams
					Repro	0.5		2	Increased preimplantation loss and decreased corpora lutea
					Develop	0.5		2	Increased incidence of cystic kidneys; increased fetal mortality
Gray and Ostby 1995									**2,3,7,8-TCDD**
38	Rat (Holtzman) 8 F	GD 15 (GO)	0, 1	DX, OF, HP	Develop			1	Decreased neonatal survival; malformations of external genitalia, decreased anogenital distance in female offspring
Gray and Ostby 1995									**2,3,7,8-TCDD**
39	Rat (Long-Evans) 8 F	GD 8 (GO)	0, 1	DX, HP	Develop			1	Malformations of external genitalia, decreased fertility, shortened reproductive lifespan
Gray and Ostby 1995									**2,3,7,8-TCDD**
40	Rat (Long-Evans) 8 F	GD 15 (GO)	0, 1	DX, HP	Develop			1	Decreased pup survival and body weight gain (19%); delayed age of vaginal opening, decreased urethral-vaginal distance, and vaginal thread
Gray et al. 1995									**2,3,7,8-TCDD**
41	Rat (Long-Evans) 8 F	GD 8 or 15 (GO)	0, 1	DX	Develop			1	Impaired development of reproductive system

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Gray et al. 1997a									**2,3,7,8-TCDD**
42	Rat (Long-Evans) 12 F	GD 15 (GO)	0, 0.05, 0.20, 0.80	DX	Develop	0.05	0.2		Urogenital morphological alterations, presence of vaginal thread, and cleft phallus
							0.05		Reduction in ejaculated sperm count
Gray et al. 1997b									**2,3,7,8-TCDD**
43	Rat (Long-Evans) 12 F	GD 15 (GO)	0, 0.05, 0.20, 0.80	DX	Develop		0.5	0.8	LOAEL: Delayed puberty in male offspring SLOAEL: Decreased pup survival from PND 3 to 22, decreased pup body weight (8–10%), decreased epididymal sperm numbers
Haavisto et al. 2001									**2,3,7,8-TCDD**
44	Rat (Han/Wistar) 2–8 F	GD 13.5 (GO)	0, 0,05, 0.1, 0.5, 1.0	DX	Develop	0.1	0.5		Decreased plasma testosterone levels in males
Haavisto et al. 2006									**2,3,7,8-TCDD**
45	Rat (Sprague-Dawley) 10 F	GD 13 (GO)	0, 0.04, 0.2, 1	DX, BI, HP	Develop	1			
Håkansson et al. 1989									**2,3,7,8-TCDD**
46	Rat (Sprague-Dawley) NS M	Once (GO)	0, 6.25, 12.5, 25, 50, 100	BI	Hepatic		6.25		Altered vitamin A storage
Hamm et al. 2000									**2,3,7,8-TCDD**
47	Rat (Long-Evans) 14 F	GD 15 (GO)	0, 1	DX, OW, HP	Develop		1		Altered development of seminal vesicles in offspring
Hanberg et al. 1989									**2,3,7,8-TCDD**
48	Rat (Sprague-Dawley) NS	Once (GO)	0, 0.12–100	BW, OW, LE	Immuno		26		ED_{50} for thymic atrophy

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Hattori et al. 2014									**2,3,7,8-TCDD**
49	Rat (NR) 4–6 F	GD 15 (GO)	0, 1	DX	Develop			1	20% decreased birth weight
Heimler et al. 1998									**2,3,7,8-TCDD**
50	Rat (Holtzman) F	GD 15 (GO)	0, 1	DX	Develop		1		Decreased number of antral and preantral ovarian follicles
Hermansky et al. 1988									**2,3,7,8-TCDD**
51	Rat (Sprague-Dawley) 6 F	3 days (GO)	0, 40	HP, CS, BI	Cardio		40		Decrease heart rate and decreased mean blood pressure
Hoegberg et al. 2003									**2,3,7,8-TCDD**
52	Rat (Sprague-Dawley) 6 M	Once (GO)	0, 0.1, 1.0, 10, 100	CS, BW, GN, OW, OF	Hepatic	1	10		Decreased hepatic retinyl esters and all trans retinoic acid
Hsu et al. 2018									**2,3,7,8-TCDD**
53	Rat (Sprague-Dawley) NR F	GD 14, GD 21, PND 7, PND 22 (GO)	0, 0.2	DX	Develop		0.2		Increased systolic blood pressure and mean arterial blood pressure in adult male offspring
Hsu et al. 2020									**2,3,7,8-TCDD**
54	Rat (Sprague-Dawley) NR F	GD 14, GD 21, PND 7, PND 22 (G)	0, 0.2	DX	Develop		0.2		Increased systolic blood pressure in adult male offspring
Hurst et al. 2002									**2,3,7,8-TCDD**
55	Rat (Long-Evans) NS F	GD 15 (GO)	0, 1	DX, GN, HP, BI	Develop		1		Altered morphogenesis of female reproductive tract

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Huuskonen et al. 1994									**2,3,7,8-TCDD**
56	Rat (Long-Evans) 9–17 F	GD 8 (GO)	1, 5	DX, OF, HP	Develop	1		5	Cleft palate, thymic atrophy, decreased number of live fetuses
Huuskonen et al. 1994									**2,3,7,8-TCDD**
57	Rat (Han/Wistar) 9–17 F	GD 8 (GO)	1, 10	DX, OF, HP	Develop	1		10	Hydronephrosis, thymic atrophy, gastrointestinal hemorrhage, decreased number of live fetuses
Huuskonen et al. 1994									**2,3,7,8-TCDD**
58	Rat (Han/Wistar) 9–17 F	GD 12 (GO)	1, 10	DX, OF, HP	Develop	1		10	Hydronephrosis, gastrointestinal hemorrhages, decreased number of live fetuses
Ikeda et al. 2002									**2,3,7,8-TCDD**
59	Rat (Sprague-Dawley) 3–6 F	GD 15 (GO)	0, 0.8, 1.6	DX	Develop			0.8	Decreased litter size on PND 2 and fetal survival on GD 20
Ikeda et al. 2005a									**2,3,7,8-TCDD**
60	Rat (Holtzman) 9 F	GD 15 (GO)	0, 0.2, 0.8	DX, BI	Develop		0.2		Demasculinization of male pups
Ishimura et al. 2002									**2,3,7,8-TCDD**
61	Rat (Holtzman) 3–6 F	GD 15 (GO)	0, 0.8, 1.6	DX	Develop	0.8		1.6	Increased number of dead fetuses
Kakeyama et al. 2003									**2,3,7,8-TCDD**
62	Rat (Long-Evans) 7–9 F	GD 15 (G)	0, 0.2, 0.8	DX, NX	Develop	0.2	0.8		Altered adult male sexual behavior after perinatal exposure
Kakeyama et al. 2007									**2,3,7,8-TCDD**
63	Rat (Long-Evans) 5–6 F	GD 15 (GO)	0, 0.2, 0.8	DX	Develop		0.2		Anxiety-like behavior and impaired performance on test of memory

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Kakeyama et al. 2008									**2,3,7,8-TCDD**
64	Rat (Long-Evans) 16–18 F	GD 15 (GO)	0, 0.2, 0.8	RX, DX, HP, BW	Develop		0.2		Premature maturation of hypothalamic-pituitary axis, gonads and genitals
Kakeyama et al. 2014									**2,3,7,8-TCDD**
65	Rat (Long-Evans) 6 F	GD 15 (G)	0, 0.2, 0.8	DX	Develop		0.2		Anxiety-like behavior and impaired learning (not observed at 0.8 µg/kg); decreased body weight gain (10-15%) in adult offspring at 0.8 ug/kg/day
Kattainen et al. 2001									**2,3,7,8-TCDD**
66	Rat Line C 4–8 F	GD 15 (GO)	0, 0.03, 0.1, 0.3, 1	BW, DX	Develop		0.03		Decreased size of molars
Kelling et al. 1985									**2,3,7,8-TCDD**
67	Rat (Fischer-344) 20–24 M	Once (GO)	0, 100	BW, OW, WI, HP, LE	Death			100	95% died
Kelling et al. 1987									**2,3,7,8-TCDD**
68	Rat (Sprague-Dawley) 6–14 M	Once (GO)	0, 6.25, 25, 100	CS	Cardio		6.25		Increased basal tension of the left atria
Kransler et al. 2007									**2,3,7,8-TCDD**
69	Rat (Holtzman) 7–15 F	GD 10 (GO)	0, 1.5, 3, 6, 18	CS, DX, BW, OW, HE, BI	Bd wt	3	6	18	LOAEL: 13% reduced final maternal body weight SLOAEL: 30% reduced final maternal body weight
					Hemato	18			
					Hepatic	18			
					Develop			1.5	Intestinal hemorrhaging in fetuses

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Kransler et al. 2009									**2,3,7,8-TCDD**
70	Rat (Holtzman) 11–18 F	GD 10 (GO)	0, 1.5, 6	OW, BW, DX, BI, HP, OF	Develop			1.5	Decreased viability on GD 20 and PND 7; lung immaturity and hypoplasia
Lewis et al. 2001									**2,3,7,8-TCDD**
71	Rat (Holtzman) 9–12 F	GD 15 (GO)	0, 1	DX, HP, BI, BW	Develop		1		Impaired mammary gland differentiation in offspring
Li et al. 1995a									**2,3,7,8-TCDD**
72	Rat (Sprague-Dawley) 5–10 F	Once (GO)	0.3, 1, 3, 10, 30, 60	OF, HP	Repro	3	10		Increased LH and FSH levels, altered ovulation
Li et al. 1995b									**2,3,7,8-TCDD**
73	Rat (Sprague-Dawley) 5–10 F	Once (GO)	0, 10	OF, HP	Repro		10		Irregular estrous cycle and ovulation
Lu et al. 2010									**2,3,7,8-TCDD**
74	Rat (Sprague-Dawley) 5 M	Once (GO)	0, 10	BW, BC, UR, OW, HP	Bd wt		10		Decreased mean body weight (11%)
					Hepatic		10		Increased relative liver weights, intermediate hepatocellular swelling and vacuolization; increased serum cholesterol and decreased serum triglycerides
Lu et al. 2009									**2,3,7,8-TCDD**
75	Rat (Sprague Dawley) 5 M	12 days (GO)	0, 10	BW, BC, OW, HP	Bd wt			10	Lower terminal body weight (28%)
					Renal		10		Increased serum creatinine and BUN; proximal tubular epithelial damage

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Mably et al. 1992a									**2,3,7,8-TCDD**
76	Rat (Holtzman) 5 F	GD 15 (GO)	0, 0.064, 0.16, 0.40, 1.0	BW, BI, OF, DX	Develop	0.064	0.16	1	SLOAEL: Decreased live birth index LOAEL: Delayed testis descent and decreased anogenital distance
Mably et al. 1992b									**2,3,7,8-TCDD**
77	Rat (Holtzman) NS	GD 15 (GO)	0, 0.064, 0.16, 0.40, 1.0	BI, OF, DX	Develop		0.064		Decreased masculine sexual behavior in male offspring
Mably et al. 1992c									**2,3,7,8-TCDD**
78	Rat (Holtzman) NS F	GD 15 (GO)	0, 0.064, 0.16, 0.40, 1.0	BI, RX, DX	Develop		0.064		Reduced sperm production in offspring at all ages
Mai et al. 2020									**2,3,7,8-TCDD**
79	Rat (Wistar) 10 F	GD 15 (GO)	0, 0.5, 1, 2	DX	Develop			0.5	Pre- and post-implantation losses in unexposed females mated to exposed F1 males, decreased sperm motility and increased abnormal sperm, degenerative changes in testes, and histological alterations in seminiferous tubules
Markowski et al. 2002									**2,3,7,8-TCDD**
80	Rat (Holtzman) 7–13 F	GD 15 (GO)	0, 0.06, 0.18, 0.54	DX, NX	Develop	0.06	0.18		Impaired performance on operant behavior test
Miettinen et al. 2002									**2,3,7,8-TCDD**
81	Rat (Line C) 5–7 F	GD 11 (GO)	0, 1	DX, BW	Develop			1	Decreased viability of neonates and arrested molar development

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Miettinen et al. 2005									**2,3,7,8-TCDD**
82	Rat (Line C) 3–5 F	GD 15 (GO)	0, 0.03, 0.1, 0.3, 1	DX, BW	Develop	0.3	1		Morphological and mechanical alterations in pup's bone
Miettinen et al. 2006									**2,3,7,8-TCDD**
83	Rat (Line C) NS F	GD 15 (GO)	0, 0.03, 0.1, 0.3, 1	DX, BW, HP	Develop		0.03	1	LOAEL: Enhanced caries susceptibility in pups SLOAEL: Increased pup perinatal mortality
Mitsui et al. 2006									**2,3,7,8-TCDD**
84	Rat (Wistar) NR F	GD 15 (GO)	0, 1	DX	Develop		1		Decreased body weight (7–8%) and impaired performance on test of contextual fear conditioning (males only)
Nayyar et al. 2002									**2,3,7,8-TCDD**
85	Rat (Sprague-Dawley) NS F	GD 15 (GO)	0, 0.25, 0.5, 1	DX, BI	Develop	0.5		1	Reduced pup weight on PNDs 3, 5, and 10 (10.5–19%)
Nguyen et al. 2013a									**2,3,7,8-TCDD**
86	Rat (Wistar) 5 F	GD 15 (G)	0, 1.0	DX	Develop		1		Increased activity and decreased social activity
Nishijo et al. 2007									**2,3,7,8-TCDD**
87	Rat (Wistar) 8–9 F	GDs 9–19 (GO)	0, 0.1	CS, DX	Develop		0.1		Decreased fetal body weight on GD 19 (10%)
							0.1		Delayed avoidance learning; reduced motor activity

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Nishimura et al. 2003									**2,3,7,8-TCDD**
88	Rat (Holtzman) 6 F	GD 15 (GO)	0, 0.2, 0.8	IX, DX, BI, HP	Develop		0.2	0.8	LOAEL: Decreased serum T4 on PND 21 (male pups only) SLOAEL: Decreased litter size; decreased serum T4 on PND 21, increased T4 on PND 49 (male pups only), increased T3 on PND 21 (female pups only), increased TSH on PND 21 and 49; thyroid hyperplasia
Nishimura et al. 2005b									**2,3,7,8-TCDD**
89	Rat (Holtzman) 12 F	GD 15 (GO)	0, 1	DX, HP, BI	Develop		1		Decreased serum T4 and increased TSH; thyroid hyperplasia
Nishimura et al. 2006									**2,3,7,8-TCDD**
90	Rat (Holtzman) 6 F	GD 15 (GO)	0, 1	DX, BI	Develop			1	Hydronephrosis, decreased pup body weight (11.7–13.4%)
Ohsako et al. 2001									**2,3,7,8-TCDD**
91	Rat (Holtzman) 6 F	GD 15 (GO)	0, 0.0125, 0.05, 0.2, 0.8	OW, RX, BC, DX, BI, HP	Develop	0.0125	0.05		Reduced anogenital distance on PND 120
Ohsako et al. 2002									**2,3,7,8-TCDD**
92	Rat (Sprague-Dawley) 5 F	GD 15 (GO)	0, 1	DX, BI	Develop		1		Decreased relative epididymal and cauda epididymal organ weights; reduced anogenital distance, decreased cauda sperm reserve
Ohsako et al. 2002									**2,3,7,8-TCDD**
93	Rat (Sprague-Dawley) 5 F	GD 18 (GO)	0, 1	DX, BI	Develop		1		Reduced anogenital distance

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Petroff et al. 2000									**2,3,7,8-TCDD**
94	Rat (Sprague-Dawley) 6–10 F	Once (GO)	0, 10	BW, RX, HP, BC	Repro		10		Reduced ovarian weight and ova shed
Potter et al. 1986									**2,3,7,8-TCDD**
95	Rat (Sprague-Dawley) 12 M	Once (GO)	0, 6.25, 12.5, 25, 50, 100	BW, FI, OW, HP, OF	Endocr		6.25		Decreased serum T4 and increased serum TSH
Raasmaja et al. 1996									**2,3,7,8-TCDD**
96	Rat (Long-Evans) 12 M	Once (GO)	0, 10, 20, 40	BW, OF	Endocr		10		Decreased serum T4 and decreased deiodination in peripheral tissues
Roth et al. 1988									**2,3,7,8-TCDD**
97	Rat (Sprague-Dawley) NS M	Once (GO)	0, 0.032, 0.32, 3.2, 10.6, 32.0	BW, BI	Endocr	0.032	0.32		Decreased serum T4 and T3 levels
Salisbury and Marcinkiewicz 2002									**2,3,7,8-TCDD**
98	Rat (Sprague-Dawley) 4–5 F	GD 15 (GO)	0, 1, 2.5	DX, BI, HP, BW	Develop			1	Reduced pup weight (8-15% at various time points) and number of days in estrous
Sanabria et al. 2016									**2,3,7,8-TCDD**
99	Rat (Wistar) 7–10 F	GD 15 (GO)	0, 0.1, 0.5, 1.0	DX	Develop	0.5	1		Decreased serum testosterone in F1 males
Schwetz et al. 1973									**2,3,7,8-TCDD**
100	Rat (Sherman) 5–10 M, F	Once (GO)	8, 16, 32, 63	CS, LE	Death			45 F	LD_{50}
								22 M	LD_{50}

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Seefeld et al. 1984a									**2,3,7,8-TCDD**
101	Rat (Sprague-Dawley) 13–37 M	Once (GO)	0, 5, 15, 25, 50	BW, FI, CS	Death			25	25% mortality
					Bd wt	5	15	25	LOAEL: 15% decreased body weight 15 days post exposure SLOAEL: Body weight loss (terminal body weight 49% lower than controls)
					Neuro		15		Decreased motor activity
Seefeld et al. 1984b									**2,3,7,8-TCDD**
102	Rat (Sprague-Dawley) 20 M	Once (GO)	0, 15	BW, FI, CS	Bd wt			15	60% decreased weight gain
Seo et al. 1995									**2,3,7,8-TCDD**
103	Rat (Sprague-Dawley) 15 F	GDs 10–16 (GO)	0.025, 0.1	DX, BI	Develop	0.025	0.1		Decreased T4 levels
Seo et al. 1999									**2,3,7,8-TCDD**
104	Rat (Sprague-Dawley) 28 F	GDs 10–16 (GO)	0, 0.1	DX, NX	Develop		0.1		Impaired visual reversal learning
Simanainen et al. 2002									**2,3,7,8-TCDD**
105	Rat (Long-Evans) 9–11 F	Once (GO)	0, 0.03–100	BW, OW, OF	Musc/skel		22		ED_{50} for incisor tooth defects
					Immuno		2.3		Decreased relative thymus weight (ED_{50})
Simanainen et al. 2002									**2,3,7,8-TCDD**
106	Rat Hans/Wistar 9–11 F	Once (GO)	0, 0.03–100	BW, OW, OF	Musc/skel		57		ED_{50} for incisor tooth defects

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Simanainen et al. 2004b									**2,3,7,8-TCDD**
107	Rat (Line C) 5–8 F	GD 15 (GO)	0, 0.03, 0.1, 0.3, 1	RX, DX, BI, OW	Develop	0.3	1		Decreased daily sperm production and cauda epididymal sperm count; decreased anogenital distance
Sommer et al. 1996									**2,3,7,8-TCDD**
108	Rat (Holtzman) 26–30 F	GD 15 (GO)	0, 1.0	DX	Develop			1	Increased offspring mortality, decreased male pup body weight (3–14%), delayed puberty, decreased daily sperm production, decreased absolute and relative ventral prostate weight, and epididymal sperm numbers
Sparschu et al. 1971									**2,3,7,8-TCDD**
109	Rat (Sprague-Dawley) 10–31 F	10 days, GDs 6–15 (GO)	0, 0.03, 0.125, 0.5, 2.0, 8.0	DX	Bd wt	0.5		2	Dam body weight on GD 20 was 22% lower than controls
					Develop	0.03	0.125		Intestinal hemorrhage in fetuses
Takeda et al. 2020									**2,3,7,8-TCDD**
110	Rat (Wistar) 109–111 F	GD 15 (GO)	0, 1	DX	Repro		1		Altered nursing behavior, decreased serum prolactin, decreased milk ejection volume
					Develop			1	Total litter loss, decreased litter size, decreased pup body weight (8–22% at various time points), decreased short-term memory in adult offspring

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Taura et al. 2014									**2,3,7,8-TCDD**
111	Rat (Wistar) NR F	GD 15 (GO)	0, 1	DX	Develop		1		Demasculinization of male sexual behavior
Theobald et al. 1991									**2,3,7,8-TCDD**
112	Rat (Sprague-Dawley) 6–9 M	Once (GO)	0, 19, 25, 33, 44, 58, 76, 100	HP, BI	Gastro		19		Increased weight of antral mucosa
Tomasini et al. 2012									**2,3,7,8-TCDD**
113	Rat (Dark-Agouti) NR F	GD 18 (GO)	0, 0.7	DX	Develop			0.7	Decreased total litter size and decreased male offspring weight on PND 60 (20%)
Viluksela et al. 2004									**2,3,7,8-TCDD**
114	Rat (Sprague-Dawley) 5 M	Once (GO)	0, 60	LE, BW, OF	Endocr		60		Decreased serum T4
Viluksela et al. 2004									**2,3,7,8-TCDD**
115	Rat (Sprague-Dawley) 5 M	Once (GO)	0, 0.1, 1, 5, 15, 30, 60	LE, BW, OF	Endocr	1	5		Decreased serum T4, decreased peripheral and thyroid gland deiodinase activity
Weissberg and Zinkl 1973									**2,3,7,8-TCDD**
116	Rat (CD) 4 F	10–14 days (GO)	0, 10	BC	Hemato		10		Increase in packed cell volume, erythrocytes, neutrophils; decrease in mean corpuscular hemoglobin and platelet count
Yang et al. 1994									**2,3,7,8-TCDD**
117	Rat (Fischer-344) 3 B	14 days (GO)	0, 0.72	IX	Immuno		0.72 F		Suppression in virus-augmented NK cell activity

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Yonemoto et al. 2005									**2,3,7,8-TCDD**
118	Rat (Long-Evans) 22 F	GD 15 (G)	0, 0.0125, 0.05, 0.2, 0.8	DX	Develop		0.0125		Decreased male/female sex ratio; not observed at doses ≥0.2 µg/kg
Yu et al. 2019									**2,3,7,8-TCDD**
119	Rat (Sprague-Dawley) 10 F	GDs 8–14 (GO)	0, 0.1, 0.5	DX	Develop		0.1		Shortened vaginal opening time in F3 generation
Yu et al. 2020									**2,3,7,8-TCDD**
120	Rat (Sprague-Dawley) 6–8 F	GDs 8–14 (GO)	0, 0.1, 0.5	DX	Develop		0.1		Decreased number of primordial follicles and increased number of primary and secondary ovarian follicles and corpora lutea in F2 generation
Zhang et al. 2018a									**2,3,7,8-TCDD**
121	Rat (Sprague-Dawley) 14 F	GDs 8–14 (GO)	0, 0.1, 0.5	DX	Develop		0.1		Decreased number of primordial follicles and increased number of secondary ovarian follicles and corpora lutea in F1 generation
Zhang et al. 2018b									**2,3,7,8-TCDD**
122	Rat (Sprague-Dawley) 4 F	GDs 8–14 (GO)	0, 0.2, 0.8	DX	Develop		0.2		Delayed negative geotaxis and cliff avoidance reflexes
Ao et al. 2009									**2,3,7,8-TCDD**
123	Mouse (C57BL/6J) 5 F	Once (GO)	0, 1.0, 3.0, 10, 50	OW, IX	Immuno		1		Suppressed IL-5 production in response to OVA exposure
Aragon et al. 2008a									**2,3,7,8-TCDD**
124	Mouse (C57BL/6N) NS F	GD 14 (GO)	0, 6	DX, HP, BI	Develop		6		Cardiac hypertrophy and mild hydronephrosis in offspring

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Aragon et al. 2008b									**2,3,7,8-TCDD**
125	Mouse (C57BL/6N) 23–24 F	GD 14.5 (GO)	0, 6	DX, OF, HP	Develop		6		Increased susceptibility of offspring to renal fibrosis and hypertension in adulthood
Blaylock et al. 1992									**2,3,7,8-TCDD**
126	Mouse (C57BL/6) 5F	GDs 6–14 (GO)	0, 1.5, 3.0	DX, OF, OW	Develop		1.5		Thymic atrophy and delayed thymocyte maturation
Boverhof et al. 2005									**2,3,7,8-TCDD**
127	Mouse (C57BL/6) 5 F	Once (GO)	0, 0.001, 0.01, 0.1, 1, 10, 100, 300	BW, OW, HP	Hepatic	0.1	1		Mild to moderate cytoplasmic vacuolization
Boverhof et al. 2006									**2,3,7,8-TCDD**
128	Mouse (C57BL/6) 5 F	Once (GO)	0, 0.001, 0.01, 0.1, 1, 10, 100, 300	BW, OW, HP	Hepatic	0.01	0.1		Cytoplasmic vacuolization
Burleson et al. 1996									**2,3,7,8-TCDD**
129	Mouse (B6C3F1) 20 F	Once (GO)	0, 0.001, 0.005, 0.01, 0.05, 0.1	IX, OW	Immuno	0.005[c]	0.01		Decreased influenza virus host resistance
Chen et al. 2013									**2,3,7,8-TCDD**
130	Mouse (BALB/c) 4–5 F	Once (GO)	0, 20	BW, OW, IX	Immuno		20		Decreased interferon-gamma, IL-2, IL-4, IL-5, and IL-10 levels and OVA-specific IgG1 and IgM levels in response to OVA exposure
Couture-Haws et al. 1991									**2,3,7,8-TCDD**
131	Mouse (C57BL/6N) 11–14 F	PND 1 (GO)	0, 6, 9, 12	DX	Develop		6		Hydronephrosis

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Couture-Haws et al. 1991									**2,3,7,8-TCDD**
132	Mouse (C57BL/6N) 10–13 F	PND 4 (GO)	0, 6, 9, 12	DX	Develop		6		Hydronephrosis
de Gannes et al. 2021									**2,3,7,8-TCDD**
133	Mouse (C57BL/6J) NR F	GD 0.5, GD 7.5, PND 10 (GO)	0, 1	DX	Develop		1		Increased systolic blood pressure and arterial pressure (females only) in response to angiotensin pathological stress in adult offspring
Endo et al. 2012									**2,3,7,8-TCDD**
134	Mouse (C57BL/6) 8 F	GD 12.5 (G)	0, 0.6, 3.0	DX	Develop		0.6		Impaired attainment of rapid behavioral shifts, compulsive repetitive behavior (0.06 µg/kg only), and low competitive dominance in adult offspring (0.6 µg/kg only)
Fader et al. 2018									**2,3,7,8-TCDD**
135	Mouse (C57BL/6) 5 M	Once (GO)	0, 30	HP	Musc/skel		30		Increased trabecular bone mass (increased bone volume fraction, thickness, bone marrow density and decreased spacing); increased cortical outer perimeter, area, and mineral content
Fletcher et al. 2001									**2,3,7,8-TCDD**
136	Mouse (C57BL/6) 5 M	Once (GO)	0, 1.6, 8, 40, 200, 1,000	LE, BW, OW, OF	Bd wt	8	40	200	SLOAEL: Decreased mean body weight gain (37%) LOAEL: Decreased mean body weight gain (13%)

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic	8			
					Immuno	40			
					Other noncancer		1.6		Decreased vitamin A content
Frawley et al. 2014									**2,3,7,8-TCDD**
137	Mouse (B6C3F1/N) 14 F	Once (GO)	0, 0.1, 0.3, 0.5, 1, 3	BW, OW, HE, IX	Bd wt	3			
					Immuno		0.1		Decreased antibody plaque forming response to sRBCs
Greig 1984; Greig et al. 1987									**2,3,7,8-TCDD**
138	Mouse (A2G-hr/+) NS B	Once (GO)	0, 75	HP, CS, BI	Dermal		75		Skin thickening
Haijima et al. 2010									**2,3,7,8-TCDD**
139	Mouse (C57BL/6J) 9 F	GD 12.5 (GO)	0, 3	DX	Develop		3		Deficits in fear memory in adult male offspring
Holladay et al. 1991									**2,3,7,8-TCDD**
140	Mouse (B6C3F1) 5 F	GDs 6–14 (GO)	0, 1.5, 3.0	OW, IX, DX	Develop		1.5		Immunosuppression in pups, thymic atrophy, abnormal fetal thymocyte-maturation
Holsapple et al. 1986									**2,3,7,8-TCDD**
141	Mouse (B6C3F1) 9 F	14 days (GO)	0, 1	OW, GN, HP, HE, BI, BC, IX	Resp	1			
					Hemato	1			
					Hepatic		1		Hydropic degeneration, increased liver weight induced microsomal enzymes
					Renal	1			
					Immuno		1		Suppressed antibody response

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Holsapple et al. 1986									**2,3,7,8-TCDD**
142	Mouse (B6C3F1) 5 F	Once (GO)	0, 0.05, 0.1, 0.5, 1.0, 2.0	BI	Immuno	0.5	1		Suppressed antibody response
Inouye et al. 2005									**2,3,7,8-TCDD**
143	Mouse (C57BL/6N) 5–6 F	Once (GO)	0, 0.3, 1.0, 3.0	BW, OW, IX	Immuno		0.3		Reduced splenocyte production of IL-5 in response to OVA exposure
Ito et al. 2002									**2,3,7,8-TCDD**
144	Mouse (C57BL/6N) 5–6 F	Once (GO)	0, 0.2, 1, 5, 20	BW, OW, IX	Immuno	0.2	1		Decreased splenocytes and production of ovalbumin-specific IgG1 and IL-5 in response to OVA exposure
Jin et al. 2010									**2,3,7,8-TCDD**
145	Mouse (C57BL/6) 10 F	PNDs 1–4 (GO)	0, 1	DX	Develop			1	Decreased pup body weights (4, 19, or 10% on PNDs 7, 21, and 30), relative and absolute testis and epididymal weights, anogenital distance, epididymal sperm counts, and testicular testosterone levels
Keller et al. 2007									**2,3,7,8-TCDD**
146	Mouse (C57BL/6N) NS F	GD 13 (GO)	0, 0.01, 0.1, 1	DX, BW, OW	Develop	0.1	1		Altered molar and mandible shape
Keller et al. 2008									**2,3,7,8-TCDD**
147	Mouse (C3H/HeJ) NS F	GD 13 (GO)	0, 0.01, 0.1, 1	DX	Develop		0.01		Altered mandible shape

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Kelling et al. 1985									**2,3,7,8-TCDD**
148	Mouse (C57BL/6) 21–22 M	Once (GO)	0, 360	BW, FI, WI, HP, LE	Death			360	69% died
Kinoshita et al. 2006									**2,3,7,8-TCDD**
149	Mouse (C57BL/6J) 5 F	Once (GO)	0, 0.1, 1.0, 5.0, 20	IX, HP	Immuno		1		Impaired oral tolerance
Li et al. 2006									**2,3,7,8-TCDD**
150	Mouse (NIH) 10 F	GDs 1–3, 4–8, or 1–8 (GO)	0, 0.002, 0.05, 0.1	RX	Repro	0.002		0.05	Preimplantation loss
Luebke et al. 1999									**2,3,7,8-TCDD**
151	Mouse (B6C3F1) 7 F	Once (GO)	0, 0.1, 1, 10, 30	IX	Immuno		1		Impaired response to *Trichinella spiralis* infection
Luebke et al. 1999									**2,3,7,8-TCDD**
152	Mouse (B6C3F1) 7 F	Once (GO)	0, 0.1, 1, 10	IX	Immuno	0.1	1		Impaired response to *Trichinella spiralis* infection
Luster et al. 1980									**2,3,7,8-TCDD**
153	Mouse (B6C3F1) NS F	GD 14, LDs 1, 7, and 14, (GO)	0, 1.0, 5.0, 15.0	BW, OW, HE	Develop	1			
Matulka et al. 1997									**2,3,7,8-TCDD**
154	Mouse (B6C3F1) 5 F	14 days (GO)	0, 0.3, 1.0, 3.0	IX	Immuno	0.3	1		Impaired response to sRBCs

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Miettinen et al. 2004									**2,3,7,8-TCDD**
155	Mouse (EGFR+/-) NS F	GD 10 (GO)	0, 1.5, 4.4, 19.1, 29.6, 30.1, 42, 55.6, 106	DX, HP	Develop	1.5	4.4		Hydronephrosis
Moore et al. 1973									**2,3,7,8-TCDD**
156	Mouse (C57BL/6) 14–27 F	GDs 10–13 (GO)	0, 1, 3	DX	Develop		1	3	LOAEL: Hydronephrosis SLOAEL: Cleft palate
Moore et al. 1973									**2,3,7,8-TCDD**
157	Mouse (C57Bl/6) 5–14 F	GD 10 (GO)	0, 1	DX	Develop		1		Hydronephrosis
Moore et al. 1973									**2,3,7,8-TCDD**
158	Mouse (C57B1/6) 3–9 F	Once at parturition (GO)	0, 1, 3, 10	DX	Develop		1		Hydronephrosis
Neubert and Dillmann 1972									**2,3,7,8-TCDD**
159	Mouse (NMRI) 10–12 F	GDs 6–15 (GO)	0, 0.3, 3.0, 4.5, 9.0	DX	Develop	0.3		3	Cleft palate
Pohjanvirta et al. 2012									**2,3,7,8-TCDD**
160	Mouse (C57BL/6Kuo) 6–12 M, 5–15 F	Once (GO)	M: 0, 125, 250, 500; F: 0, 250, 500; F: 0, 250, 500, 1,000, 2,000, 2,500, 5,000	LE, CS, BW	Death			500 M	100% mortality; LD_{50} of 305 ug/kg

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Pohjanvirta et al. 2012									**2,3,7,8-TCDD**
161	Mouse (C57BL/6NTac) 3–4 M, 3–4 F	Once (GO)	0, 120, 240, 480	LE, CS, BW	Death			240 M	75% mortality
					Bd wt	480 F		120 M	Weight loss (1.5–95% whereas controls gained weight)
Pohjanvirta et al. 2012									**2,3,7,8-TCDD**
162	Mouse (C57BL/6JBOMTac) 4–6 M, 6 F	Once (GO)	M: 0, 70, 140, 280 F: 0, 300, 900	LE, CS, BW	Death			900 F	100% mortality
								280 M	100% mortality
Safe and Luebke 2016									**2,3,7,8-TCDD**
163	Mouse (C57BL/6) 4 F	GD 12 (GO)	0, 0.5	DX	Develop		0.5		Ototoxicity (shift in auditory brainstem response)
Sha et al. 2021									**2,3,7,8-TCDD**
164	Mouse (C57BL/6J) 15 F	GDs 0.5 and 12.5, PND 7.5 (G)	0, 0.1, 10	DX	Develop		0.1	10	LOAEL: Hyperactive-like behaviors
									SLOAEL: Pup mortality
Silkworth et al. 1989b									**2,3,7,8-TCDD**
165	Mouse (C57BL/6J) 12–15 F	GDs 6–15 (GO)	0, 0.5, 1, 2, 4	BW, IX, DX	Bd wt	4			
					Immuno	0.5	1		Decreased relative thymus weight
					Develop		0.5		Hydronephrosis
Silkworth et al. 1989b									**2,3,7,8-TCDD**
166	Mouse (DBA/6J) 14–15 F	GDs 6–15 (GO)	0, 0.5, 1, 4, 8	BW, IX, DX	Bd wt	8			
					Develop		0.5		Hydronephrosis

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Smialowicz et al. 1997									**2,3,7,8-TCDD**
167	Mouse (B6C3F1) 8 F	Once (GO)	0, 0.1, 1.0, 10.0	BW, OW, IX	Immuno	0.1	1		Impaired response to sRBC; decreased relative spleen and thymus weights
Smith et al. 1976									**2,3,7,8-TCDD**
168	Mouse (CF-1) 14–41 F	10 days, GDs 6–15 (GO)	0, 001, 0.01, 1.0, 3.0	BW, CS, DX	Bd wt	3			
					Develop	0.1		1	Cleft palate
Sobolewski et al. 2014									**2,3,7,8-TCDD**
169	Mouse (C57BL/6) 7–11 F	GD 7, GD 14, and PND 2 (GO)	0, 0.25	DX	Develop		0.25		Delayed habituation, reduction in exploration of novel objects, slight memory deficits, altered response rates
Thackaberry et al. 2005a									**2,3,7,8-TCDD**
170	Mouse (C57BL/6N) 4–21 F	GD 14.5 (GO)	0, 1.5, 3, 6, 12, 24	OW, DX, BW, BI	Develop	1.5	3		Reduced relative fetal heart weight
Vorderstrasse et al. 2003									**2,3,7,8-TCDD**
171	Mouse (C57BL/6) 7–12 F	Once (GO)	0, 1, 2.5, 5, 7.5, 10	IX	Immuno		1		Decreased IgG2a and increased IgA levels in response to influenza virus
Vorderstrasse et al. 2004									**2,3,7,8-TCDD**
172	Mouse (C57BL/6J) 6–8 F	GDs 0, 7, and 14 (GO)	0, 1	BC, HP	Repro		1		Suppression of mammary gland differentiation; decreased serum progesterone and estradiol levels on GD 17

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
White et al. 1986									**2,3,7,8-TCDD**
173	Mouse (B6C3F1) 6–8 F	14 days (GO)	0, 0.01, 0.05, 0.1, 0.5, 1.0, 2.0	BC, BI	Immuno		0.01		Suppressed serum total hemolytic complement activity
Yang et al. 2005									**2,3,7,8-TCDD**
174	Mouse C57BL/6 5 M	Once (GO)	0, 40	OF	Hepatic		40		Decreased hepatic all-trans retinol and all-trans retinoic acid
Yang et al. 2005									**2,3,7,8-TCDD**
175	Mouse C57BL/6 5 M	14 days (GO)	0, 0.1	OF	Hepatic		0.1		Decreased hepatic all-trans retinol and all-trans retinoic acid
Zinkl et al. 1973									**2,3,7,8-TCDD**
176	Mouse (CD-1) 3–4 F	Once (GO)	0, 1, 10, 50	HE	Hemato		1		Reversible decreases in leukocyte and lymphocyte counts
Fletcher et al. 2001									**2,3,7,8-TCDD**
177	Hamster (Golden Syrian) 5 M	Once (GO)	0, 1.6, 8, 40, 200, 1,000	LE, BW, OW, OF	Bd wt	8	40	200	LOAEL: Decreased mean body weight (15%) SLOAEL: Decreased mean body weight (20%)
					Hepatic		1.6		Decreased vitamin A content
Hanberg et al. 1989									**2,3,7,8-TCDD**
178	Hamster (Golden Syrian) NS	Once (GO)	0, 1.6–1,000	BW, OW, LE	Hepatic		14		ED_{50} for liver enlargement
					Immuno		48		ED_{50} for thymic atrophy
Kransler et al. 2007									**2,3,7,8-TCDD**
179	Hamster (Golden Syrian) 9–12 F	Once GD 9 (GO)	0, 1.5, 3, 6, 18	CS, BI, DX, BW, OW, HE	Bd wt	18			
					Hemato		1.5		2-Fold increase in leukocytes
					Develop		1.5		Decreased thymus weight, kidney congestion

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Olson and McGarrigle 1992									**2,3,7,8-TCDD**
180	Hamster (Golden Syrian) NS F	GD 7 or 9 (GO)	0, 1.5, 3.6, 18	DX, OW, GN, HE	Develop		1.5	18	LOAEL: Hydronephrosis SLOAEL: Fetal mortality (58%)
Olson et al. 1980a									**2,3,7,8-TCDD**
181	Hamster (Golden Syrian) 4–5 B	Once (GO)	0, 5, 25, 100, 250, 500, 750, 2,000, 3,000	BW, HP, CS, BI, LE	Immuno	250	500		Thymic atrophy
Yellon et al. 2000									**2,3,7,8-TCDD**
182	Hamster (Siberian) 16–34 B	Once (GO)	0, 0.1, 2, 100	LE, CS, RX, DX, IX, BI	Death			2	Increased mortality during 20-week observation period (30%)
					Repro	0.1	2		Increased time to pregnancy
Giavini et al. 1982									**2,3,7,8-TCDD**
183	Rabbit (New Zealand) 10–15 F	GDs 6–15 (GO)	0, 0.1, 0.25, 0.5, 1.0	BW, GN, HP, CS, DX, LE	Bd wt	0.1		0.25	44% decreased weight gain in dams
					Develop		0.1		Skeletal anomalies (extra ribs)
Fletcher et al. 2001									**2,3,7,8-TCDD**
184	Guinea pig (Hartley) 5 M	Once (GO)	0, 0.012, 0.047, 0.18, 0.66, 2.5	LE, BW, OW, OF	Death			2.5	Death of 3/5 animals
					Bd wt	0.18		0.66	Decreased mean body weight gain (22%)
					Hepatic	0.047	0.18		Decreased vitamin A content
					Immuno	2.5			
Hanberg et al. 1989									**2,3,7,8-TCDD**
185	Guinea pig (Hartley) NS	Once (GO)	0, 0.012–2.5	BW, OW, LE	Immuno		0.8		ED_{50} for thymic atrophy

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Hochstein et al. 1988									**2,3,7,8-TCDD**
186	Mink 4 M	Once (GO)	0, 2.5, 5, 7.5	BW, OW, GN, BC, CS	Bd wt		2.5	5	LOAEL: 11% weight loss SLOAEL: 27% weight loss
					Gastro	2.5		5	Gastrointestinal ulcerations
					Hemato	7.5			
					Hepatic	2.5			
					Renal	2.5			
					Neuro	2.5			
Olson and McGarrigle 1992									**2,3,7,8-TCDD**
187	Guinea pig (Hartley) 5 F	GD 14 (GO)	0, 0.15, 1.5	DX	Develop	0.15		1.5	Fetal mortality, increased resorption, decreased spleen and thymus weight
Turner and Collins 1983									**2,3,7,8-TCDD**
188	Guinea pig (Hartley) 1 M, 4–6 F	Once (G)	0, 0.1, 0.5, 2.5, 12.5, 20.0	GN, HP, CS, LE	Hepatic		0.1		Focal necrosis
INTERMEDIATE EXPOSURE									
Allen et al. 1977									**2,3,7,8-TCDD**
189	Monkey (Rhesus) 8 F	9 months (F)	0.011	BW, GN, HP, BC, LE	Death			0.011	5/8 died
					Bd wt		0.011		12% weight loss
					Resp			0.011	Lung hemorrhage
					Cardio			0.011	Hemorrhage in epicardium, myocardium, and endocardium
					Gastro			0.011	Hypertrophy, hyperplasia, and metaplasia of gastric epithelium
					Hemato			0.011	Pancytopenia, bone marrow atrophy; lack of lymphoid germinal centers in spleen

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Musc/skel			0.011	Hemorrhage in muscles from the extremities
					Hepatic			0.011	Epithelial biliary hyperplasia; focal hemorrhages
					Renal		0.011		Tubular epithelial hyperplasia; petechial hemorrhages in urinary bladder
					Dermal		0.011		Facial alopecia, squamous metaplasia, hyperkeratoses; subcutaneous edema; petechial hemorrhaging
					Ocular		0.011		Periorbital edema
					Immuno		0.011		Lymph nodes atrophy
					Neuro			0.011	Hemorrhages in meninges
McNulty 1984									**2,3,7,8-TCDD**
190	Monkey (Rhesus) 2–4 F	3 weeks, 3 days/week (GO)	0, 0.02, 0.1, 0.6	BW, CS, DX, LE	Death			0.6	2/2 died
					Bd wt	0.02		0.1	Weight loss in mothers
					Resp	0.02	0.1		Epistaxis
					Gastro	0.02	0.1		Metaplasia of gastric mucosa
					Hemato	0.02		0.1	Anemia, bone marrow hypoplasia
					Hepatic		0.1		Biliary hyperplasia
					Dermal	0.02	0.1		Hair loss, periorbital edema, hyperkeratosis, squamous metaplasia of sebaceous glands
					Ocular	0.02	0.1		Thickening and reddening of eyelids

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Ahmed 2011									**2,3,7,8-TCDD**
191	Rat (Wistar) 6 F	GD 1–LD 30 (GO)	0, 0.2, 0.4	CS, DX	Develop		0.2		Decreased offspring T4, T3, and growth hormone levels and increased TSH levels; decreased cerebellar neurotransmitter levels on PNDs 10–30
Bell et al. 2007b									**2,3,7,8-TCDD**
192	Rat (Wistar) 65–75 F	12 weeks premating and during gestation and lactation periods (F)	0, 0.0024, 0.008, 0.046	CS, NX, BW, RX, OW, DX, HP	Repro Develop	0.046	 0.0024		 Delayed preputial separation
Chen et al. 2009									**2,3,7,8-TCDD**
193	Rat (Sprague-Dawley) 8 F	29 weeks 1 time/week (GO)	0, 0.02, 0.05, 0. 125	BW, OW, BI	Bd wt Musc/skel	0.05 0.125	0.125		12.2% reduced final body weight
Dhanabalan et al. 2010									**2,3,7,8-TCDD**
194	Rat (Wistar/NIN) 6 M	15 days (GO)	0, 0.1	BW, OW, BC, RX	Repro		0.1		Decreased epididymal sperm count, mobility, and viability and decreased serum testosterone levels
Dhanabalan et al. 2011									**2,3,7,8-TCDD**
195	Rat (Wistar/NIN) 6 M	15 days (GO)	0, 0.1	BW, OW, BC, RX	Repro		0.1		Decreased testicular daily sperm production and epididymal sperm motility, viability, and count; decreased serum testosterone levels

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
El-Tawil and Elsaieed 2005									**2,3,7,8-TCDD**
196	Rat (Sprague-Dawley) 10 M	60 days (GO)	0, 0.05, 0.1, 0.2	CS, BW, OW, RX, HP	Repro		0.05		Decreased epididymal sperm count and motility; increased sperm mortality and abnormalities; decreased reproductive organ weights
Erdemli et al. 2020									**2,3,7,8-TCDD**
197	Rat (Wistar) 10 M	1 month (GO)	0, 1	BC, HP	Renal		1		Glomerular and proximal and distal tubular epithelial damage
Gül et al. 2018									**2,3,7,8-TCDD**
198	Rat (Wistar) 10–15 F	16 weeks, 1 time/week (GO)	0, 0.14	BW, HP	Bd wt			0.14	56% decrease in total weight gain
					Repro		0.14		Decreased number of ovarian follicles at the post-primordial phase and corpus luteum
Harrill et al. 2015									**2,3,7,8-TCDD**
199	Rat (Sprague-Dawley) 10 F	4 weeks 4–5 days/week (GO)	0, 0.003, 0.022, 0.1, 0.3, 1	BW, HE, BC, OW, HP	Resp	1			
					Cardio	1			
					Hemato	0.022	0.1		Increased RBC and decreased MCV
					Hepatic	0.003	0.022		Increased relative liver weight and hepatocytic hypertrophy
					Renal	1			
					Immuno	0.1	0.3		Decreased relative thymus weight and thymic atrophy
					Repro	0.3			

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Harrill et al. 2016									**2,3,7,8-TCDD**
200	Rat (Sprague-Dawley) 10 F	4–5 days/week, 4 weeks (GO)	0, 0.003, 0.022, 0.1, 0.3, 1	BW, BC, HE, OW, HP	Hepatic	0.003	0.022		Hepatic hypertrophy, increased relative liver weight, increased serum cholesterol levels
					Immuno	0.022	0.1		Decreased relative thymus weight
Ikeda et al. 2005b									**2,3,7,8-TCDD**
201	Rat (Holtzman) 12 F	9 weeks, 1 day/week (GO)	0, 0.02	DX, RX, BW, OW	Develop		0.02		Reduced male/female ratio in F2 offspring on PND 2; decreased pup body weight and ventral prostate weight
İlhan et al. 2015									**2,3,7,8-TCDD**
202	Rat (Sprague-Dawley) 6 M	4 weeks (GO)	0, 0.5	OF	Cardio		0.5		Increased systolic blood pressure
Jablonska et al. 2010									**2,3,7,8-TCDD**
203	Rat Lewis-Furth 24 F	GDs 14 and 21 PNDs 7 and 14 PNDs 21–240 (GO)	0, 0.007	DX, BI	Develop		0.007		Accelerated onset of acyclicity in female rats
Latchoumycandane et al. 2002									**2,3,7,8-TCDD**
204	Rat (Wistar) 24 M	45 days (GO)	0, 0.001, 0.01, 0.1	BI, HP	Repro		0.001		Reduced epididymal sperm count
Li and Rozman 1995									**2,3,7,8-TCDD**
205	Rat (Sprague-Dawley) 6–7 M	10 weeks, 1 day/week (GO)	0, 0.003, 0.03, 0.16, 0.5, 1, 1.6	BI, BW, OW, LE	Death			1.6	57% mortality; mean time to death was 54 days
					Bd wt	0.03		0.16	38% decrease in body weight gain

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Endocr	0.003	0.03		Almost 50% reduction in total serum T4
Ma et al. 2010									**2,3,7,8-TCDD**
206	Rat (Sprague-Dawley) 32 M	29 weeks 1 time/week (GO)	0, 0.02, 0.05, 0.125	CS, BI, RX, BW, BC	Bd wt	0.05	0.125		14% reduced final body weight
					Repro	0.02	0.05		Reduced sperm counts; reduced serum testosterone
Murray et al. 1979									**2,3,7,8-TCDD**
207	Rat (Sprague-Dawley) 10–16 M, 20–32 F	3 generations (F)	0, 0.001, 0.01, 0.1	OW, GN, HP, DX	Repro	0.01		0.1	Decreased fertility in F0
					Develop			0.001	Decreased postnatal survival in F1 pups
NTP 1982b									**2,3,7,8-TCDD**
208	Rat (Osborne-Mendel) 10 M, 10 F	13 weeks, 2 days/week (GO)	0, 0.07, 0.14, 0.28, 0.56, 1.12	BW, HP, CS, LE	Bd wt	0.28 M	1.12 F	0.56 M	LOAEL: 16% lower body weight than controls at week 6 SLOAEL: 20% lower body weights than controls at week 6
					Resp	0.56 F			
NTP 2006									**2,3,7,8-TCDD**
209	Rat (Sprague-Dawley) 81–82 F	5 days/week 14 weeks (GO)	0, 0.002, 0.0071, 0.016, 0.032, 0.071	LE, CS, BW, BI, OW, GN, HP	Bd wt	0.071			
					Resp	0.071			
					Gastro	0.071			
					Hepatic	0.002	0.0071		30% increase in absolute liver weight
					Endocr	0.0071	0.016		Decreased FT4 and TT4; thyroid follicular cells hypertrophy
					Immuno	0.0071	0.016		Thymic atrophy
					Repro	0.071			

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 2006									**2,3,7,8-TCDD**
210	Rat (Sprague-Dawley) 81–82 F	5 days/week 31 weeks (GO)	0, 0.002, 0.0071, 0.016, 0.032, 0.071	LE, CS, BW, BI, OW, GN, HP	Bd wt	0.071			
					Resp	0.071			
					Gastro		0.071		Squamous hyperplasia of forestomach
					Hepatic	0.002	0.0071		Hepatocyte pigmentation; increased relative and absolute liver weight
					Endocr	0.0071	0.016		Decreased serum FT4 and TT4
					Immuno	0.016	0.032		Thymic atrophy
					Repro	0.071			
					Other noncancer	0.032	0.071		Vacuolization of acinar cell in pancreas
Sarihan et al. 2015									**2,3,7,8-TCDD**
211	Rat (Sprague-Dawley) 7 M	45 days (GO)	0, 0.3	BW, OW, HP, OF	Cardio			0.3	Decreased blood pressure, heart rate, oxygen saturation, arrythmias, long QT intervals, mild and moderate cardiac lesions
Sewall et al. 1995									**2,3,7,8-TCDD**
212	Rat (Sprague-Dawley) 6–9 F	30 weeks, 1 time/ 2 weeks (GO)	0, 0.0001, 0.00035, 0.001, 0.0035, 0.011, 0.036, 0.125	BI	Endocr	0.011	0.036		Reduction in serum T4

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Van Birgelen et al. 1995									**2,3,7,8-TCDD**
213	Rat (Sprague-Dawley) 8 F	13 weeks (F)	0, 0.014, 0.026, 0.047, 0.320, 1.02	BI, BW, OW, FI, BI, BC	Bd wt	0.026	0.047	1.02	LOAEL: 10% reduction in body weight gain SLOAEL: 72% reduction in body weight gain
					Hepatic		0.014		Reduction in hepatic retinol
					Renal		0.047		Increased relative kidney weight
					Endocr	0.026	0.047		Reduction in total serum T4
					Immuno		0.014		Decreased absolute and relative thymus weight
Viluksela et al. 1994									**2,3,7,8-TCDD**
214	Rat (Sprague-Dawley) 20 M	13 weeks, 10 doses (GO)	0, 0.8	BW, HE, LE, OW	Bd wt			0.8	30% decrease in body weight gain
					Hemato		0.8		Decrease in platelet count
					Hepatic		0.8		Increased relative liver weight and liver EROD activity; decreased liver PEPCK activity
					Immuno		0.8		Decreased absolute and relative thymus weight
Vos et al. 1973									**2,3,7,8-TCDD**
215	Rat (CD) 10 F	6 weeks, 1 day/week (GO)	0, 0.028, 0.14, 0.71	BW, HP, BC	Hemato	0.71			
					Immuno	0.14	0.71		Decreased absolute and relative thymus weight and slight cortical atrophy
Zinkl et al. 1973									**2,3,7,8-TCDD**
216	Rat (CD) 3–4 F	30 days (GO)	0, 0.1, 1.0, 10	BC, HE	Hemato		0.1		Thrombocytopenia
					Hepatic	0.1	1		Increased serum cholesterol

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
DeVito et al. 1994									**2,3,7,8-TCDD**
217	Mouse (B6C3F1) 5 F	13 weeks, 5 days/week (F)	0, 0.0011, 0.0032, 0.011, 0.032, 0.11	BI, BW, OW	Immuno	0.11			
Fader et al. 2015									**2,3,7,8-TCDD**
218	Mouse C57BL/6 8 F	28 days, once every 4 days (seven doses) (GO)	0, 0.0003, 0.003, 0.008, 0.03, 0.08, 0.3, 0.8, 10, 3, 8	BW, BC, OW, HP	Bd wt	8			
					Gastro	8			
					Hepatic	0.3	0.8		Increased relative liver weight, minimal centriacinar microvesicular vacuolization (indicative of hepatic steatosis), increased macrophage infiltration
Fader et al. 2015									**2,3,7,8-TCDD**
219	Mouse C57BL/6 8–16 M/F	28 days, once every 4 days (seven total exposures) (GO)	0, 8	IX	Immuno		8		Altered immune cell population in intestinal lamina propria
Fader et al. 2017a, 2017b									**2,3,7,8-TCDD**
220	Mouse C57BL/6 8 M	28 days, once every 4 days (seven doses) (GO)	0, 0.0003, 0.003, 0.008, 0.03, 0.08, 0.3, 0.8, 10, 3, 8	BW, BC, OW, HP	Bd wt	3		8	Decreased terminal body weight (27%)
					Gastro	3	8		Increased gastroduodenal and colonic para-cellular permeability, decreased gut motility
					Hepatic	0.03	0.08		Increased relative liver weight

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Fader et al. 2018									**2,3,7,8-TCDD**
221	Mouse (C57BL/6) 8 M, 8 F	28 days, once every 4 days (7 doses) (GO)	0, 8	BC, HP	Musc/skel		8		Increased trabecular bone mass (bone mineral density and content, thickness, and bone volume fraction), decreased trabecular spacing and number, and decreased bone marrow adiposity in both sexes; decreased osteoclasts in females and increased osteoblasts in males
Fader et al. 2018									**2,3,7,8-TCDD**
222	Mouse (C57BL/6) 8 M	28 days, once every 4 days (7 doses) (GO)	0, 0.003, 0.008, 0.03, 0.08, 0.3, 0.8, 3, 8	HP	Musc/skel	0.08	0.3		Decreased trabecular spacing
Herlin et al. 2013									**2,3,7,8-TCDD**
223	Mouse (C57BL/6J) 6 M, 6 F	10 weeks 1 time/week (GO)	0, 2.9; one time loading dose of 40 µg/kg followed by nine doses of 18 µg/kg (total dose over study of 200 µg/kg)	BW, BC, OW, HP	Bd wt Musc/skel	2.9	 2.9		Increased trabecular bone mass (increased bone volume fraction, bone mineral deposits, decreased spacing) and decreased cortical bone thickness in both sexes; imbalance of serum bone remodeling markers and mechanically weaker bones in females

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Hogaboam et al. 2008									**2,3,7,8-TCDD**
224	Mouse (C57BL/6) NS F	GDs 0, 7, and 14 LD 2 (GO)	0, 0.17	DX, IX, BI	Develop		0.17		Altered immune function (decreased virus specific CD8+ T cells and increased neutrophils and interferon-gamma levels in BALF) in response to influenza infection in adult offspring
Ishihara et al. 2007									**2,3,7,8-TCDD**
225	Mouse (ICR) 40 M	5 weeks (GO)	0, 0.0001, 0.1	DX	Repro	0.0001	0.1		Decreased male/female ratio in PND 0 pups
Ishihara et al. 2010									**2,3,7,8-TCDD**
226	Mouse (ICR) 49–59 M	5 weeks 1 time/week (GO)	0, 0.1	DX	Repro		0.1		Decreased F1 male/female ratio in embryos
Kopf et al. 2010									**2,3,7,8-TCDD**
227	Mouse C57BL/6 12–14 M	5 weeks, 5 days/week (F)	0, 0.13	BW, OW, OF	Bd wt	0.13			
					Cardio		0.13		Increased mean arterial pressure
					Hepatic		0.13		Increased absolute liver weight
Maranghi et al. 2013									**2,3,7,8-TCDD**
228	Mouse (BALB/c) 10–15 F	28 days (F)	0, 0.09	CS, BW, FI, BC, OW, GN, HP	Bd wt	0.09			
					Hepatic		0.09		Increased necrotic hepatocytes (incidences of pyknotic nuclei in hepatocytes) and tissue congestion
					Endocr		0.09		Thyroid follicular cell hypertrophy (increased follicular epithelium area to number of nuclei ratio)

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Immuno		0.09		Increased incidences of lymphocyte apoptosis in the thymus, follicular hyperplasia with germinal center development in the spleen
					Repro		0.09		Increased serum testosterone levels and testosterone/estradiol ratio
Ono et al. 2010									**2,3,7,8-TCDD**
229	Mouse (Hos:HR-1) 10 NR	54 days (GO)	0, 0.0003, 0.001	CS	Dermal	0.001			
Rasinger et al. 2018									**2,3,7,8-TCDD**
230	Mouse (BALB/c) 10 F	28 days (F)	0, 0.0009	CS, BW, FI, BC, OW, GN, HP	Bd wt	0.0009			
					Hepatic		0.0009		Lymphocytic inflammation in liver
					Immuno	0.0009			
Smialowicz et al. 2008									**2,3,7,8-TCDD**
231	Mouse (B6C3F1) 8–15 F	13 weeks, 5 days/week (GO)	0, 0.0011, 0.011, 0.11, 0.32	BW, OW, IX	Bd wt	0.0011	0.011		
					Immuno		0.0011		Decreased antibody response to sRBC
Sugita-Konishi et al. 2003									**2,3,7,8-TCDD**
232	Mouse (C57BL/6NCji) 8 F	LDs 0–17 (W)	0, 0.001, 0.011	DX, IX, BC, BI	Develop	0.001	0.011		Impaired clearance of bacteria from pups' spleen
Thigpen et al. 1975									**2,3,7,8-TCDD**
233	Mouse (C57BL/6Jfh) 60 M	4 weeks, 1 day/week (GO)	0, 0.07, 0.14, 0.71	BW, CS	Immuno	0.07	0.14		Impaired response to bacterial infection

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Thomas and Hinsdill 1979									**2,3,7,8-TCDD**
234	Mouse (Swiss-Webster) 10 F	4 weeks prior to mating and during gestation and lactation (F)	0, 0.13, 0.325, 0.65, 1.3, 2.6	DX, LE	Dermal	0.65	1.3		Alopecia, edema in dams
					Develop			1.3	Decreased pup survival
							0.325		Thymus atrophy; impaired response to sRBC
Umbreit et al. 1987									**2,3,7,8-TCDD**
235	Mouse (C57B/6) 10 F	25 weeks, 3 days/week (GO)	0, 1.3	CS, LE	Death			1.3	70% died
Vecchi et al. 1983									**2,3,7,8-TCDD**
236	Mouse (C57BL/6, DBA/2) NS M	5-8 weeks, 1 day/week (GO)	0, 0.07, 0.3	IX	Immuno		0.07		Decreased response to sRBC
Vorderstrasse et al. 2006									**2,3,7,8-TCDD**
237	Mouse (C57BL/6J) NS F	GDs 0, 7, and 14; LD 2 (GO)	0, 0.04, 0.1, 0.5	DX, IX, BI	Develop			0.5	Reduced pup survival
						0.04	0.1		Suppressed CD8+ T cell response to infection in offspring
Vos et al. 1973									**2,3,7,8-TCDD**
238	Mouse (B6D2F1) 5–7 M	4 weeks, 1 day/week (GO)	0, 0.028, 0.14, 0.71, 3.6	BW, GN, HP	Bd wt	0.71	3.6		17% reduced weight gain
					Immuno	0.14	0.71		Suppressed response in graft versus host test
Yang et al. 2005									**2,3,7,8-TCDD**
239	Mouse C57BL/6 5 M	28 or 42 days (GO)	0, 0.1	OF	Hepatic		0.1		Decreased hepatic all-trans retinol and all-trans retinoic acid

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Yin et al. 2012									**2,3,7,8-TCDD**
240	Mouse (NS) 8 M	7 weeks (GO)	0, 0.1	BC, HP	Repro		0.1		Decreased testicular FSH and LH levels and serum testosterone levels; decreased testicular spermatozoa levels; necrosis of spermatocytes and spermatogonia
DeCaprio et al. 1986									**2,3,7,8-TCDD**
241	Guinea pig (Hartley) 10 M, 10 F	90 days (F)	0, 0.0001, 0.0007, 0.005, 0.03	BW, OW, HP, BI, LE	Bd wt	0.0007	0.005		12–15% reduced weight gain
					Hemato	0.005			
					Hepatic	0.0007	0.005		Hepatocellular inclusions, hypertriglyceridemia
					Immuno	0.0007 M	0.005 M		Decreased absolute and relative thymus weight
Hochstein et al. 2001									**2,3,7,8-TCDD**
242	Mink Standard dark 12 F	132 days *ad libitum* (F)	0.00003, 0.0008, 0.003, 0.007, 0.07	BC, DX, HP, BI, HE, BW, OW, CS	Develop			0.003	Reduced kit survival in first 3 weeks
Vos et al. 1973									**2,3,7,8-TCDD**
243	Guinea pig (Hartley) 10 F	8 weeks, 1 day/week (GO)	0, 0.001, 0.006, 0.03, 0.14	BW, GN, LE	Hemato		0.001		Decreased lymphocytes
					Immuno		0.006		Impaired delayed hypersensitivity response to tuberculin and decreased thymus weight

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
CHRONIC EXPOSURE									
Bowman et al. 1989a, 1989b; Hong et al. 1989; Schantz and Bowman 1989; Schantz et al. 1986, 1992									**2,3,7,8-TCDD**
244	Monkey (Rhesus) 8 F	Up to 3.5–4 years (F)	0, 0.00012, 0.00064	CS, BW, RX, DX, IX	Repro	0.00012		0.00064	Decreased reproductive success
					Develop		0.00012[d]		Increased close, social contact between mothers and infants, impaired learning, and altered peer group social behavior and self-directed behaviors
Rier et al. 2001a									**2,3,7,8-TCDD**
245	Monkey (Rhesus) 8 F	3.5–4 years (F)	0, 0.00012, 0.00064	IX	Immuno		0.00012[d]		Impaired response to T-mitogen
Kociba et al. 1978									**2,3,7,8-TCDD**
246	Rat (Sprague-Dawley) 50 M, 50 F	2 years (F)	0, 0.001, 0.01, 0.1	BW, OW, FI, GN, HP, CS, BI	Death			0.1 F	Increased cumulative mortality
					Resp	0.001 F	0.01 F		Focal alveolar hyperplasia
					Cardio	0.01		0.1	Myocardial degeneration in females and periarteritis
					Gastro	0.1			
					Hemato	0.01	0.1		Decreased erythrocytes
					Musc/skel	0.1			
					Hepatic	0.001	0.01		Atrophy of hepatic cords, cytoplasmic vacuolization, fatty metamorphosis, hepatic necrosis and inflammation, bile duct hyperplasia, fibrosis, and periportal inflammation
					Renal	0.1			

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Endocr	0.01	0.1		Adrenal gland hyperplastic nodules, hematocysts, and cortical necrosis and hemorrhage; thyroid gland follicular cysts (males only), and pancreatic fibrosis (females only)
					Neuro	0.01 F		0.1 F	Hemorrhage in brain
					Repro	0.1			
					Cancer			0.1	CEL: hepatocellular carcinoma (females), squamous cell carcinoma in lung (females) squamous cell carcinoma of hard palate or nasal turbinates (males and females)
Murray et al. 1979									**2,3,7,8-TCDD**
247	Rat (Sprague-Dawley) 20 M, 20 F	12 months prior to mating (F)	0, 0.1	RX	Repro			0.1 F	Increased resorption in females mated with unexposed males
NTP 1982b									**2,3,7,8-TCDD**
248	Rat (Osborne-Mendel) 50–75 M, 50–75 F	104 weeks, 2 days/week (GO)	0, 0.0014, 0.0071, 0.071	BW, HP, GN, CS, LE	Bd wt	0.0071	0.071		12–19%% lower body weight than controls
					Resp	0.071			
					Cardio	0.071			
					Gastro	0.071			
					Hemato	0.071			
					Musc/skel	0.071			

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic	0.0071	0.071		Toxic hepatitis (lipidosis, hydropic hepatocellular degeneration, proliferation of periportal bile ductules, mild fibrosis)
					Renal	0.071			
					Dermal	0.071			
					Ocular	0.071			
					Endocr	0.071			
					Immuno	0.071			
					Neuro	0.071			
					Repro	0.071			
					Cancer			0.071 F	CEL: increased incidence of neoplastic nodules in liver or hepatocellular carcinoma
								0.0071 M	CEL: increased incidence of thyroid follicular cell adenoma or carcinoma
NTP 2006									**2,3,7,8-TCDD**
249	Rat (Sprague-Dawley) 81–82 F	5 days/week 105 weeks (GO)	0, 0.002, 0.0071, 0.016, 0.032, 0.071	LE, CS, BW, BI, OW, GN, HP	Bd wt	0.032	0.071		16% reduced final body weight
					Resp		0.002		Bronchiolar metaplasia of alveolar epithelium
					Cardio	0.002	0.0071		Cardiomyopathy
					Gastro	0.032	0.071		Squamous hyperplasia of forestomach and squamous hyperplasia of gingival mucosa
					Hepatic		0.002		Hepatocyte hypertrophy and inflammation

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Renal	0.016	0.032		Hyperplasia of transitional renal epithelium
					Dermal	0.071			
					Ocular	0.071			
					Endocr	0.0071	0.016		Hyperplasia of adrenal gland cortex; thyroid follicular cell hypertrophy, increased T4 levels
					Immuno	0.002	0.0071		Thymic atrophy
					Neuro	0.071			
					Repro	0.0071	0.016		Dilation of clitoral gland ducts
					Cancer			0.071	CEL: liver, lung, and oral mucosa malignant tumors
Della Porta et al. 1987									**2,3,7,8-TCDD**
250	Mouse (B6C3) 43–50 M, 42–49 F	52 weeks, 1 day/week (GO)	0, 0.36, 0.72	BW, HP, GN, LE	Death			0.36	Increased mortality
					Bd wt			0.36	33% decreased weight gain
					Dermal		0.36		Dermatitis
					Cancer			0.36	CEL: hepatocellular adenoma or carcinoma
NTP 1982b									**2,3,7,8-TCDD**
251	Mouse (B6C3F1) 50–75 M, 50–75 F	104 weeks, 2 day/week (GO)	M: 0, 0.0014, 0.0071, 0.071; F: 0, 0.006, 0.03, 0.3	BW, GN, HP, CS, LE	Bd wt	0.3			
					Resp	0.3			
					Cardio	0.3			
					Gastro	0.3			
					Hemato	0.3			
					Musc/skel	0.3			

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic	0.0071	0.071		Toxic hepatitis (lipidosis, bile duct hyperplasia, pericellular fibrosis)
					Renal	0.0071	0.071		Lymphocytic inflammatory infiltration in kidneys
					Dermal	0.3			
					Ocular	0.3			
					Endocr	0.3			
					Immuno	0.3			
					Neuro	0.3			
					Repro	0.3			
					Cancer			0.3 F	CEL: Thyroid follicular cell adenoma and histiocytic lymphomas
								0.071 M	CEL: Hepatocellular adenoma or carcinoma
Oughton et al. 1995									**2,3,7,8-TCDD**
252	Mouse (C57BL/6N) 10–14 F	14–15 months, 1 day/week (GO)	0, 0.03	BW, HE, OW, BI, BC	Bd wt	0.03			
					Hemato	0.03			
					Immuno		0.03		Decreased percentage of splenic memory T cells, increased percentage of splenic naïve T helper cells

Table 2-2. Levels of Significant Exposure to 2,3,7,8-Tetrachloroibenzo-*p*-Dioxin – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Toth et al. 1979									**2,3,7,8-TCDD**
253	Mouse (Swiss) 45 M	1 year, 1 day/week (GO)	0, 0.001, 0.1, 1.0	BW, GN, HP, CS, LE	Death			1	Decreased survival (34% decreased life span)
					Dermal		0.001		Skin lesions and generalized amyloidosis
					Cancer			0.1	CEL: hepatocellular carcinoma

[a]Doses adjusted for intermittent exposure.
[b]The number corresponds to entries in Figure 2-4; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-4. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[c]Used to derive a provisional acute-duration oral minimal risk level (MRL) of 0.0002 µg/kg/day ($2x10^{-4}$ µg/kg/day) for 2,3,7,8-TCDD based on a NOAEL of 0.005 µg/kg/day and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability) and a modifying factor of 0.7 (to adjust for the higher bioavailability of 2,3,7,8-TCDD from an oil gavage vehicle than from food).
[d]Used to derive a provisional chronic-duration oral minimal risk level (MRL) of $4x10^{-7}$ µg/kg/day for 2,3,7,8-TCDD based on a LOAEL of 0.00012 µg/kg/day for neurodevelopmental and immunological effects in the mothers (Bowman et al. 1989a, 1989b; Hong et al. 1989; Rier et al. 2001a; Schantz et al. 1986, 1992; Schantz and Bowman 1989) and divided by a total uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

ACTH = adrenocorticotropin hormone; B = both males and females; BALF = bronchioalveolar fluid; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DTH = delayed-type hypersensitivity; DX = developmental toxicity; ED_{30} = effective dose that produces a 30% response; ED_{50} = median effective dose; Endocr = endocrine; EROD = 7-ethoxy-resorufin-O-deethylase; (F) = feed; F = female(s); FFA = free fatty acid; FI = food intake; FSH = follicle-stimulating hormone; FT4 = free thyroxine; (G) = gavage; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil; HE = hematology; Hemato = hematological; HP = histopathology; Ig = immonuglobulin; IL = interleukin; Immuno = immunological; IX = immune function; LD = lactation day; LD_{50} = median lethal dose; LE = lethality; LH = luteinizing hormone; LOAEL = lowest-observed-adverse-effect level; M = male(s); MCV = mean corpuscular volume; Musc/skel = musculoskeletal; Neuro = neurological; NK = natural killer; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OVA = ovalbumin; OW = organ weight; PEPCK = phosphoenolpyruvate carboxykinase; PND = postnatal day; RBC = red blood cell; Repro = reproductive; Resp = respiratory; RX = reproductive function; sRBC = sheep red blood cell; SLOAEL = serious lowest-observed-adverse-effect level; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; TT4 = total thyroxine; UR = urinalysis; WI = water intake

Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Acute (≤14 days)

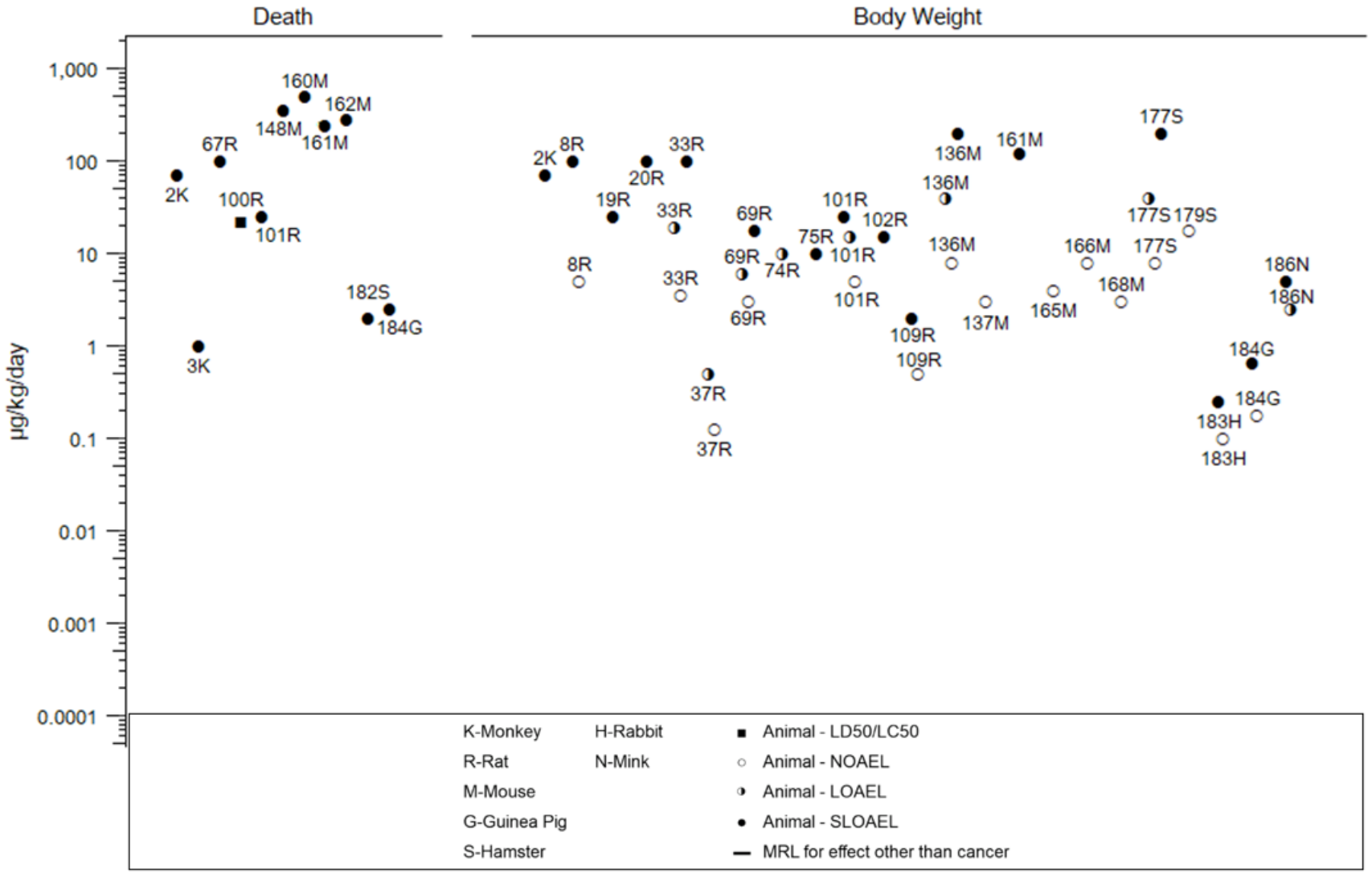


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Acute (≤14 days)

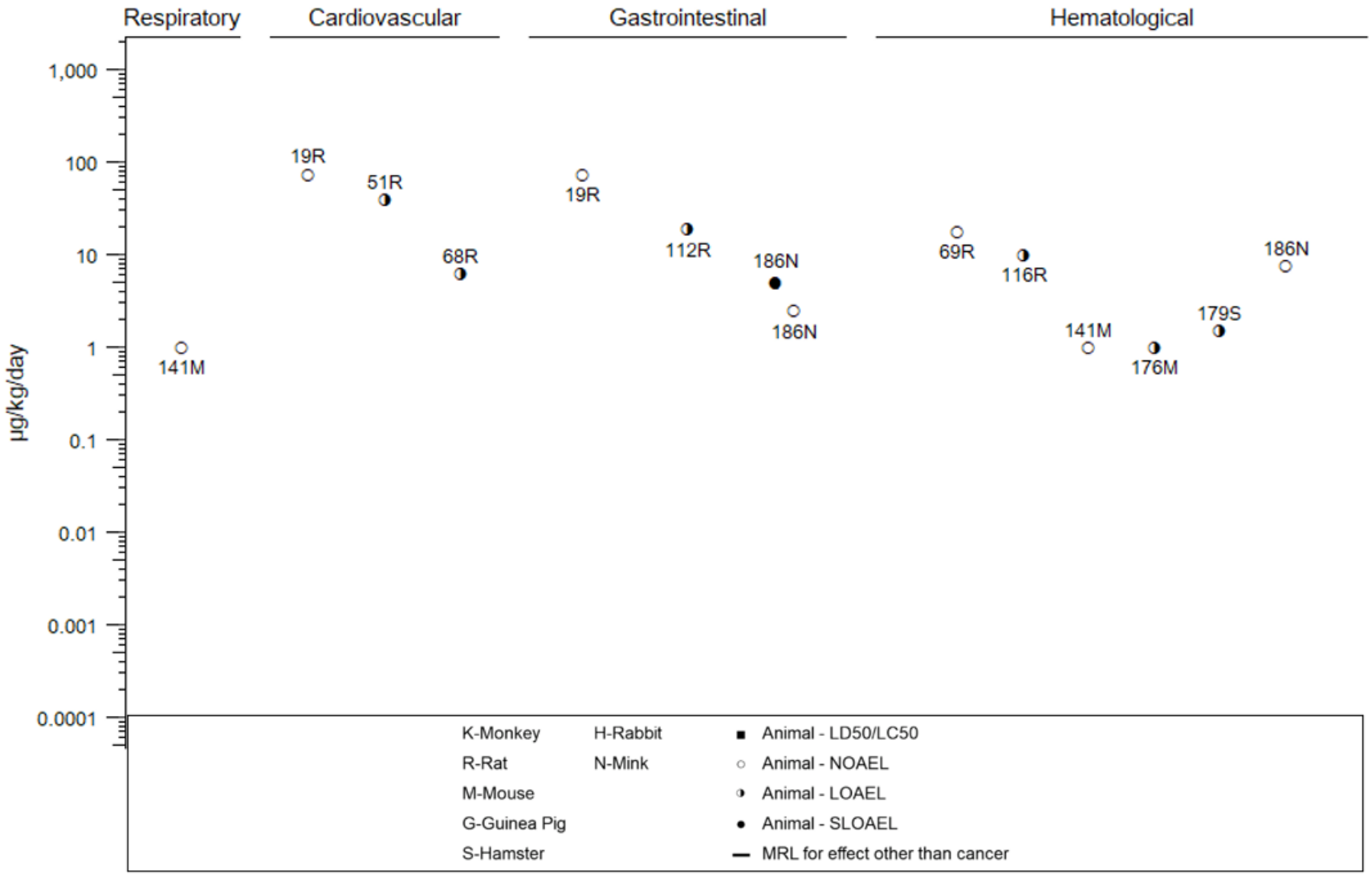


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Acute (≤14 days)

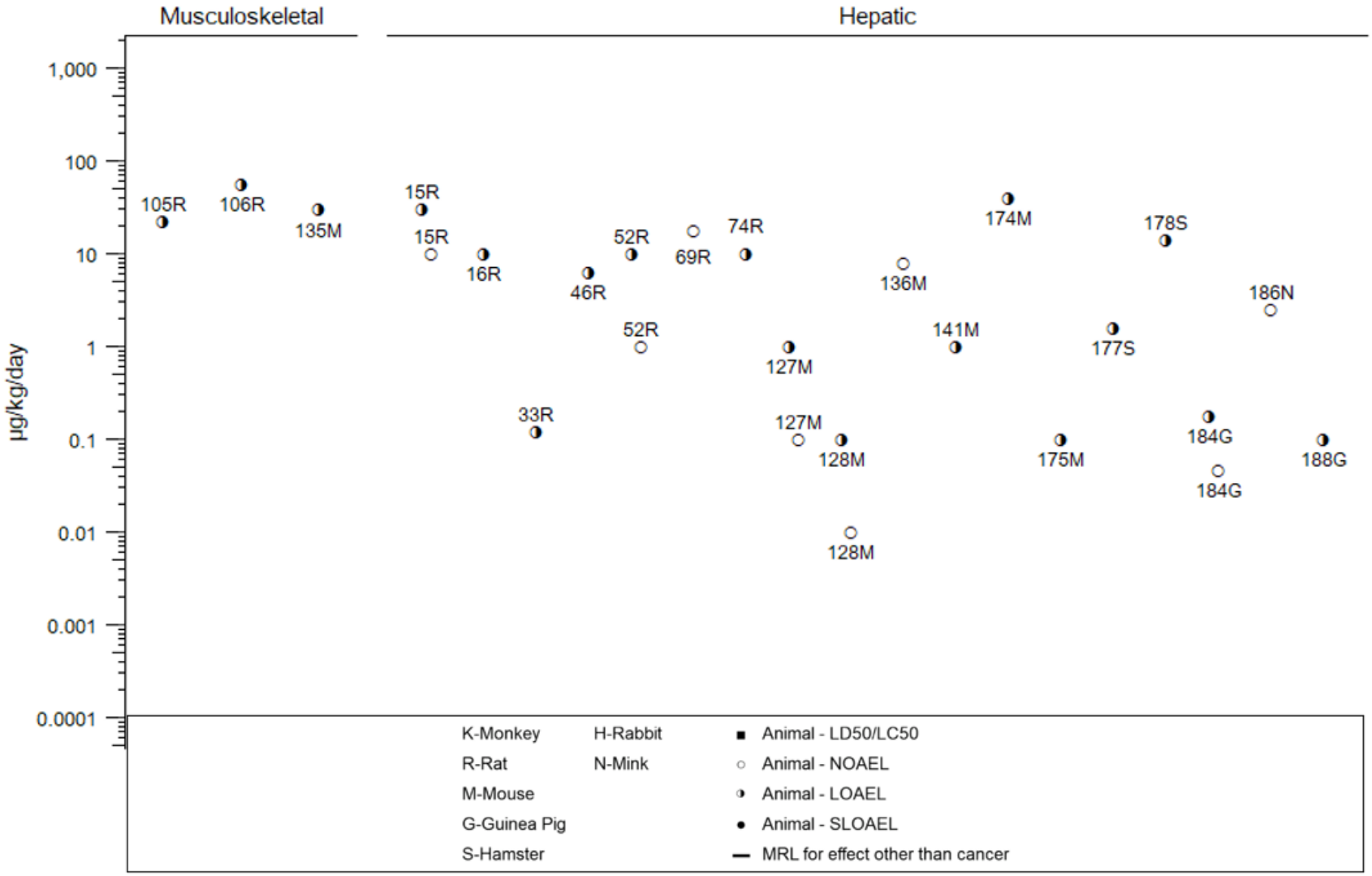


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Acute (≤14 days)

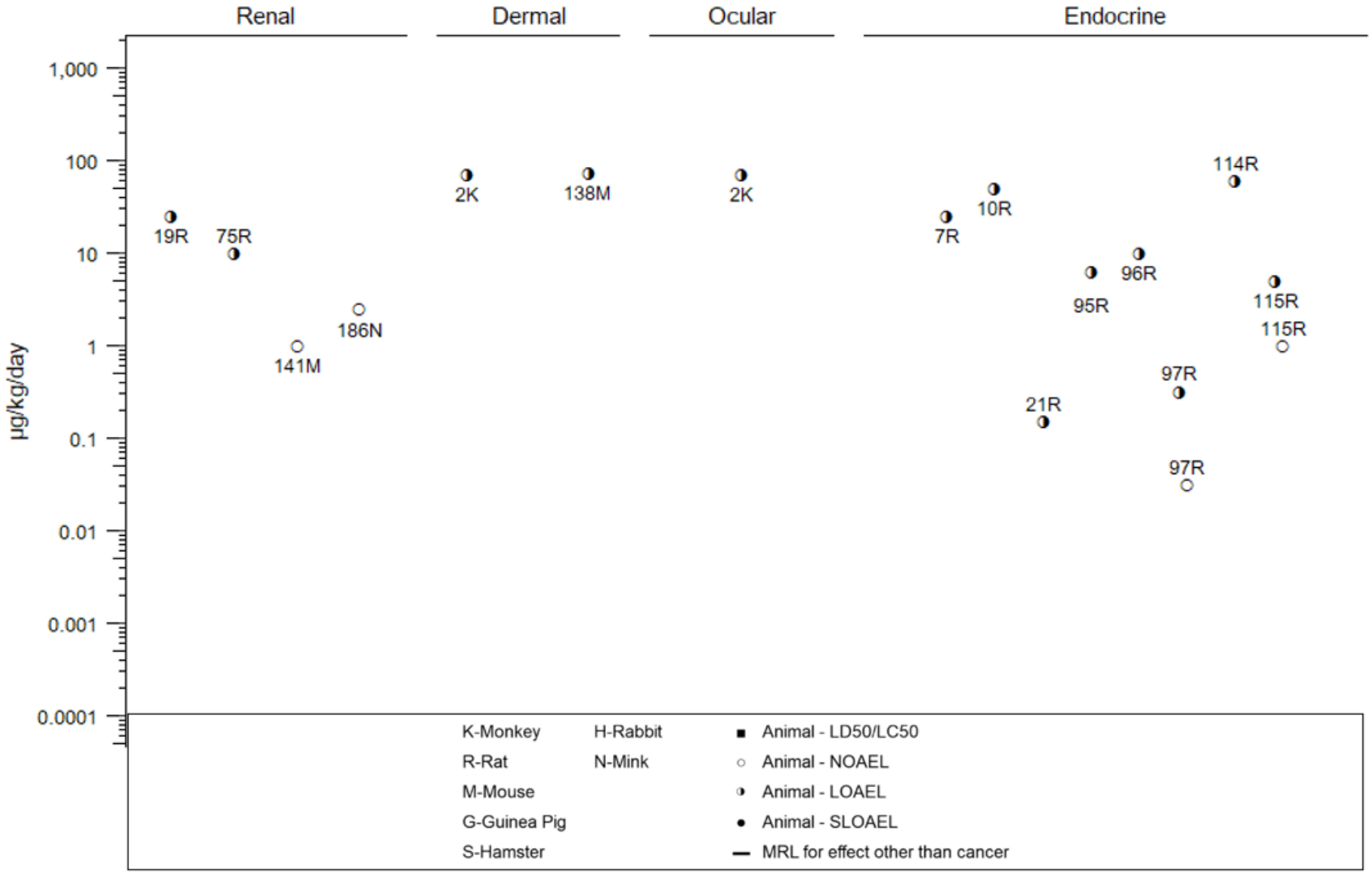


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Acute (≤14 days)

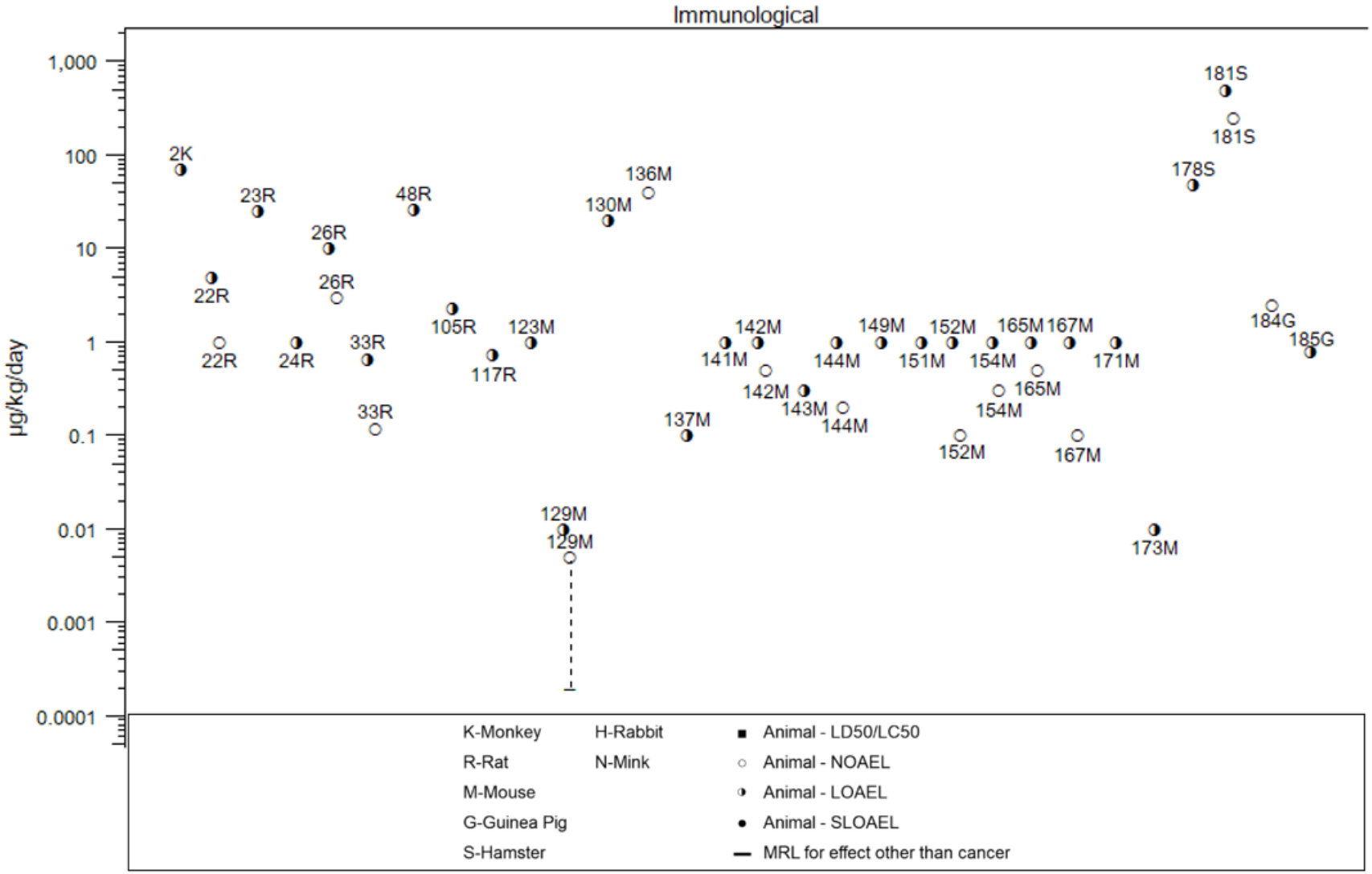


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Acute (≤14 days)

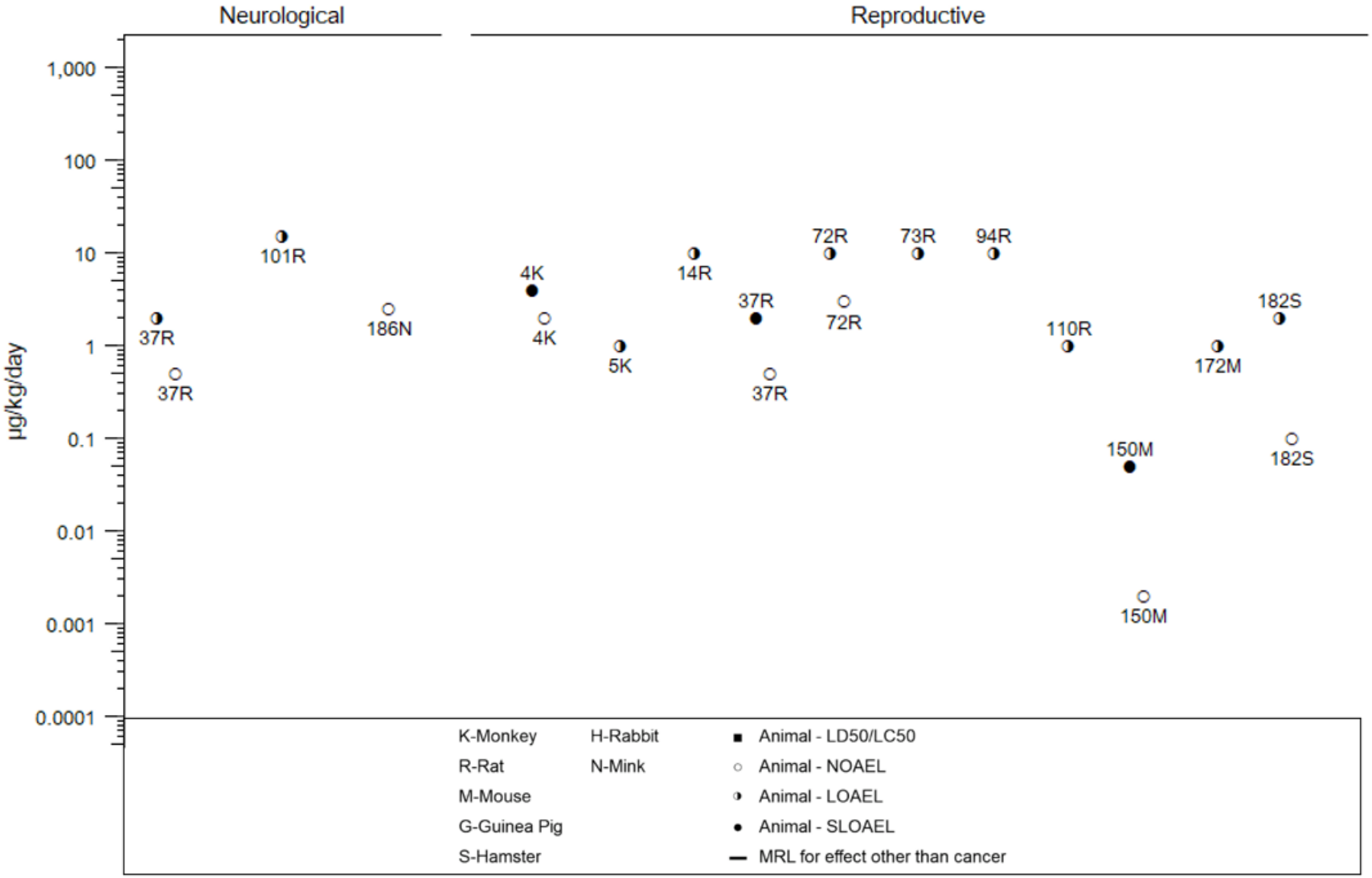


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Acute (≤14 days)

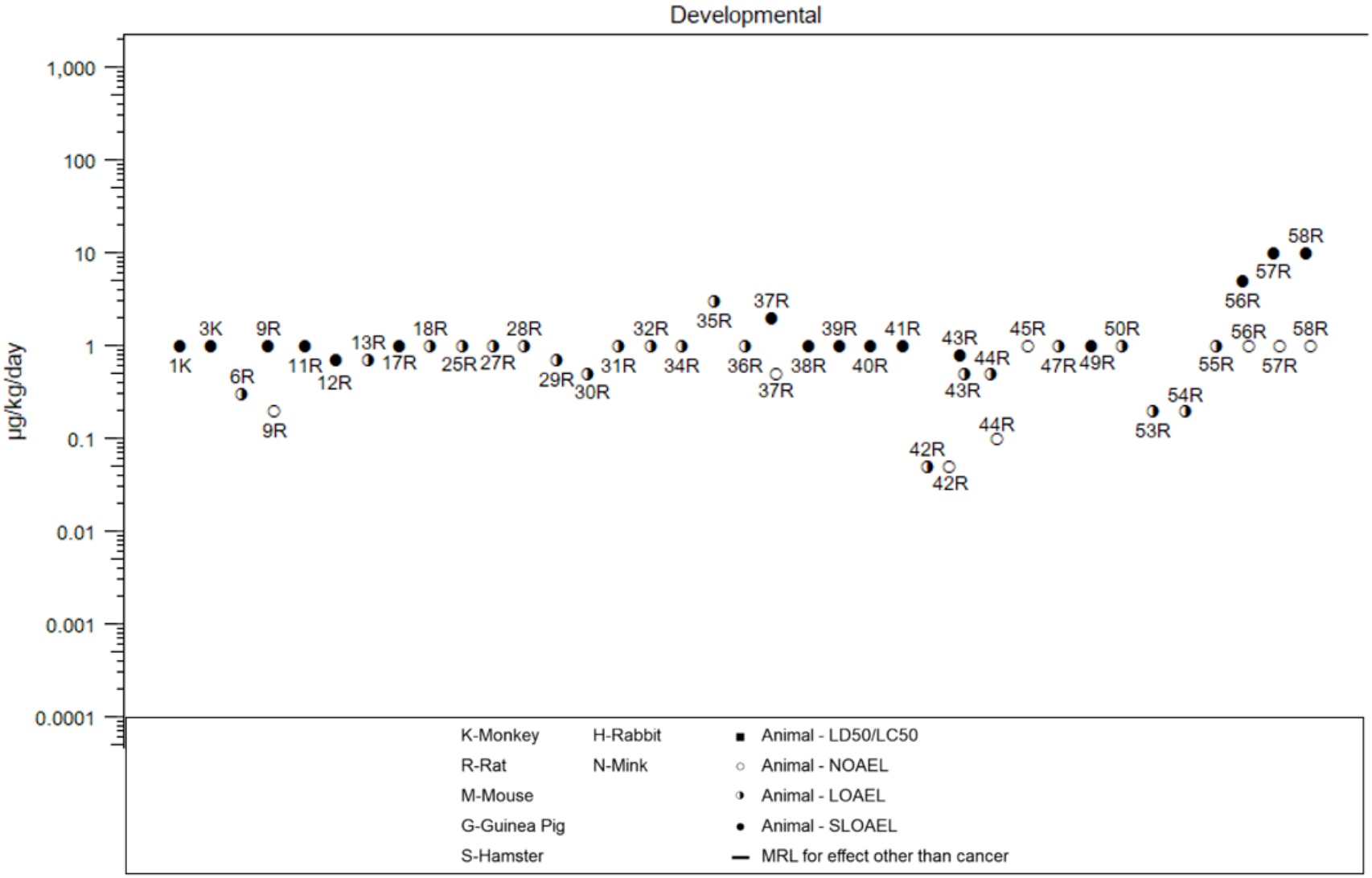


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Acute (≤14 days)

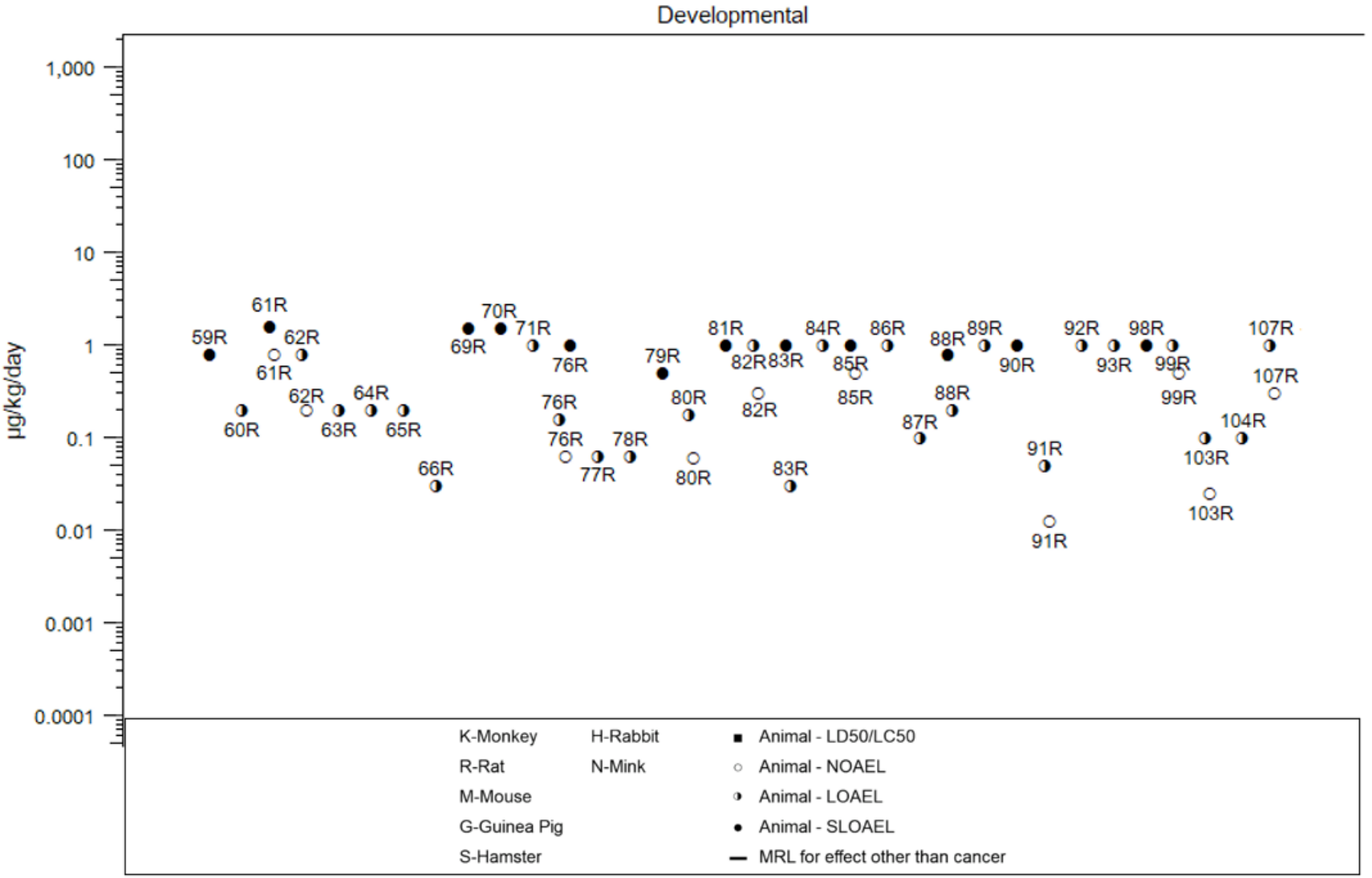


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Acute (≤14 days)

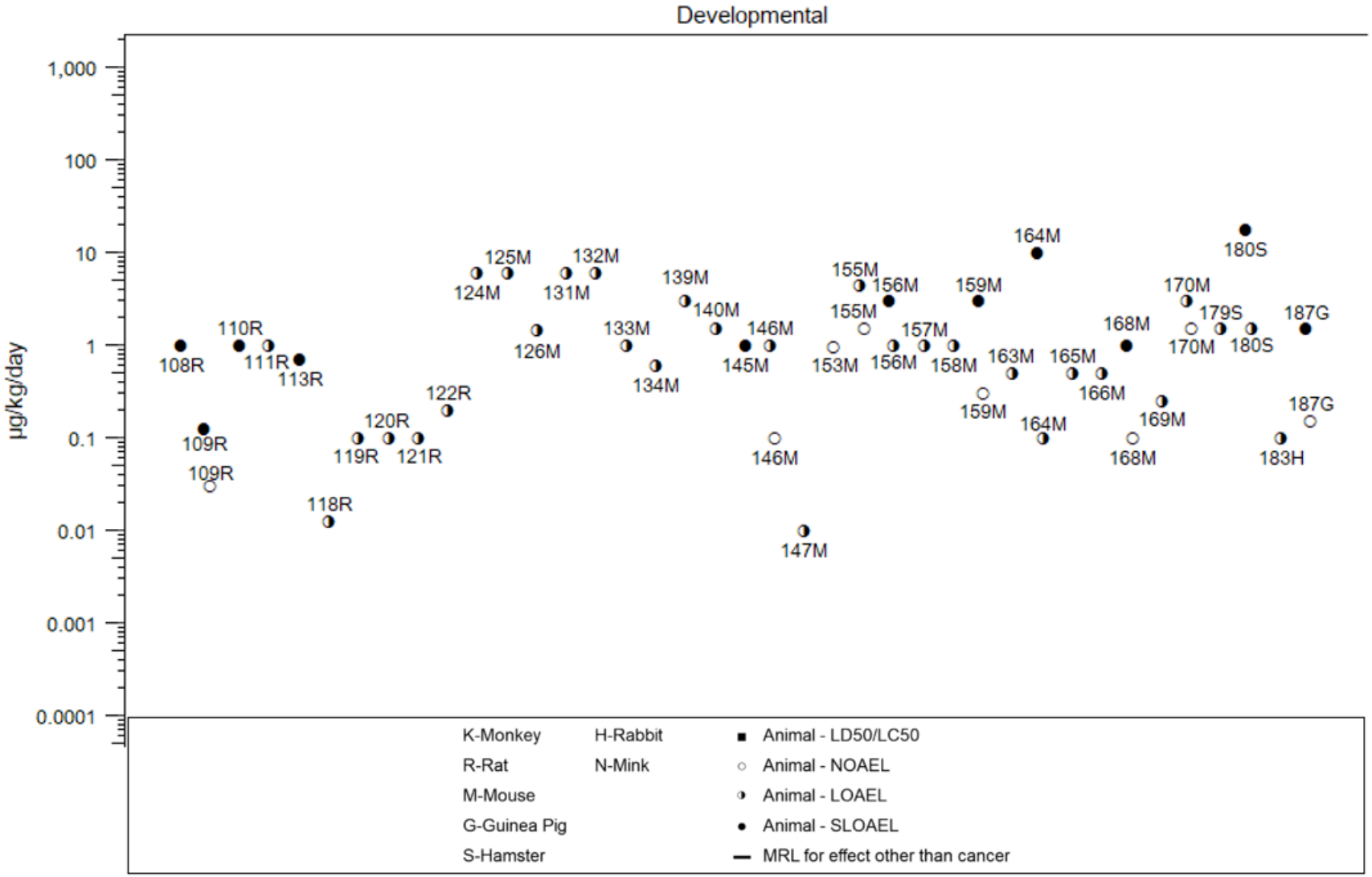


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Acute (≤14 days)

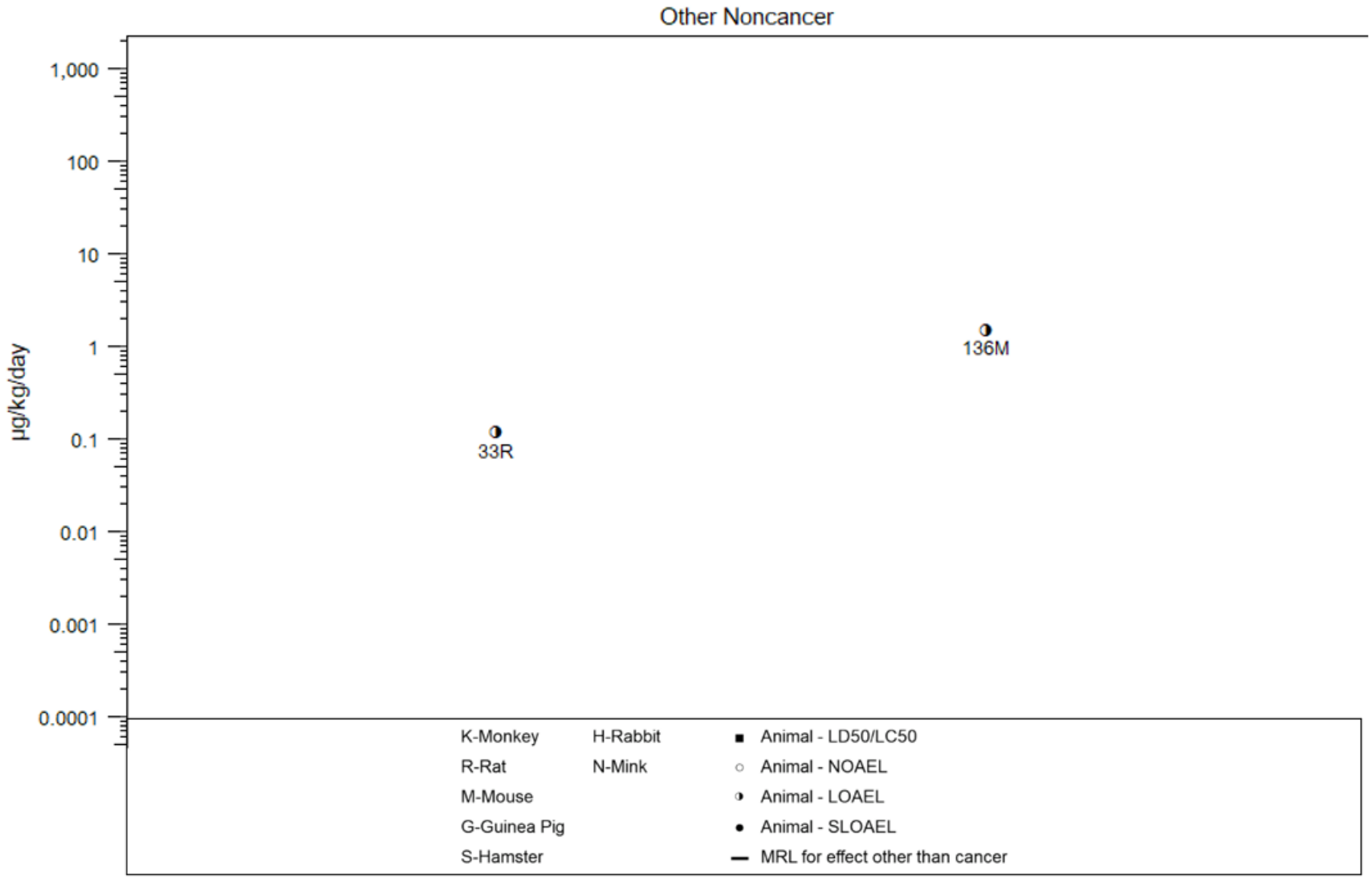


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Intermediate (15–364 days)

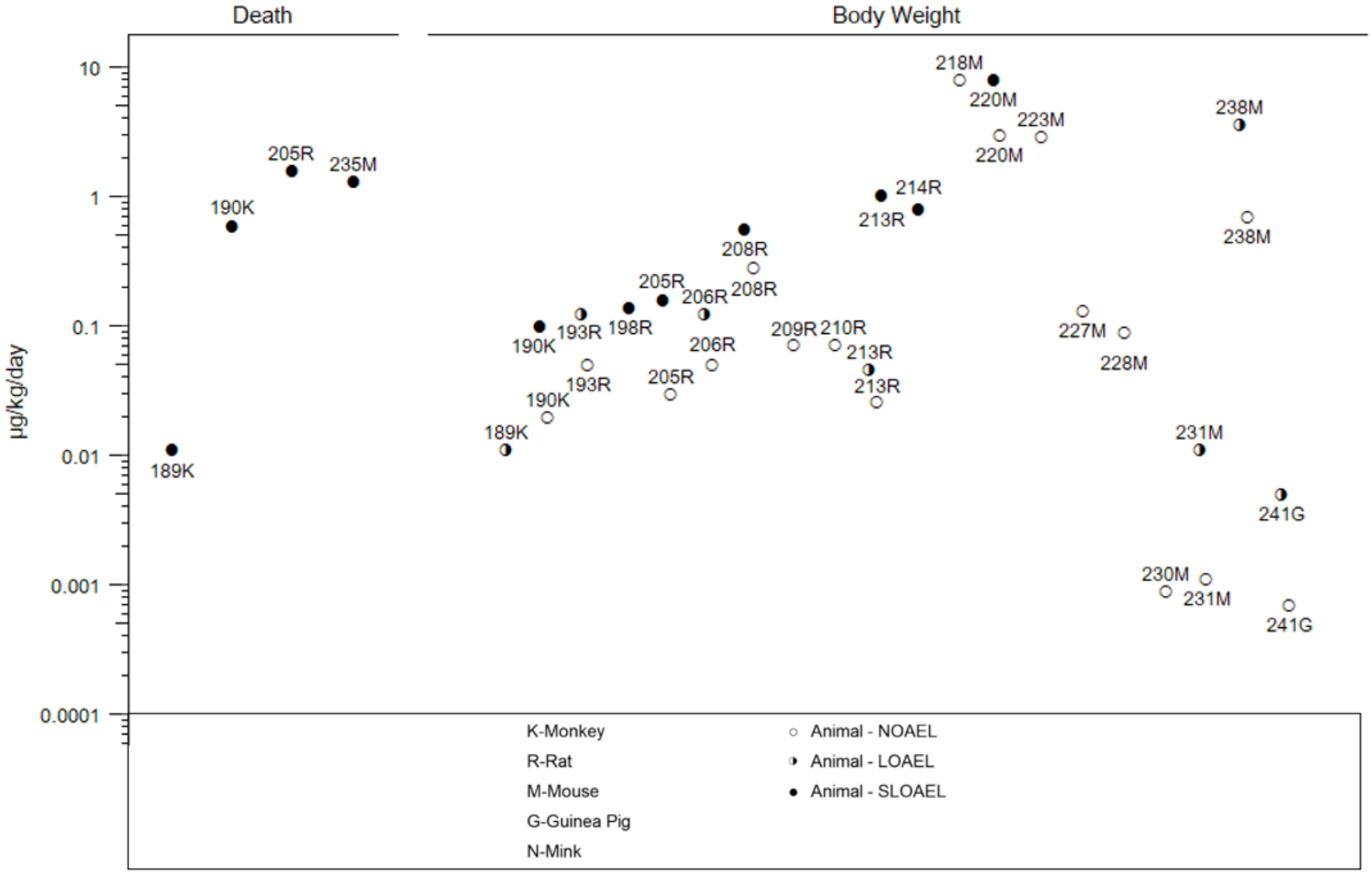


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Intermediate (15–364 days)

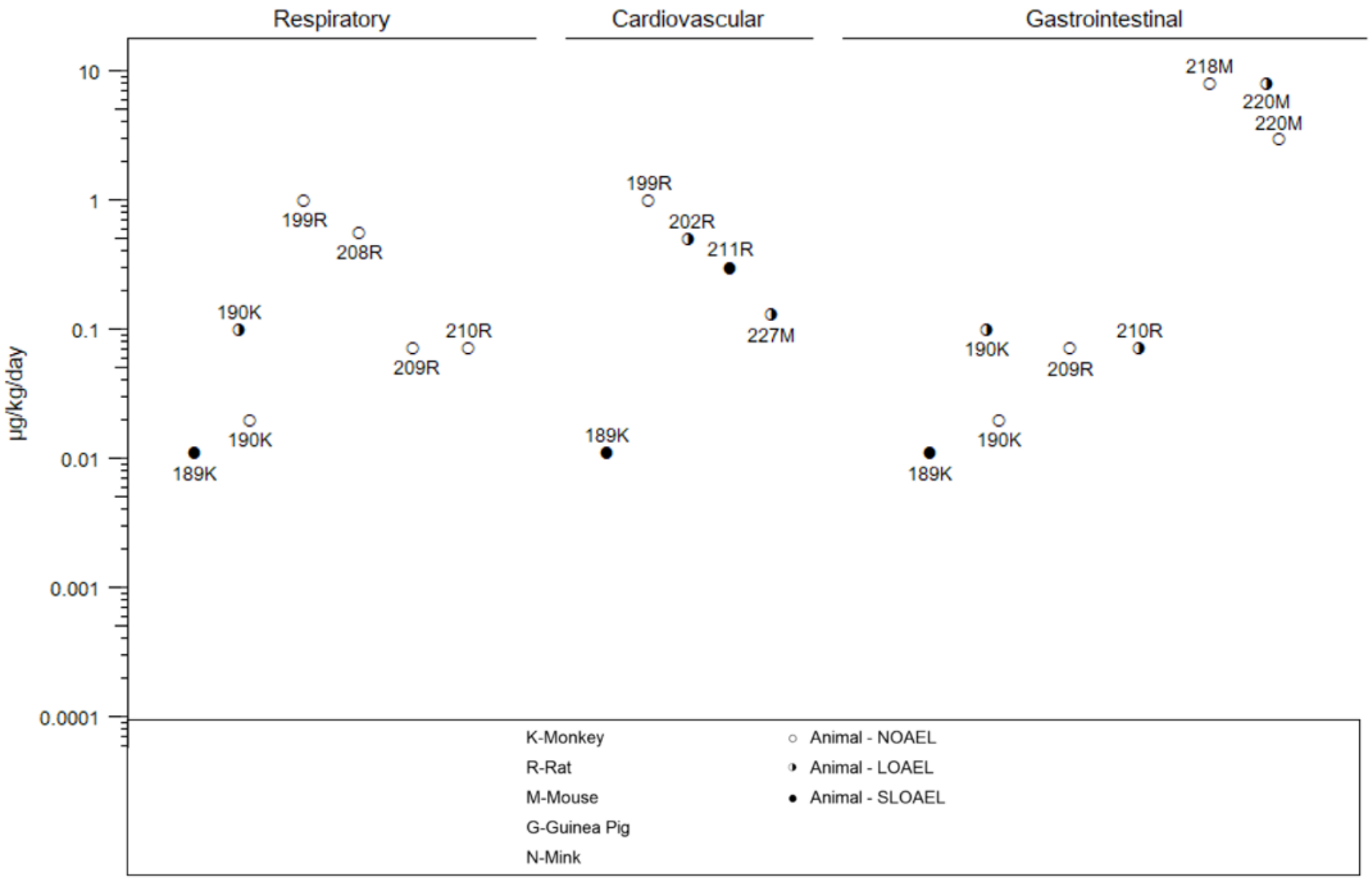


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Intermediate (15–364 days)

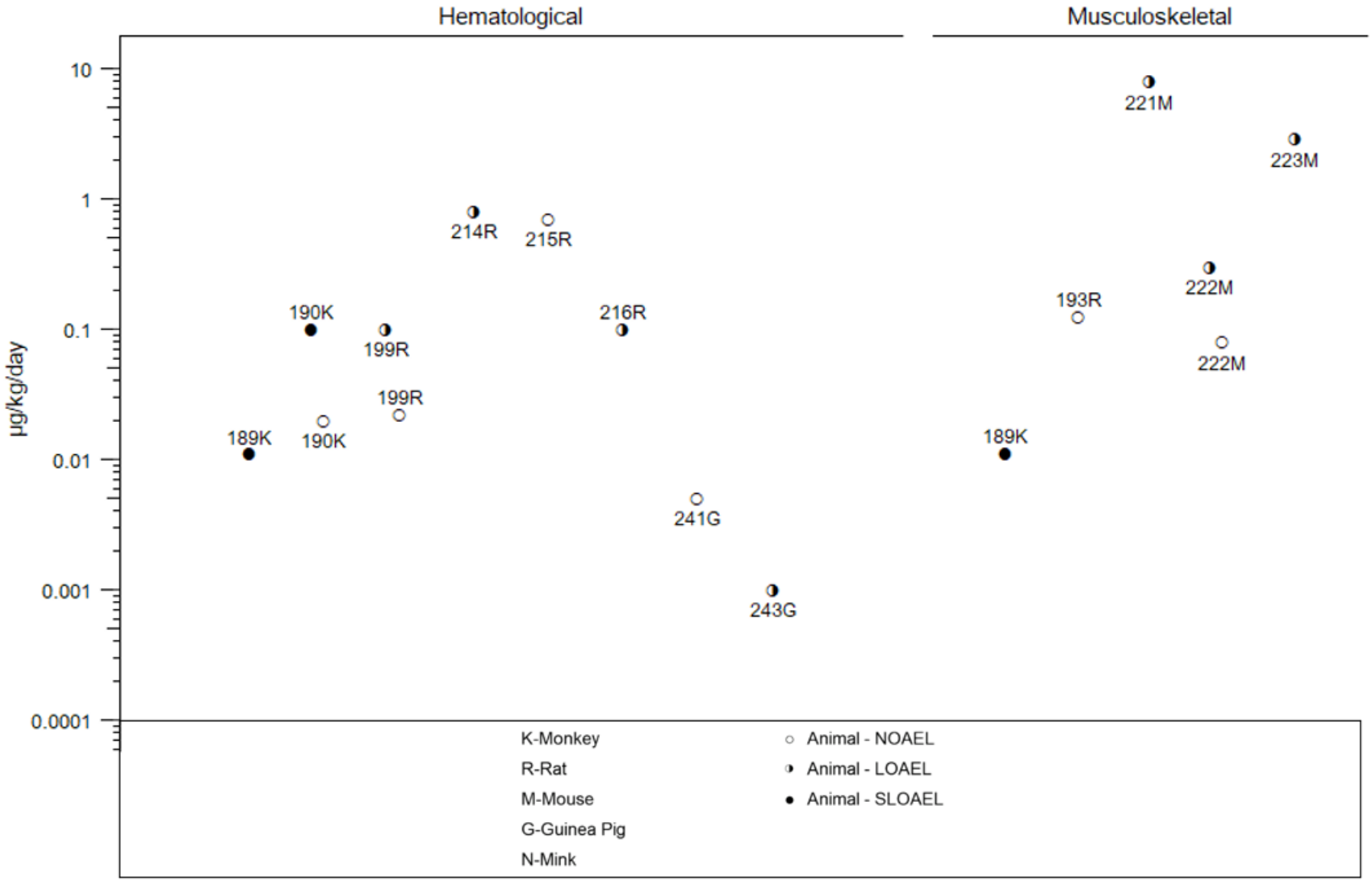


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Intermediate (15–364 days)

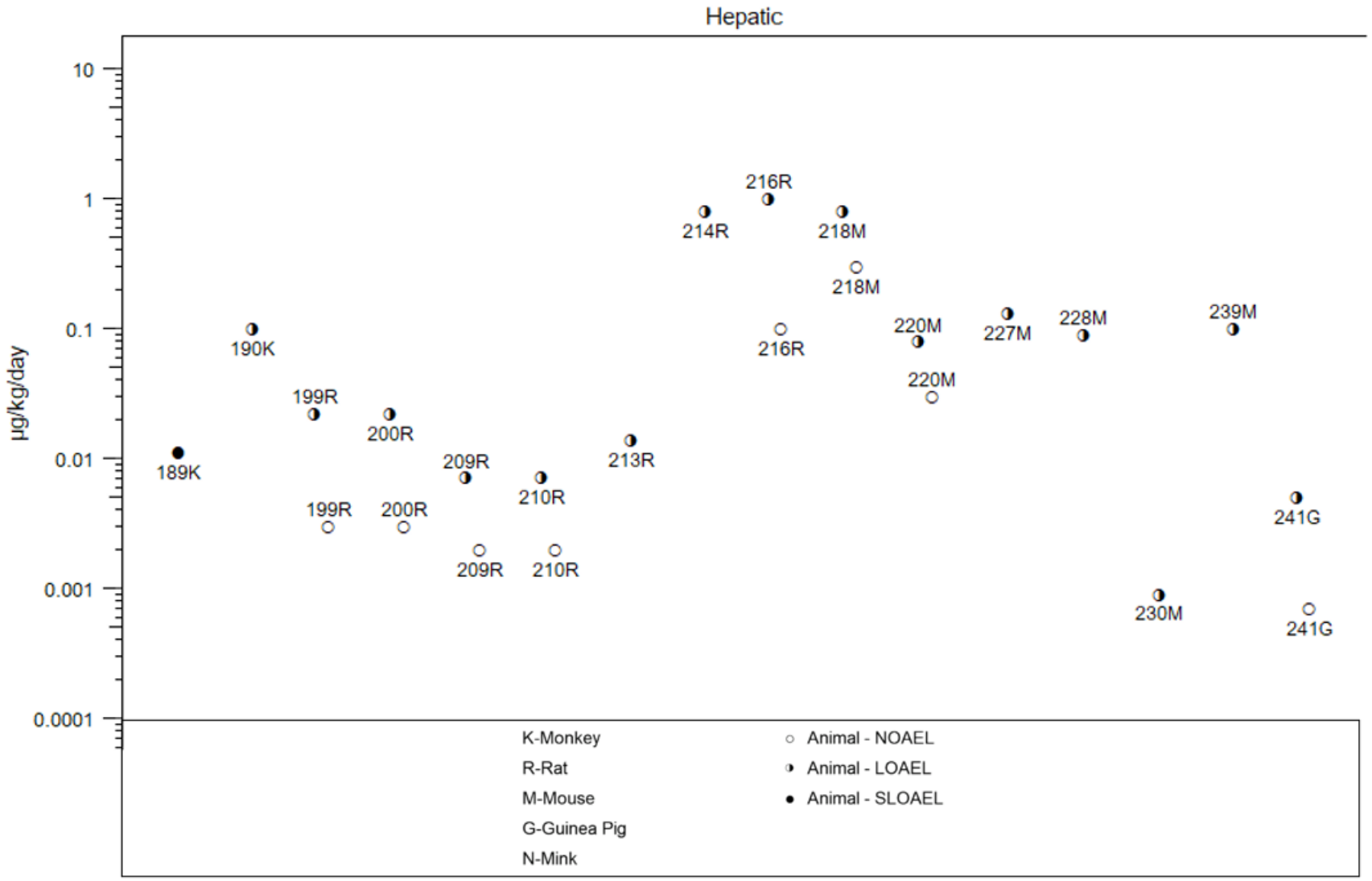


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Intermediate (15–364 days)

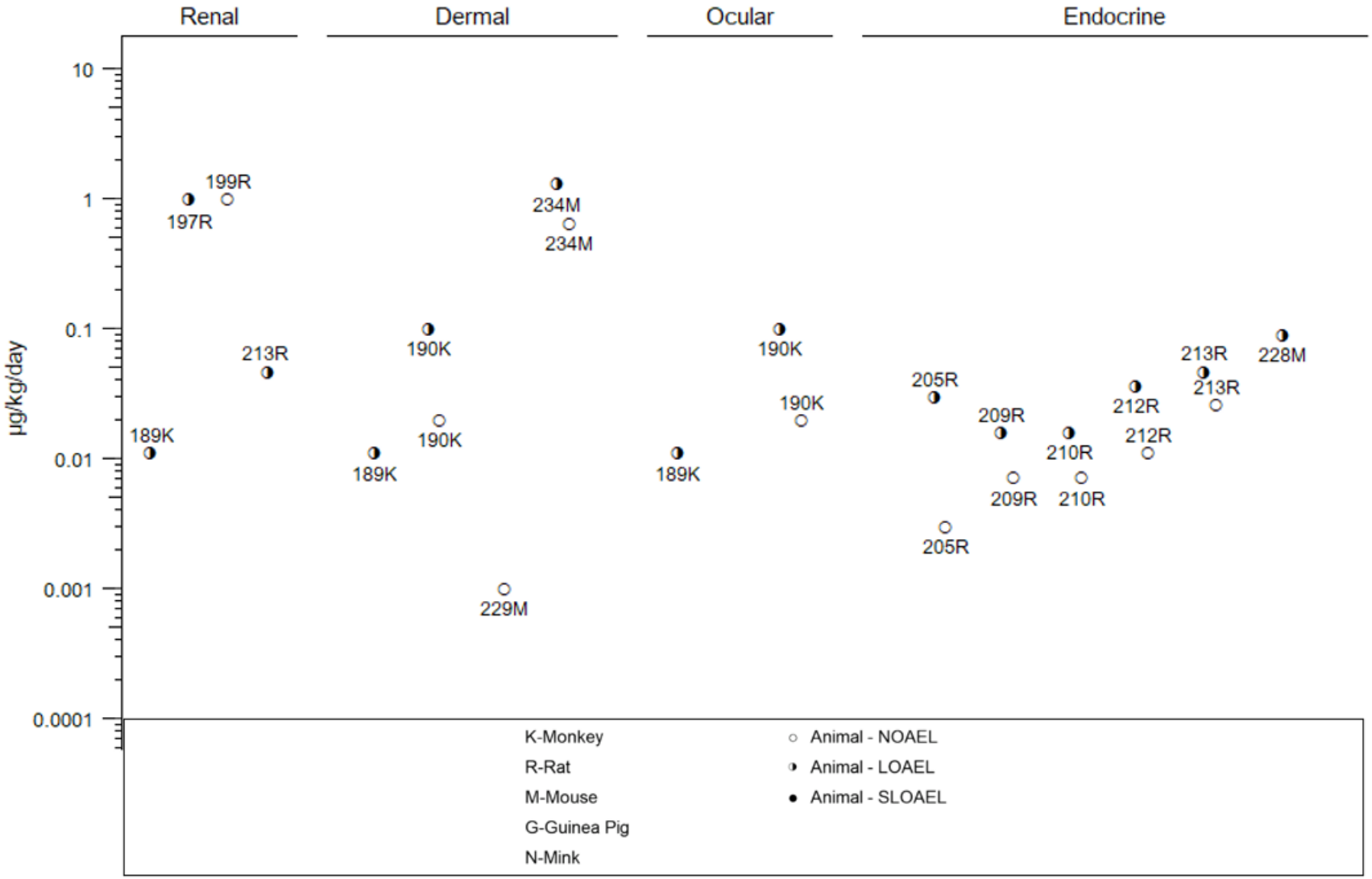


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Intermediate (15–364 days)

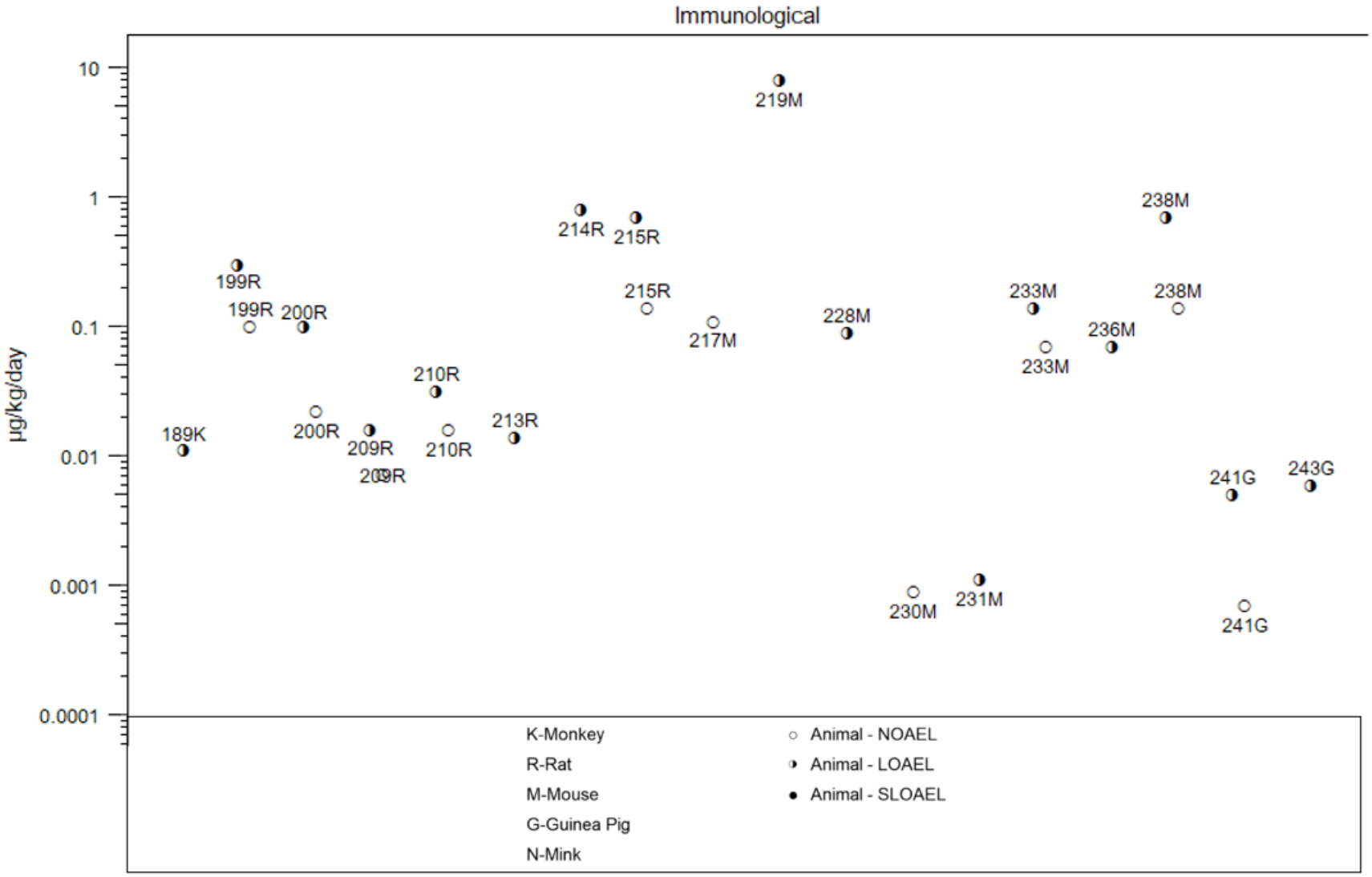


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Intermediate (15–364 days)

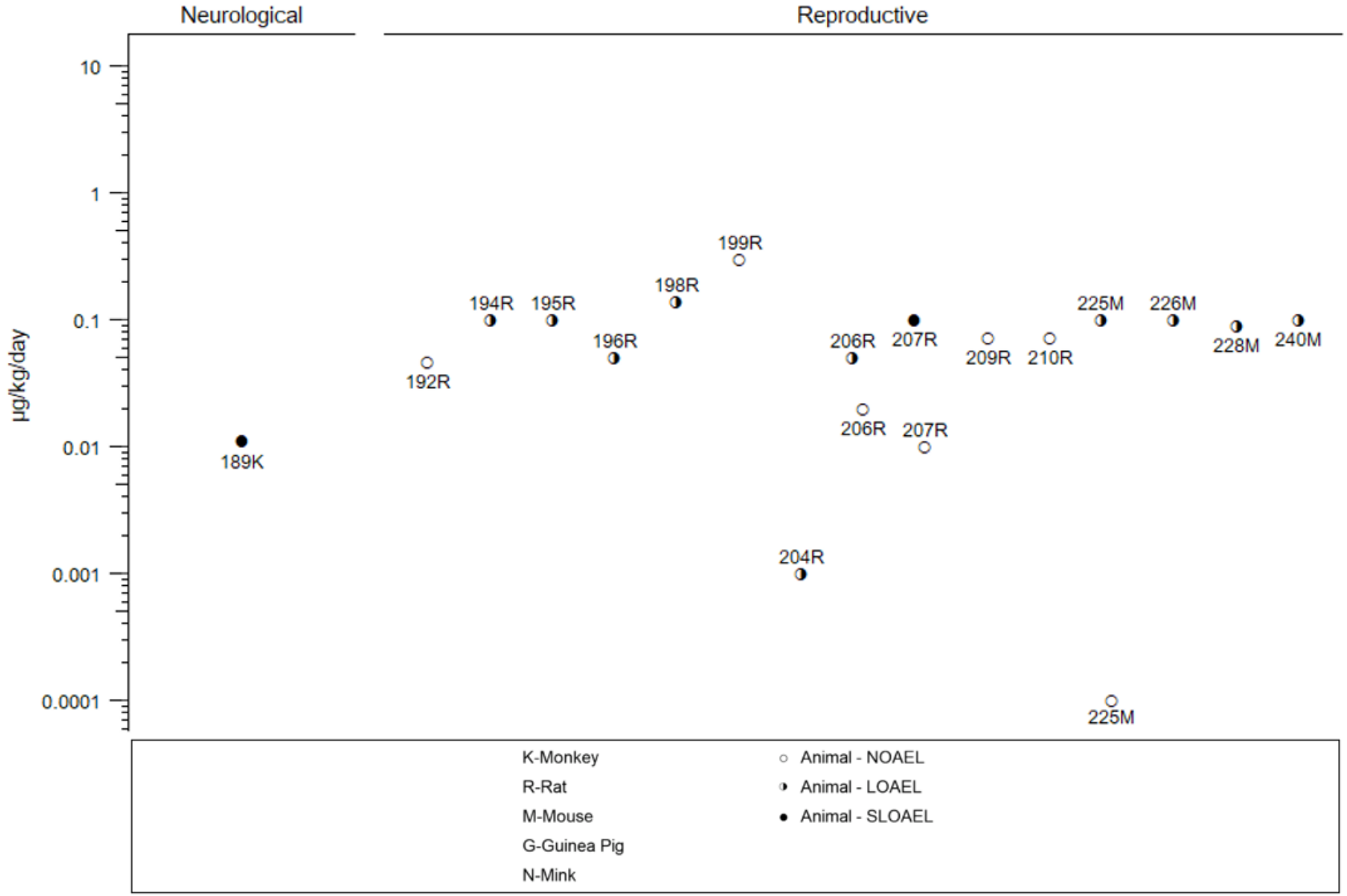


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Intermediate (15–364 days)

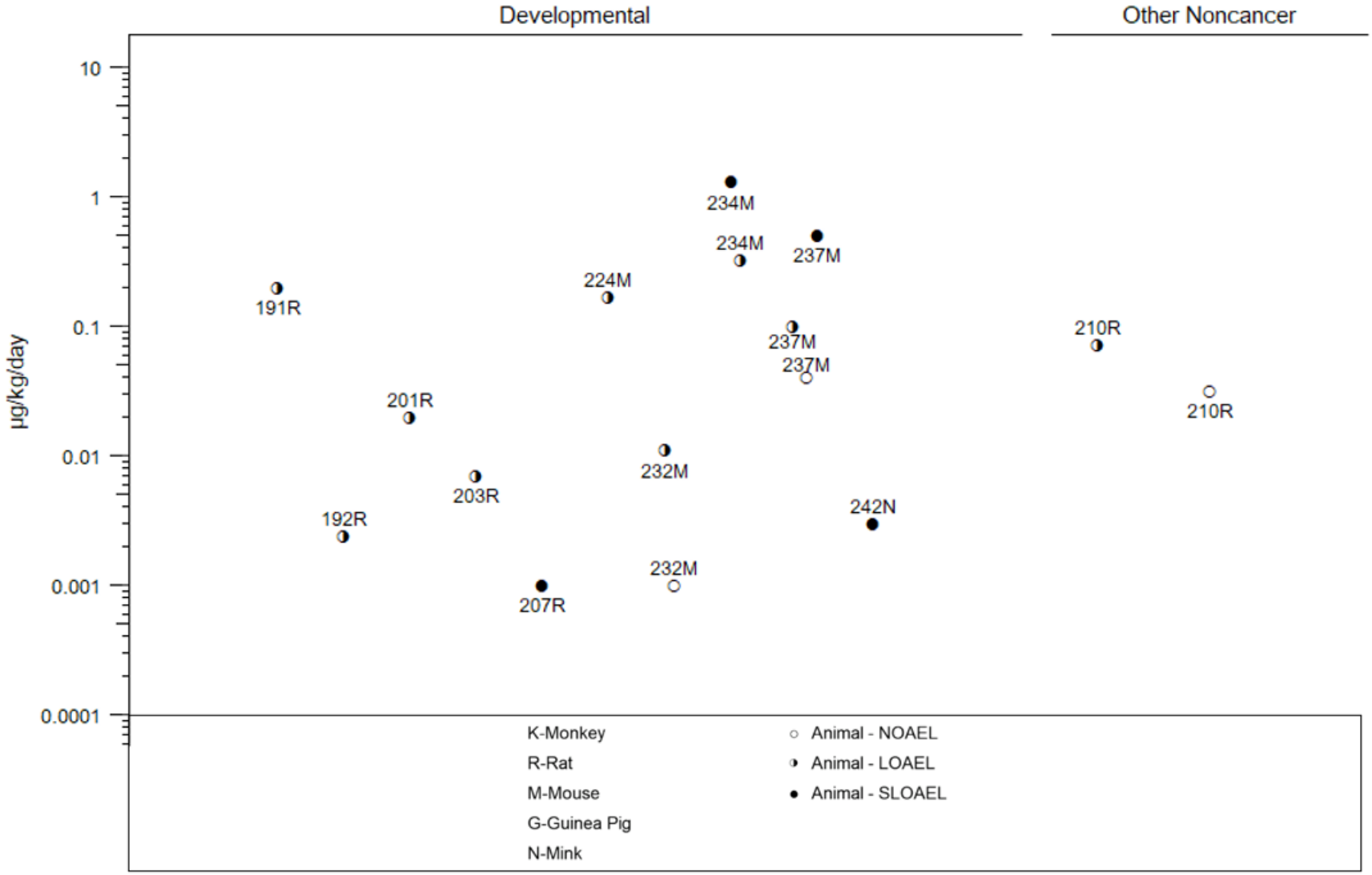


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Chronic (≥365 days)

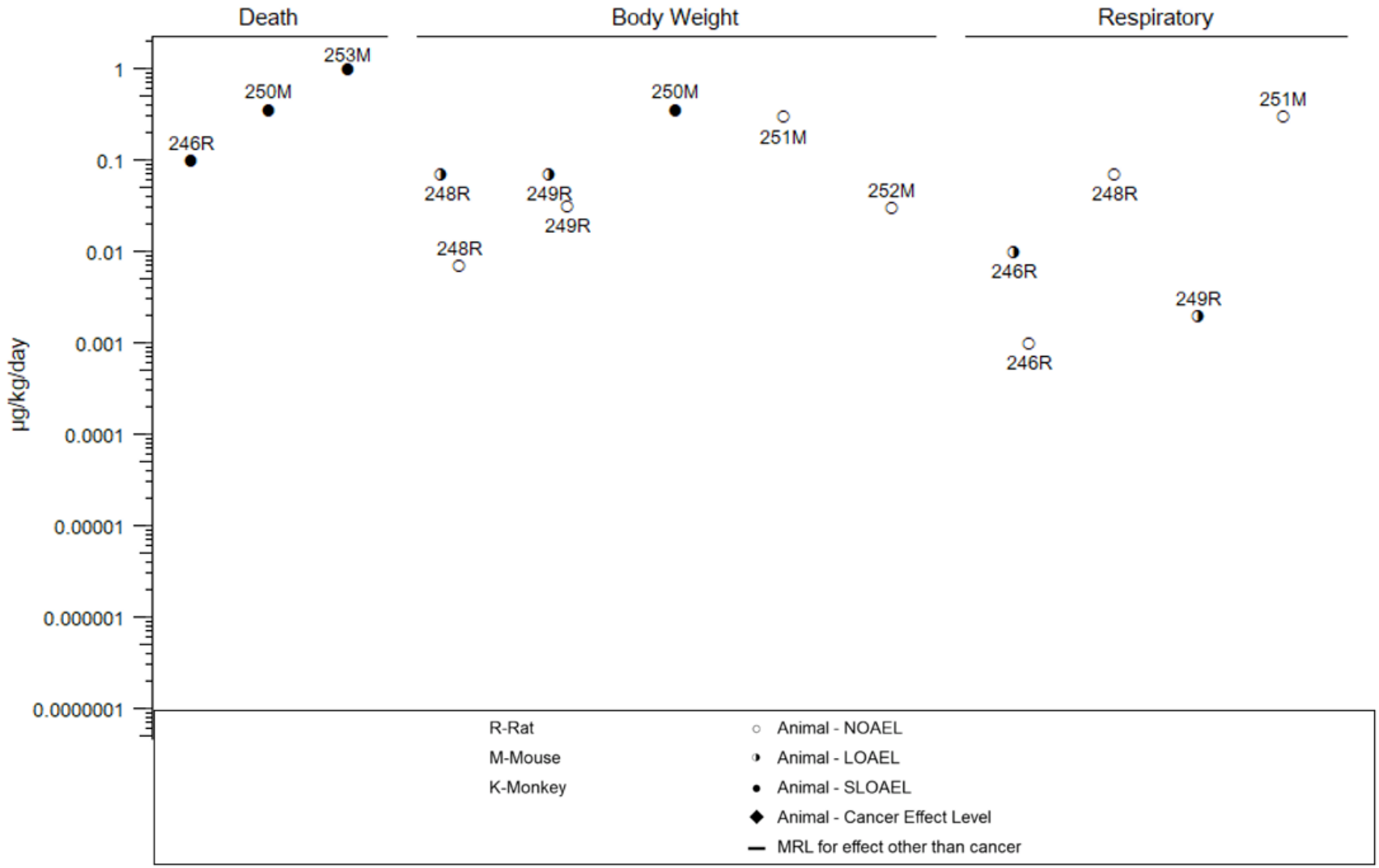


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Chronic (≥365 days)

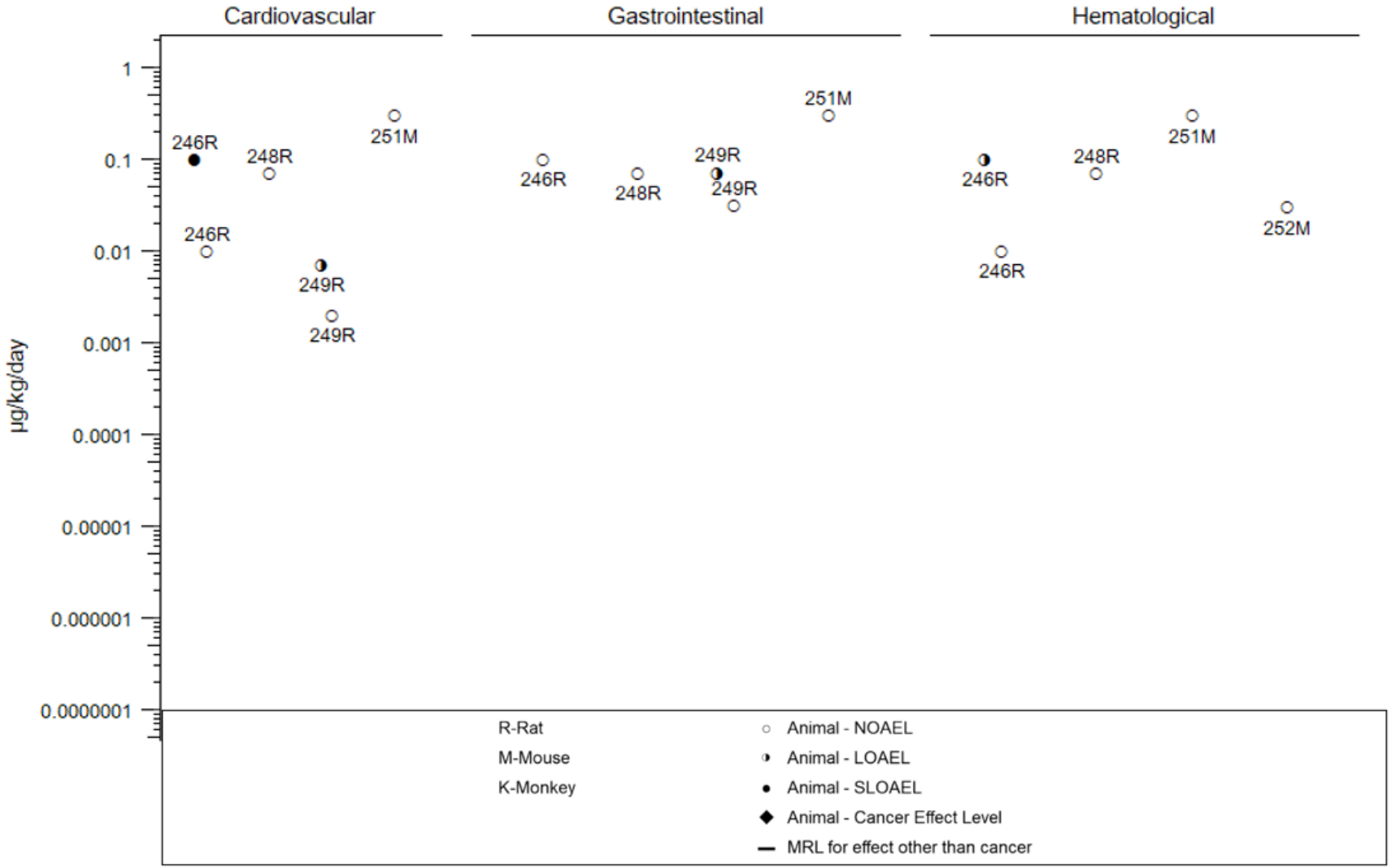


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Chronic (≥365 days)

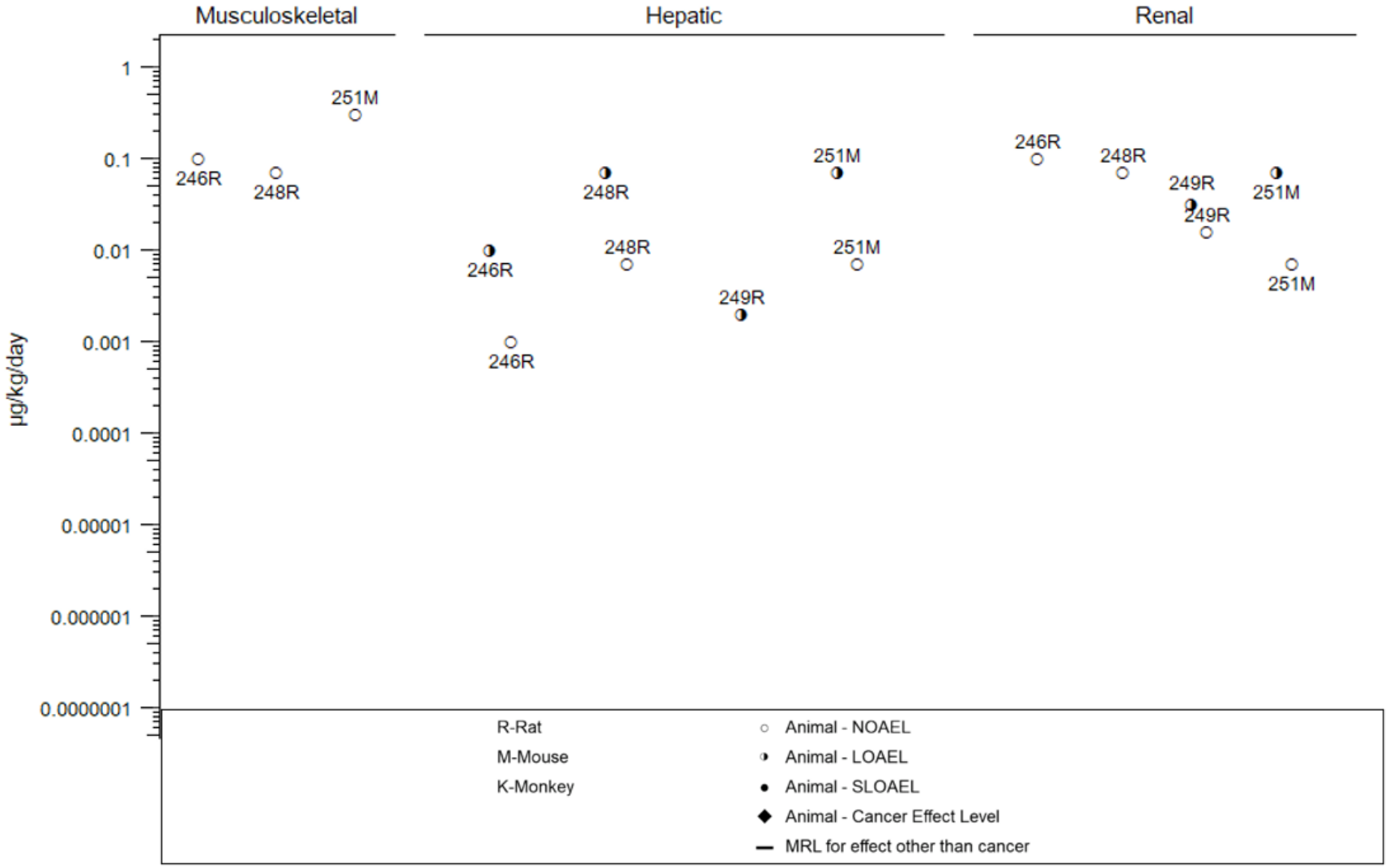


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Chronic (≥365 days)

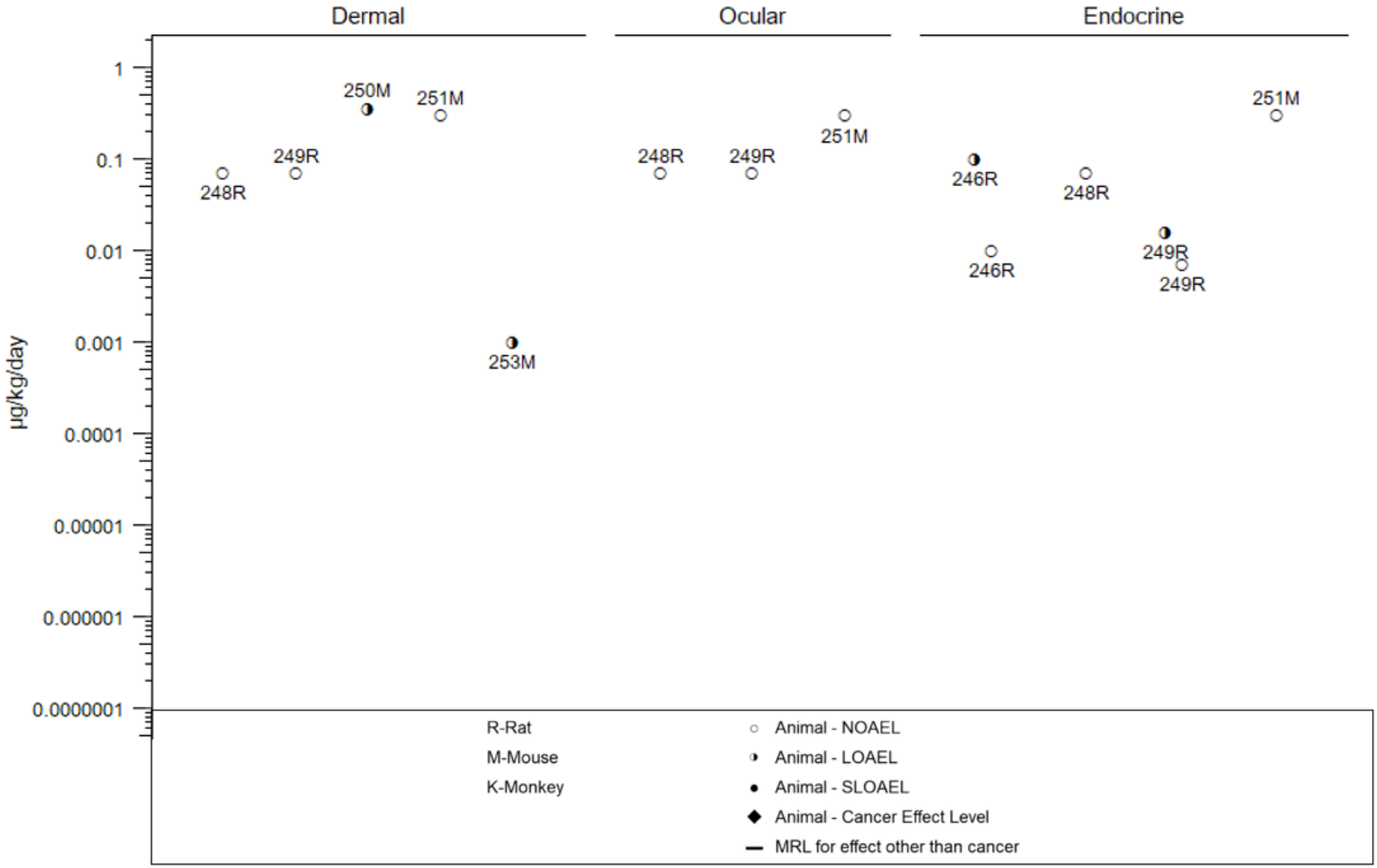


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Chronic (≥365 days)

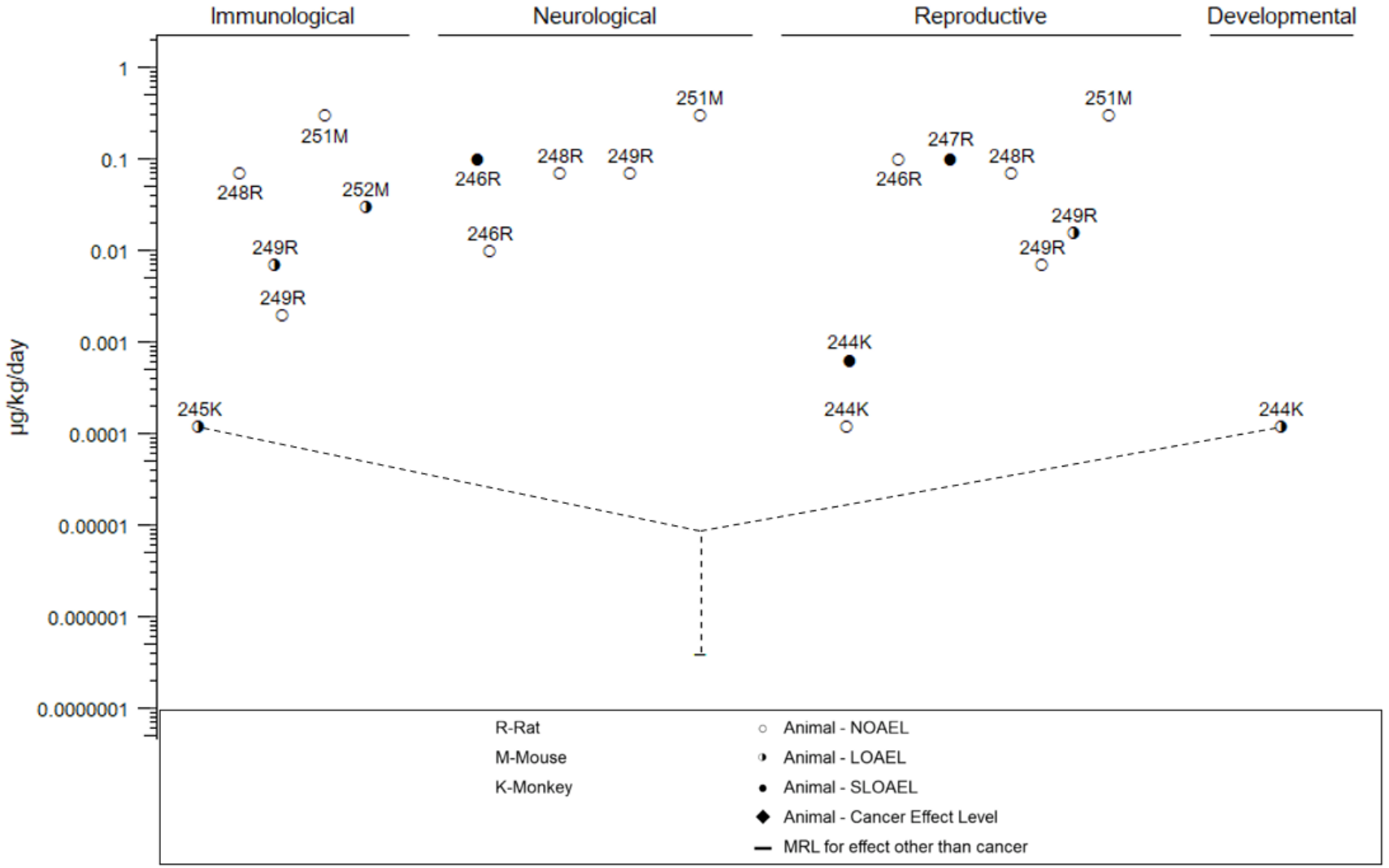


Figure 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Oral
Chronic (≥365 days)

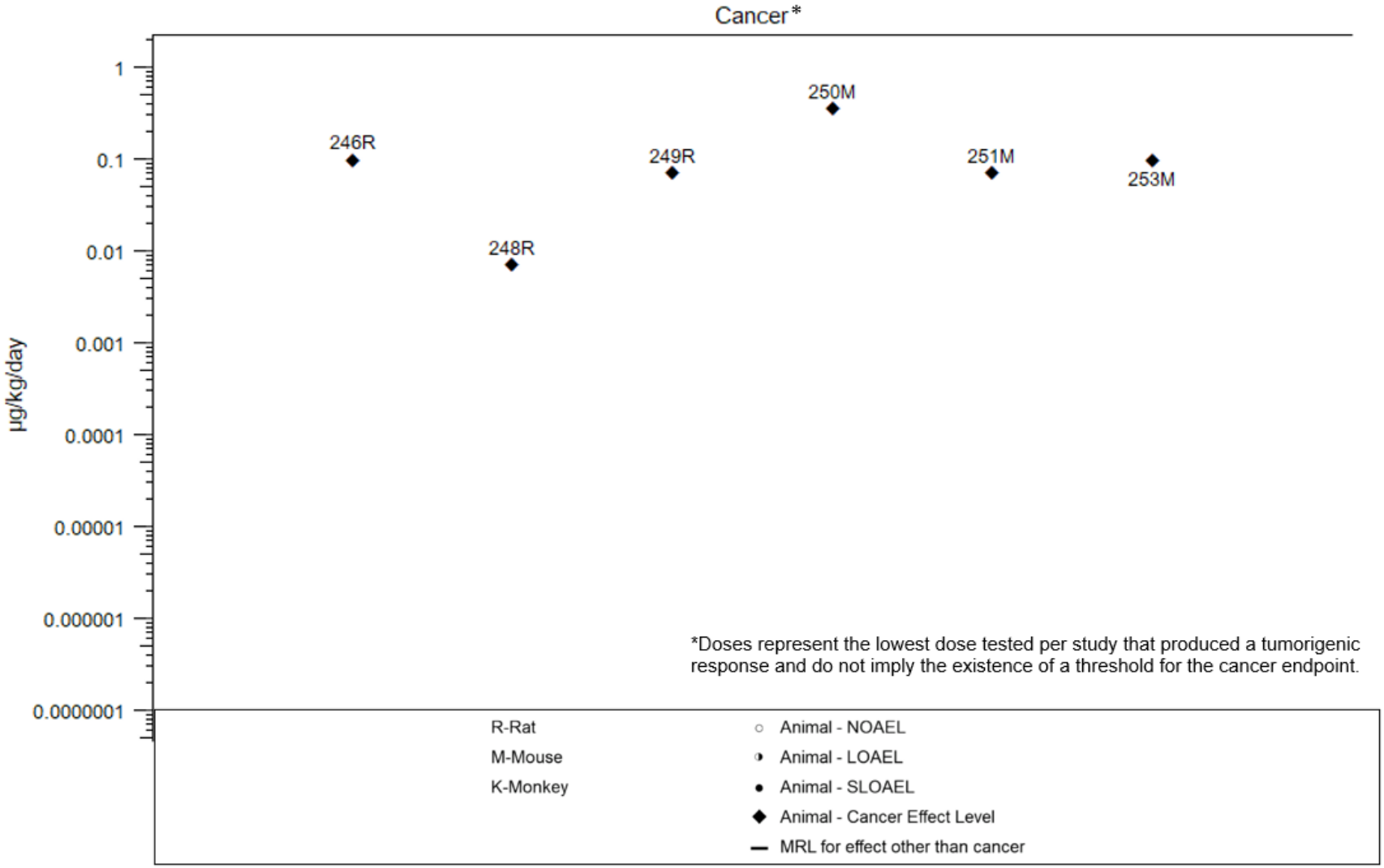


Table 2-3. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Couture et al. 1988									**OCDD**
1	Rat (Fischer-344) 5 M	2 weeks, 5 days/week (GO)	0, 36	BC, BI	Hemato	36			
					Hepatic	36			
Crofton et al. 2005									**1,2,3,7,8-PeCDD**
2	Rat (Long-Evans) 4–14 F	Once (GO)	0, 0.003–10	BW, OF	Bd wt	10			
					Endocr		1.51		30% decrease in serum T4
Khera and Ruddick 1973									**2,3-DCDD**
3	Rat (Wistar) 11–12 F	GDs 6–15 (GO)	0, 1,000, 2,000	DX	Develop	2,000			
Khera and Ruddick 1973									**1,2,3,4-TCDD**
4	Rat (Wistar) 10–15 F	GDs 6–15 (GO)	0, 50, 100, 200, 400, 800	DX	Develop	800			
Khera and Ruddick 1973									**2,7-DCDD**
5	Rat (Wistar) 13–15 F	GDs 6–15 (GO)	0, 250, 500, 1,000, 2,000	DX, RX	Develop	2,000			
Khera and Ruddick 1973									**2-MCDD**
6	Rat (Wistar) 11–12 F	GDs 6–15 (GO)	0, 1,000, 2,000	DX	Develop	2,000			
Madsen and Larsen 1989									**1,2,3,7,8-PeCDD**
7	Rat (Wistar) 8–10 F	GD 16 (G)	0, 0.5, 2, 10	DX	Develop		0.5		Decreased thymus weight

Table 2-3. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NCI/NTP 1980									**1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD mixture**
8	Rat (Osborne-Mendel) 4 M, 4 F	Once (GO)	500, 10,000	CS, LE	Death			800 F	LD_{50}
								1,800 M	LD_{50}
Rozman et al. 2005									**1,2,3,4,6,7,8-HpCDD**
9	Rat (Sprague-Dawley) 30–36 F	Once (GO)	0, 1,000, 2,800, 3,100, 3,400, 3,800, 4,100		Cancer			3,400	CEL: lung cancer
Schwetz et al. 1973									**2,7-DCDD**
10	Rat (Sprague-Dawley) 7 F	GDs 6–15 (GO)	100,000	DX	Develop	100,000			
Schwetz et al. 1973									**HxCDD, unspecified mixture**
11	Rat (Sprague-Dawley) 10 F	GDs 6–15 (GO)	0.1, 1.0, 10, 100	DX	Bd wt	1		10	39% decreased maternal weight gain
					Develop	0.1	1		Subcutaneous edema
Schwetz et al. 1973									**OCDD**
12	Rat (Sprague-Dawley) 10 F	GDs 6–15 (GO)	100,000, 500,000	DX, RX	Develop	100,000	500,000		Subcutaneous edema
Simanainen et al. 2002									**1,2,3,7,8-PeCDD**
13	Rat (Long-Evans) 9–11 F	Once (GO)	0, 0.1–300	BW, OW, OF	Bd wt			14	Decreased body weight (ED_{50})
					Musc/skel		24		ED_{50} for incisor tooth defects
					Endocr		3.6		Decreased serum T4 (ED_{50})

Table 2-3. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Immuno		7.2		Decreased relative thymus weight (ED_{50})
Simanainen et al. 2002									**1,2,3,4,7,8-HxCDD**
14	Rat (Long-Evans) 9–11 F	Once (GO)	0, 0.3-300	BW, OW, OF	Bd wt			140	Decreased body weight (ED_{50})
					Musc/skel		130		ED_{50} for incisor tooth defects
					Endocr		21		Decreased serum T4 (ED_{50})
					Immuno		37		Decreased relative thymus weight (ED_{50})
Simanainen et al. 2002									**1,2,3,4,6,7,8-HpCDD**
15	Rat (Long-Evans) 9–11 F	Once (GO)	0, 0.3–3,000	BW, OW, OF	Bd wt			980	Decreased body weight (ED_{50})
					Musc/skel		630		ED_{50} for incisor tooth defects
					Endocr		47		Decreased serum T4 (ED_{50})
					Immuno		150		Decreased relative thymus weight (ED_{50})
Simanainen et al. 2002									**1,2,3,7,8-PeCDD**
16	Rat Hans/Wistar 9–11 F	Once (GO)	0, 0.1–300	BW, OW, OF	Bd wt			32	Decreased body weight (ED_{50})
					Musc/skel		27		ED_{50} for incisor tooth defects
					Endocr		1.4		Decreased serum T4 (ED_{50})
					Immuno		10		Decreased relative thymus weight (ED_{50})
Simanainen et al. 2002									**1,2,3,4,7,8-HxCDD**
17	Rat Hans/Wistar 9–11 F	Once (GO)	0, 0.3–300	BW, OW, OF	Bd wt			390	Decreased body weight (ED_{50})
					Musc/skel		64		ED_{50} for incisor tooth defects
					Endocr		5.1		Decreased serum T4 (ED_{50})
					Immuno		14		Decreased relative thymus weight (ED_{50})

Table 2-3. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Simanainen et al. 2002									**1,2,3,4,6,7,8-HpCDD**
18	Rat Hans/Wistar 9–11 F	Once (GO)	0, 0.3–3,000	BW, OW, OF	Bd wt			2,500	Decreased body weight (ED_{50})
					Musc/skel		760		ED_{50} for incisor tooth defects
					Endocr		99		Decreased serum T4 (ED_{50})
					Immuno		610		Decreased relative thymus weight (ED_{50})
Stahl et al. 1992									**1,2,3,7,8-PeCDD**
19	Rat (Sprague-Dawley) 5–10 M	Once (GO)	0, 100, 150, 200, 300	BW, LE	Death			206	LD_{50}
Stahl et al. 1992									**1,2,3,4,7,8-HxCDD**
20	Rat (Sprague-Dawley) 5–10 NS	1 day, 2 times/day (GO)	0, 700, 1,000, 1,400	BW, LE	Death			887	LD_{50}
Stahl et al. 1992									**1,2,3,4,6,7,8-HpCDD**
21	Rat (Sprague-Dawley) 5–10 NS	1 day, 4 times/day (GO)	0, 300, 5,000, 8,000	BW, LE	Death			6,325	LD_{50}
Ao et al. 2009									**1,2,3,7,8-PeCDD**
22	Mouse (C57BL/6J) 5 F	Once (GO)	0, 1.0, 3.0, 10, 50	OW, IX	Immuno		1		Suppressed IL-5 production in response to OVA exposure
Courtney 1976									**OCDD**
23	Mouse (CD-1) 6 F	GDs 7–16 (GO)	0, 5, 20	BW, OW, DX	Develop	20			

Table 2-3. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Courtney 1976									**1,2,3,4-TCDD**
24	Mouse (CD-1) 4–15 F	GDs 7–16 (GO)	0, 100, 250, 500, 1,000	BW, OW, DX	Develop	1,000			
Holsapple et al. 1986									**OCDD**
25	Mouse (B6C3F1) 5–9 F	14 days, 1 time/day (GO)	0, 1, 10	BI	Immuno	10			
Holsapple et al. 1986									**2,7-DCDD**
26	Mouse (B6C3F1) 5–9 F	14 days (GO)	0, 0.1, 1, 10	BI	Hepatic	10			
					Immuno		0.1		Suppressed antibody response to sRBC
Kerkvliet and Brauner 1987									**1,2,3,4,6,7,8-HpCDD**
27	Mouse (C57B1/6) 3–12 B	Once (GO)	0, 20, 100, 500	IX	Immuno		20		Decreased splenic antibody response to sRBC
McConnell et al. 1978b									**1,2,3,7,8-PeCDD**
28	Mouse (C57BL/6) 6–9 M	Once (GO)	NS	BW, GN, HP, CS, LE	Death			337.5	LD_{50}
McConnell et al. 1978b									**1,2,3,4,7,8-HxCDD**
29	Mouse (C57BL/6) 6–9 M	Once (GO)	NS	BW, GN, HP, CS, LE	Death			825	LD_{50}
McConnell et al. 1978b									**1,2,3,6,7,8-HxCDD**
30	Mouse (C57BL/6) 6–9 M	Once (GO)	NS	BW, GN, HP, CS, LE	Death			1,250	LD_{50}

Table 2-3. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NCI/NTP 1980									**1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD mixture**
31	Mouse (B6C3F1) 4 M, 4 F	Once (GO)	500–10,000	LE	Death			500 F	LD_{50}
								750 M	LD_{50}
White et al. 1986									**1,2,3,6,7,8-HxCDD**
32	Mouse (B6C3F1) 6–8 F	14 days (GO)	0, 0.1, 1.0, 10	BC, CS, BI	Immuno	0.1	1		Suppressed serum complement activity
McConnell et al. 1978b									**1,2,3,4,7,8-HxCDD**
33	Guinea pig (Hartley) 6–9 M	Once (GO)	NS	BW, GN, HP, CS, LE	Death			72.5	LD_{50}
McConnell et al. 1978b									**1,2,3,7,8-PeCDD**
34	Guinea pig (Hartley) 6–9 M	Once (GO)	NS	BW, GN, HP, CS, LE	Death			3.1	LD_{50}
McConnell et al. 1978b									**2,3,7-TrCDD**
35	Guinea pig (Hartley) 6–9 M	Once (GO)	NS	BW, GN, HP, CS, LE	Death			29,444	LD_{50}
McConnell et al. 1978b									**1,2,3,6,7,8-HxCDD**
36	Guinea pig (Hartley) 6–9 M	Once (GO)	NS	BW, GN, HP, CS, LE	Death			70	LD_{50}
McConnell et al. 1978b									**1,2,4,7,8-PeCDD**
37	Guinea pig (Hartley) 6–9 M	Once (GO)	NS	BW, GN, HP, CS, LE	Death			1,125	LD_{50}

Table 2-3. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE									
Couture et al. 1988									**OCDD**
38	Rat (Fischer-344) 5 M	4–13 weeks, 5 days/week (GO)	0, 36	BC, BI	Hemato		36		Increased lymphocytes, decreased MCH, MCV, HGB
					Hepatic		36		Cytoplasmic vacuolization
NCI/NTP 1980									**1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD mixture**
39	Rat 10 M, 10 F	13 weeks, 1 day/week (GO)	0, 0.36, 0.71, 1.4, 7.1, 14	BW, CS, HP	Bd wt	0.36	0.71		13–18% decreased body weight gain
					Hemato	1.4	7.1		Splenic hyperplasia
					Hepatic	1.4	7.1 M		Moderate hepatotoxicity
Viluksela et al. 1994									**1,2,3,4,6,7,8-HpCDD**
40	Rat (Sprague-Dawley) 20 M	13 weeks, 10 doses (GO)	0, 0.3, 4, 24, 73, 110	BW, LE, HE, OW, BI, BC	Death			110	50% mortality; first death on day 31
					Bd wt	24	73	110	LOAEL: 13% decrease in body weight gain SLOAEL: 48% decrease in body weight gain
					Hemato	24	73		Decrease in platelet count
					Hepatic	0.3	4		Increased relative liver weight and EROD activity
					Endocr	4	24		Decrease in serum total T4
					Immuno	0.3	4		Decrease in absolute and relative thymus weight

Table 2-3. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Viluksela et al. 1998a, 1998b									**1,2,3,7,8-PeCDD**
41	Rat (Sprague-Dawley) 20 M, 20 F	13 weeks, 10 doses (GO)	M: 0, 3.8; F: 0, 2.6	BW, LE, HE, BC, BI, CS	Death			2.6 F	15/20 died during treatment period; first death on day 16
					Bd wt		2.6 F		Body weight reduced by 18% relative to controls at the end of dosing period
								3.8 M	Body weight reduced by 27% relative to controls at the end of dosing period
					Hemato		2.6 F		Decreased hematocrit; reduced platelet count
					Dermal		2.6 F		Occasional hair loss; sores in ears, nose, neck, tail, and feet
					Endocr		3.8 M		69% decrease in serum T4
Viluksela et al. 1998a, 1998b									**1,2,3,4,7,8-HxCDD**
42	Rat (Sprague-Dawley) 20 M, 20 F	13 weeks, 10 doses (GO)	M: 0, 15.4; F: 0, 10.3	BW, LE, HE, BI, BC, CS	Death			10.3 F	5/20 died during treatment period; first death on day 61
					Bd wt	10.3 F			
								15.4 M	Body weight reduced by 24% relative to controls at the end of dosing period
					Hemato		10.3 F		Decreased hematocrit; reduced platelet count
					Dermal		10.3 F		Occasional hair loss; sores in ears, nose, neck, tail, and feet
					Endocr		15.4 M		69% decrease in serum T4

Table 2-3. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NCI/NTP 1980									**1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD mixture**
43	Mouse (B6C3F1) 10 M, 10 F	13 weeks, 1 day/week (GO)	0, 0.18, 0.36, 0.71, 1.4, 7.1	BW, HP, CS	Bd wt		0.18		13–17% decreased weight gain
					Hepatic	0.71	1.4		Mild hepatotoxicity
CHRONIC EXPOSURE									
NCI/NTP 1979									**2,7-DCDD**
44	Rat (Osborne-Mendel) 35 M, 35 F	110 weeks, 7 days/week (F)	0, 250,000, 500,000	BW, GN, HP, CS	Bd wt		250,000		17% decreased body weight gain
					Resp	500,000			
					Cardio	500,000			
					Gastro	500,000			
					Hemato	500,000			
					Musc/skel	500,000			
					Hepatic		250,000		Fatty changes
					Renal	500,000			
					Dermal	500,000			
NCI/NTP 1980									**1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD mixture**
45	Rat (Osborne-Mendel) 50–75 M	104 weeks, 2 days/week (GO)	0, 0.18, 0.34, 0.7	BW, OW, GN, HP, CS	Bd wt			0.18	38% decreased weight gain
					Resp		0.18		Adenomatous hyperplasia of the lungs
					Cardio	0.7			
					Gastro	0.7			
					Hemato	0.7			
					Musc/skel	0.7			
					Hepatic		0.18		Toxic hepatitis (lipidosis, mild fibrosis, bile duct hyperplasia)
					Renal	0.7			

Table 2-3. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Dermal	0.7			
					Cancer			0.34	CEL: hepatocellular carcinoma or liver neoplastic nodules
NCI/NTP 1979									**2,7-DCDD**
46	Mouse (B6C3F1) 50 M, 50 F	90 weeks, 7 days/week (F)	0, 650,000, 1,300,000	BW, GN, HP, CS	Bd wt		650,000		16% decreased body weight gain
					Resp	1,300,000			
					Cardio	1,300,000			
					Gastro	1,300,000			
					Hemato	1,300,000			
					Musc/skel	1,300,000			
					Hepatic	650,000 F	1,300,000 F		Focal necrosis
					Renal	1,300,000			
					Dermal	1,300,000			
					Cancer			650,000 M	CEL: hepatocellular carcinoma or adenoma, lymphoma, leukemia, hemangiosarcomas
NCI/NTP 1980									**1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD mixture**
47	Mouse (B6C3F1) 50–75 M	104 weeks, 2 days/week (GO)	M: 0, 0.18, 0.34, 0.7; F: 0, 0.34, 0.7, 1.4	BW, OW, GN, HP, CS	Bd wt	1.4			
					Resp	1.4			
					Cardio	1.4			
					Gastro	1.4			
					Hemato	1.4			
					Musc/skel	1.4			

Table 2-3. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral (µg/kg/day)[a]

Figure key[b]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic		0.7		Toxic hepatitis (degenerative hepatocellular changes and/or necrosis associated with mild fibrosis)
					Renal	1.4			
					Dermal	1.4			
					Cancer			0.7	CEL: hepatocellular carcinomas and adenomas

[a]Doses adjusted for intermittent exposure.
[b]The number corresponds to entries in Figure 2-5; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-5. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

B = both males and females; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; DCDD = dichlorodibenzo-*p*-dioxin; Develop = developmental; DX = developmental toxicity; ED_{50} = median effective dose; Endocr = endocrine; EROD = 7-ethoxy-resorufin-O-deethylase; (F) = feed; F = female(s); (G) = gavage; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil; HE = hematology; Hemato = hematological; HGB = hemoglobin; HP = histopathology; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; IL = interleukin; Immuno = immunological; IX = immune function; LD_{50} = median lethal dose; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MCDD = monochlorodibenzo-*p*-dioxin; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OCDD = octachlorodibenzo-*p*-dioxin; OF = organ function; OVA = ovalbumin; OW = organ weight; PeCDD = pentachlorodibenzo-*p*-dioxin; Repro = reproductive; Resp = respiratory; RX = reproductive function; sRBC = sheep red blood cell; SLOAEL = serious lowest-observed-adverse-effect level; T4 = thyroxine; TCDD = tetrachlorodibenzo-*p*-dioxin;

Figure 2-5. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral
Acute (≤14 days)

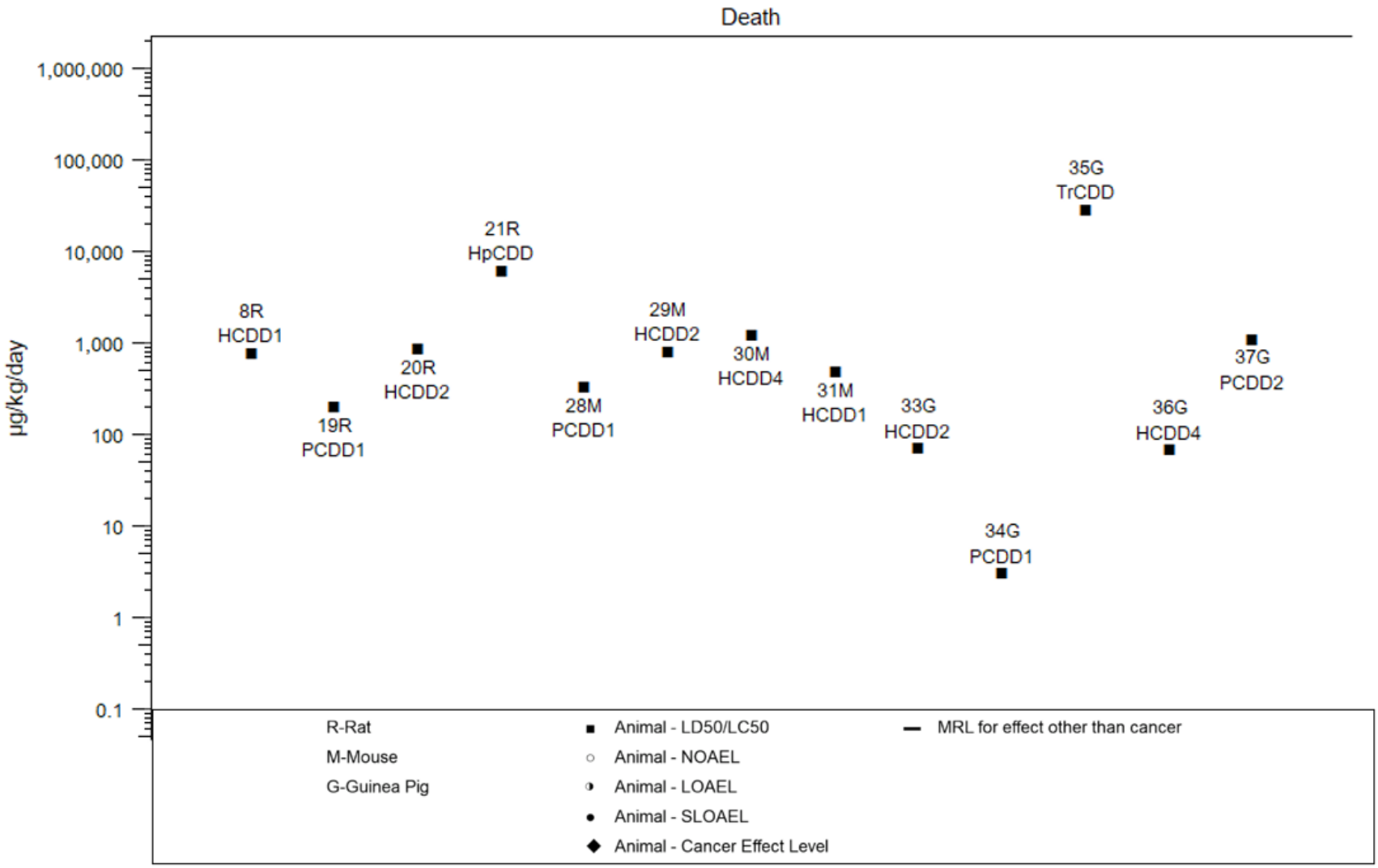


Figure 2-5. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral
Acute (≤14 days)

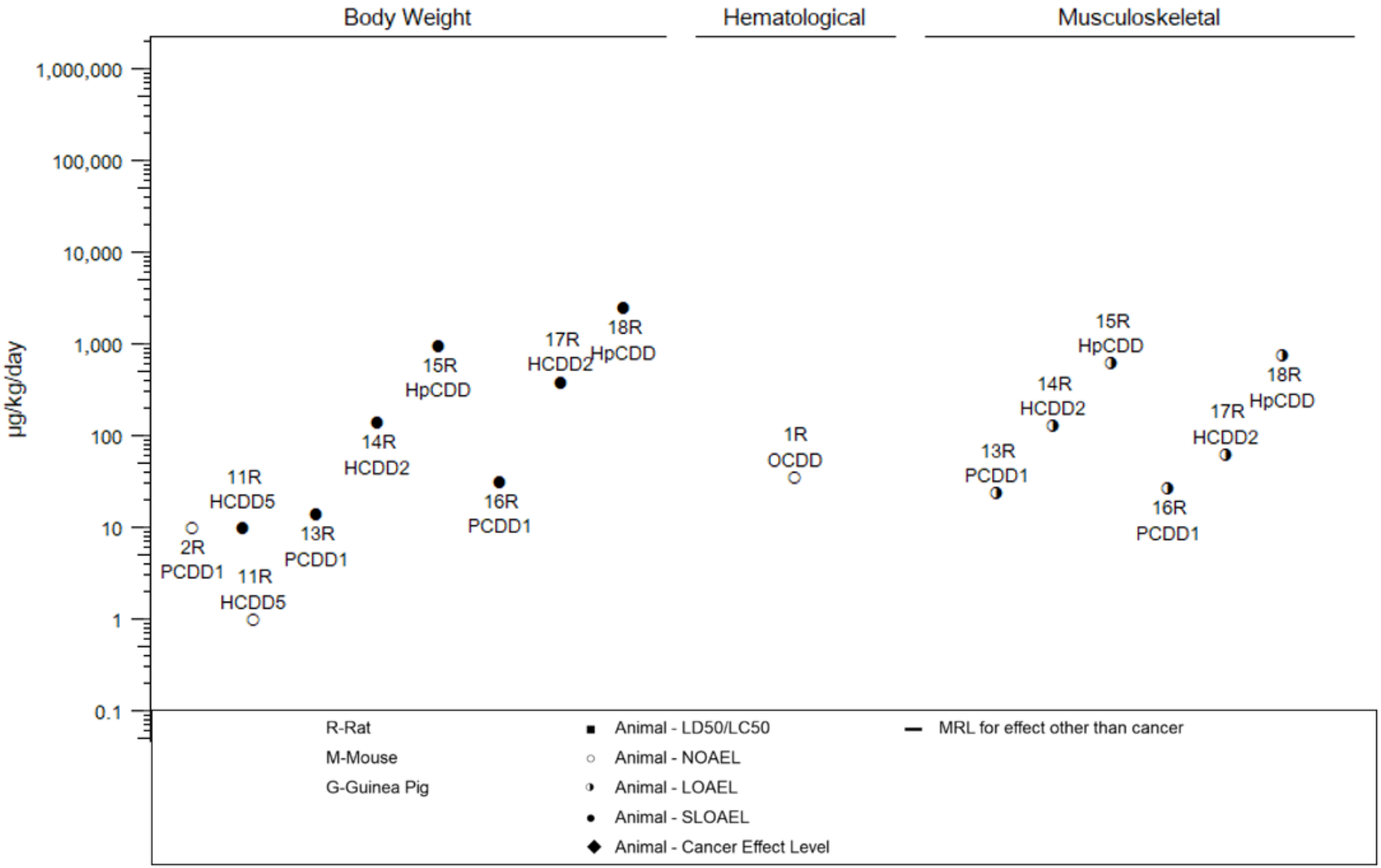


Figure 2-5. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral
Acute (≤14 days)

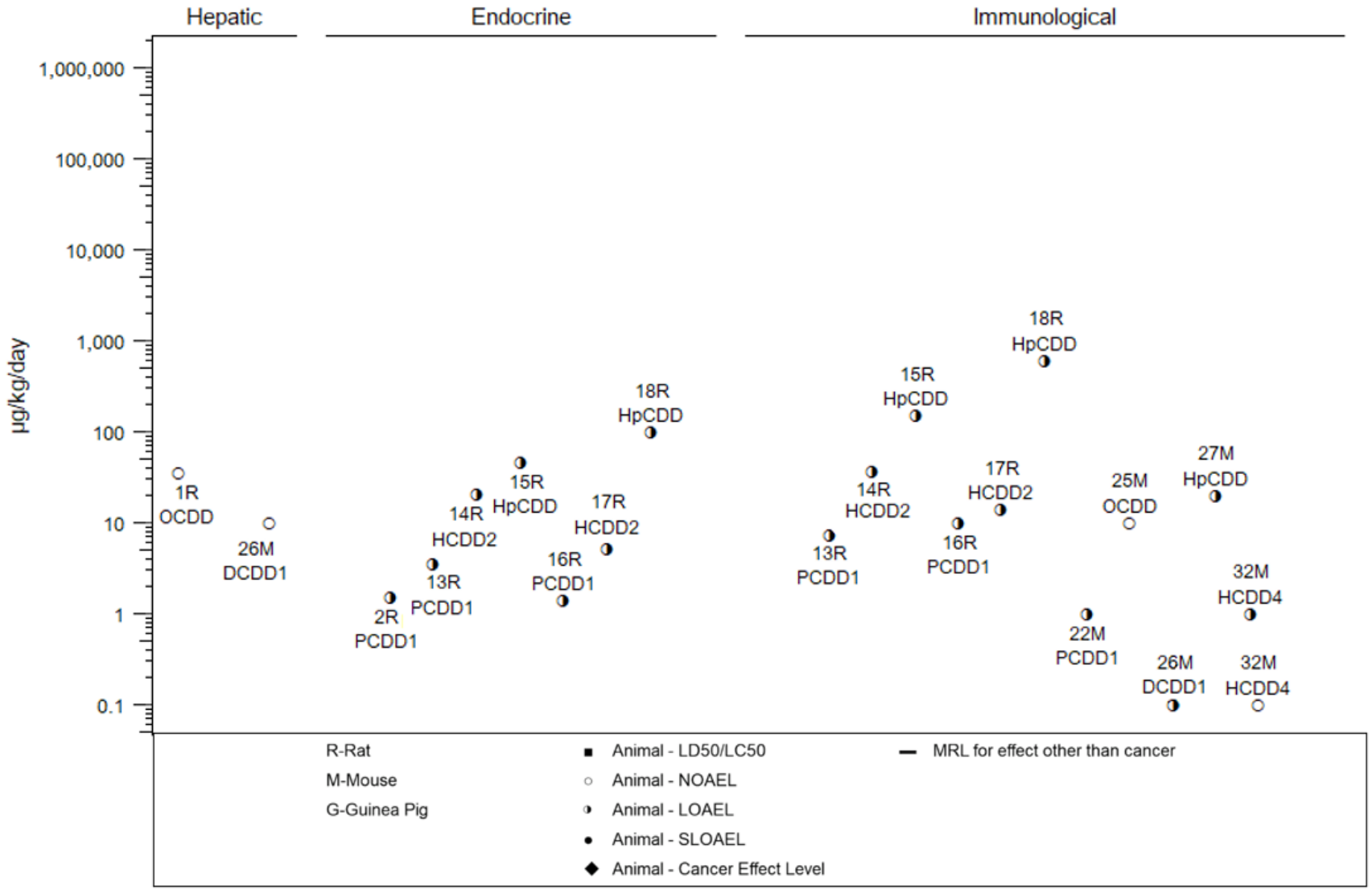


Figure 2-5. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral
Acute (≤14 days)

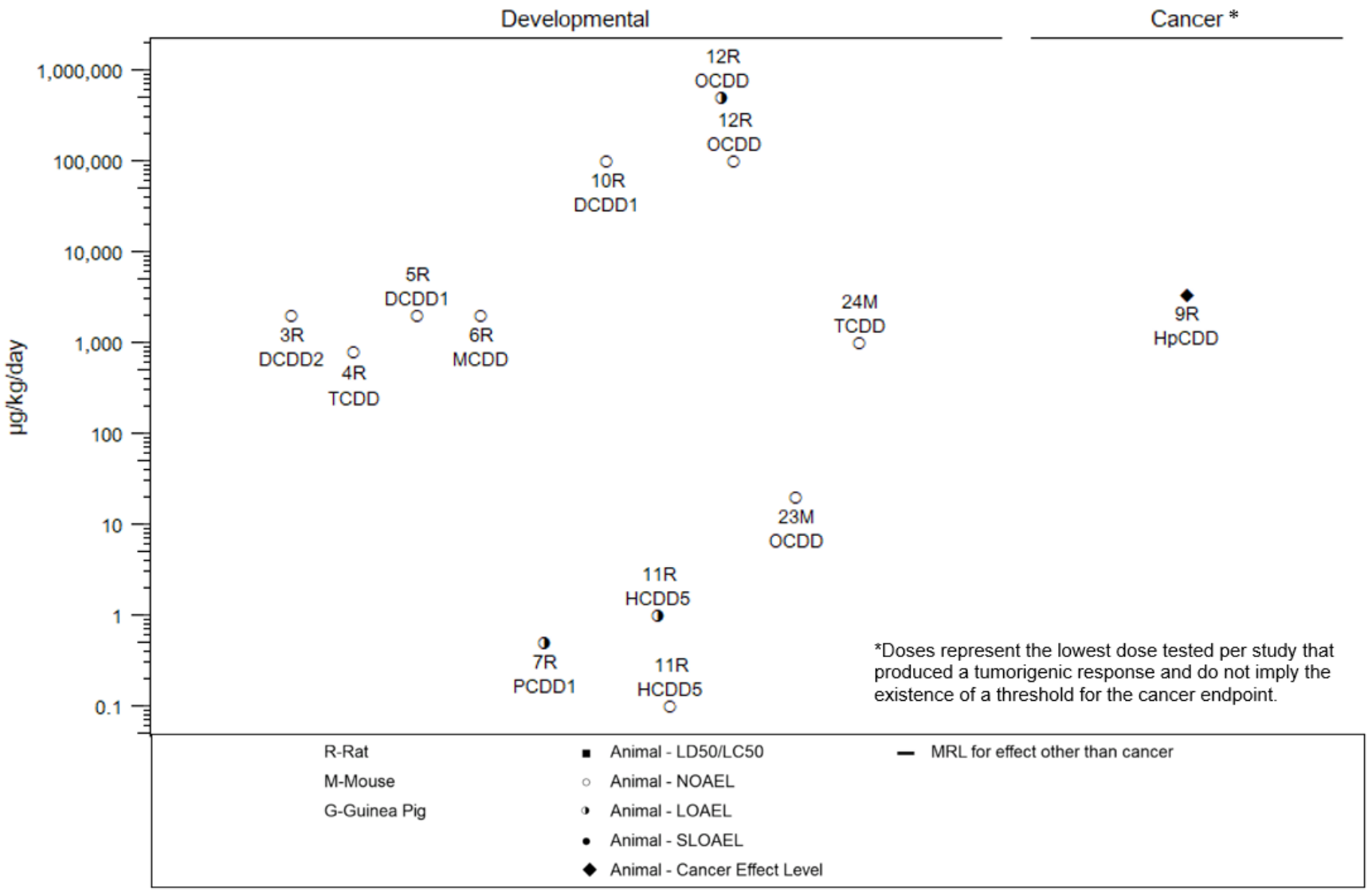


Figure 2-5. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral
Intermediate (15–364 days)

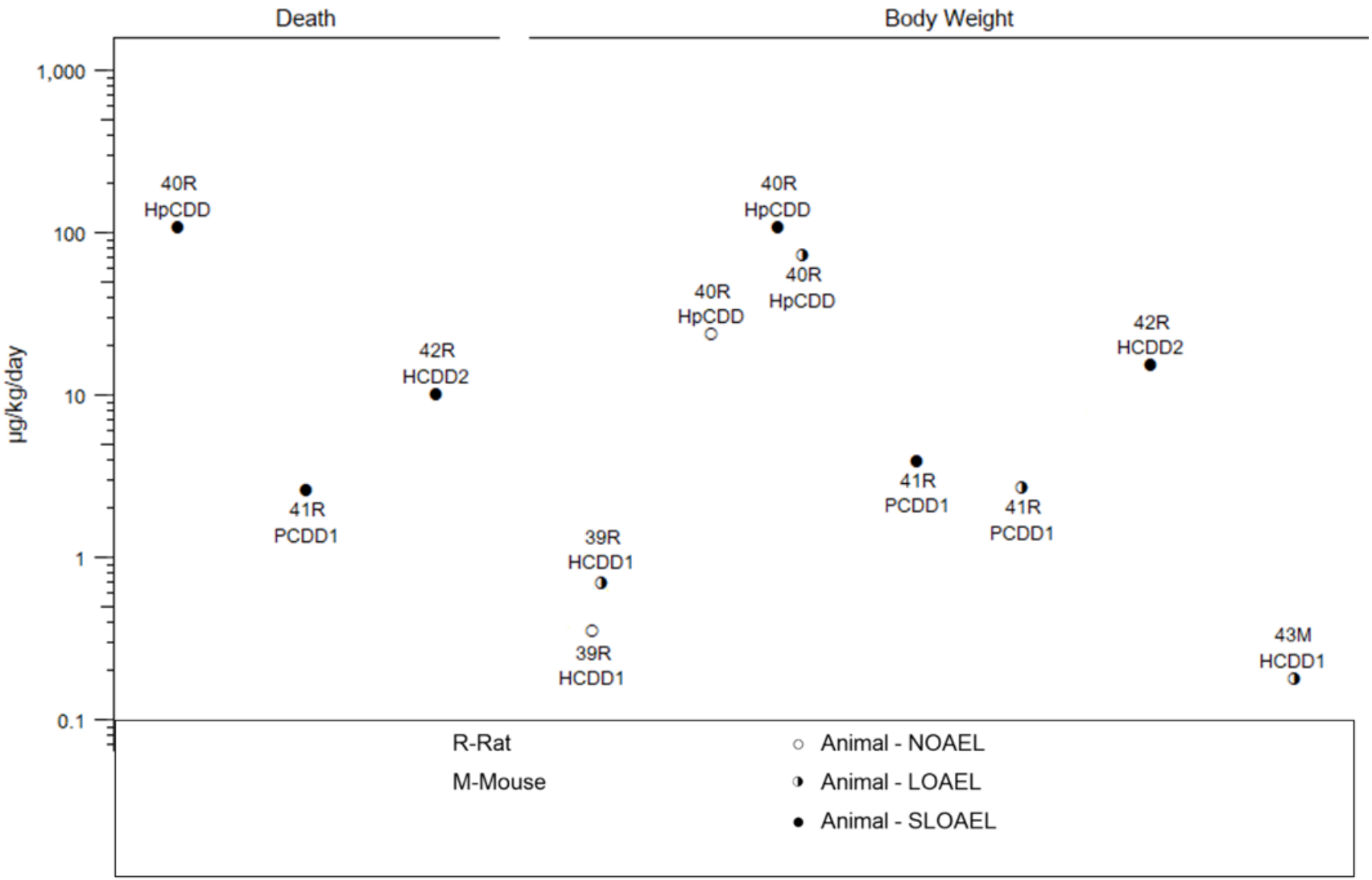


Figure 2-5. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral
Intermediate (15–364 days)

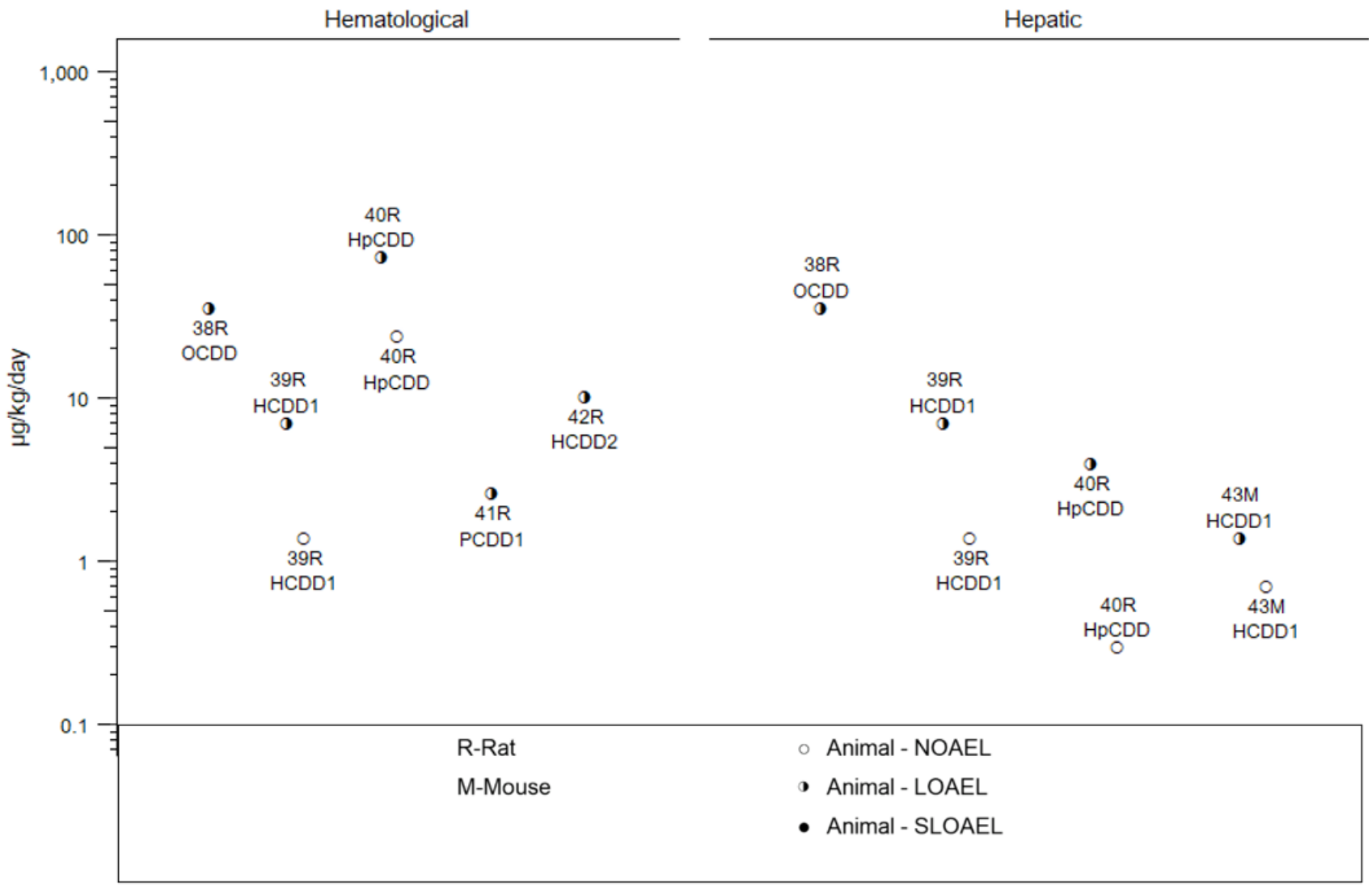


Figure 2-5. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral
Intermediate (15–364 days)

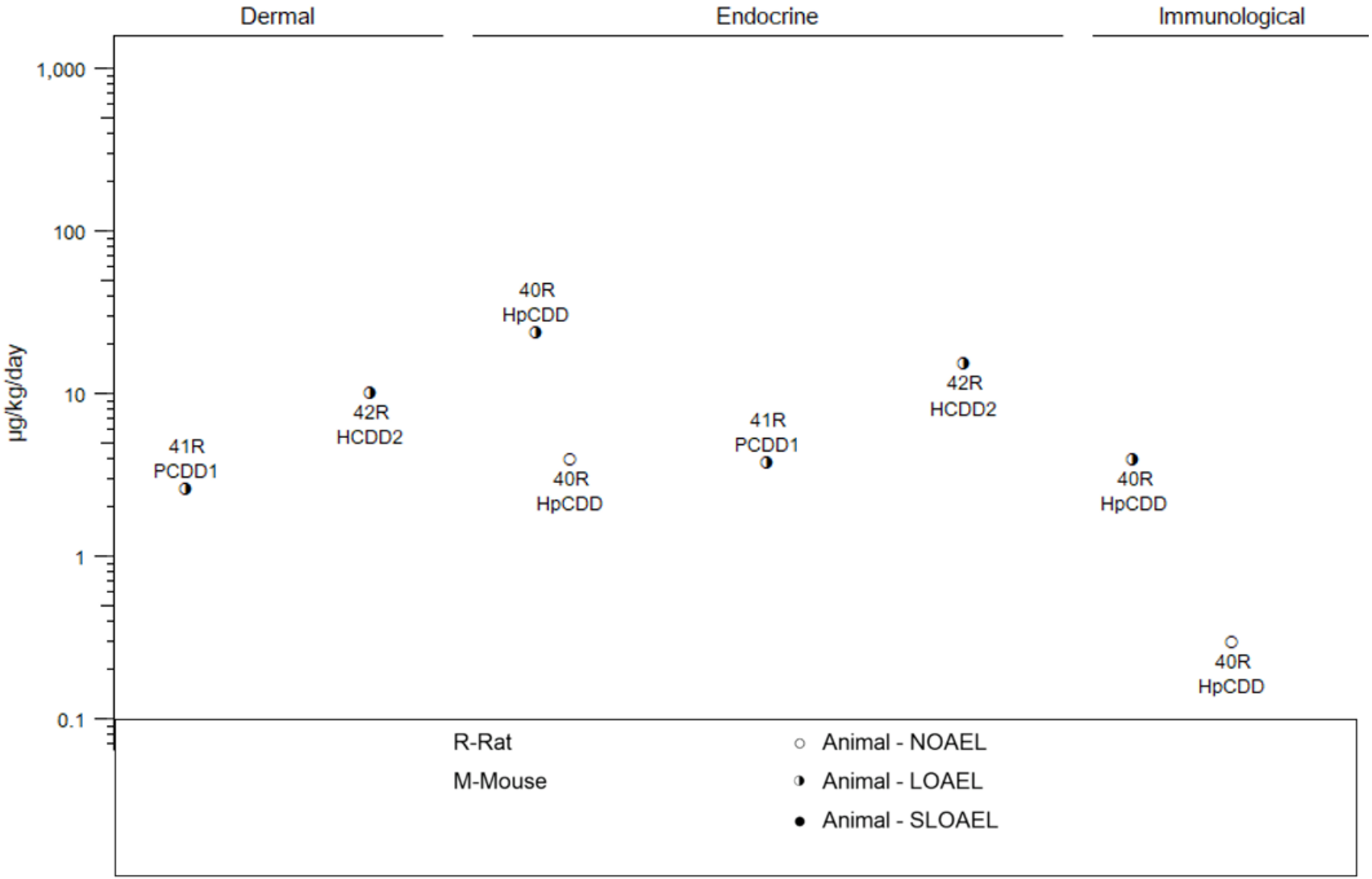


Figure 2-5. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral
Chronic (≥365 days)

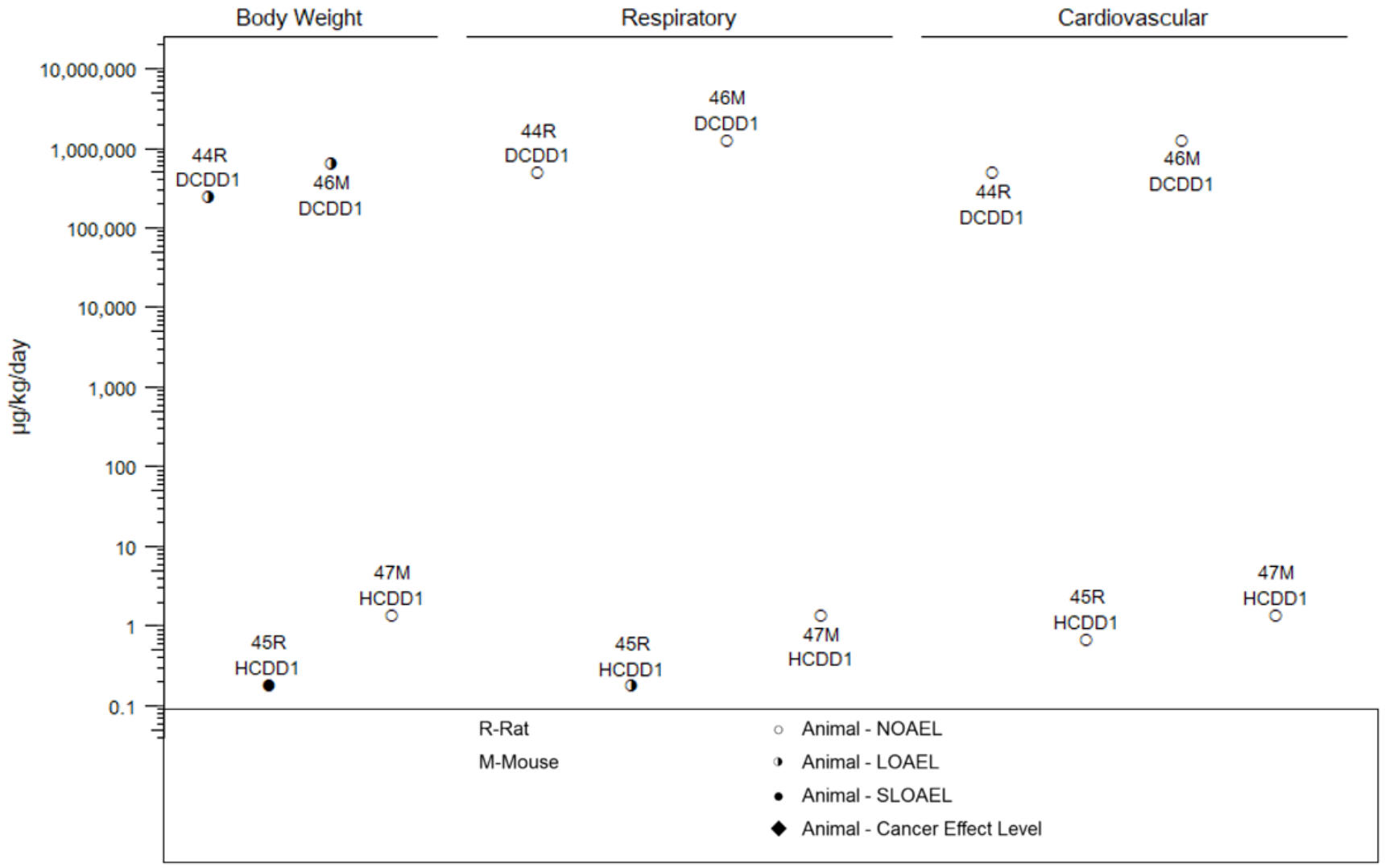


Figure 2-5. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral
Chronic (≥365 days)

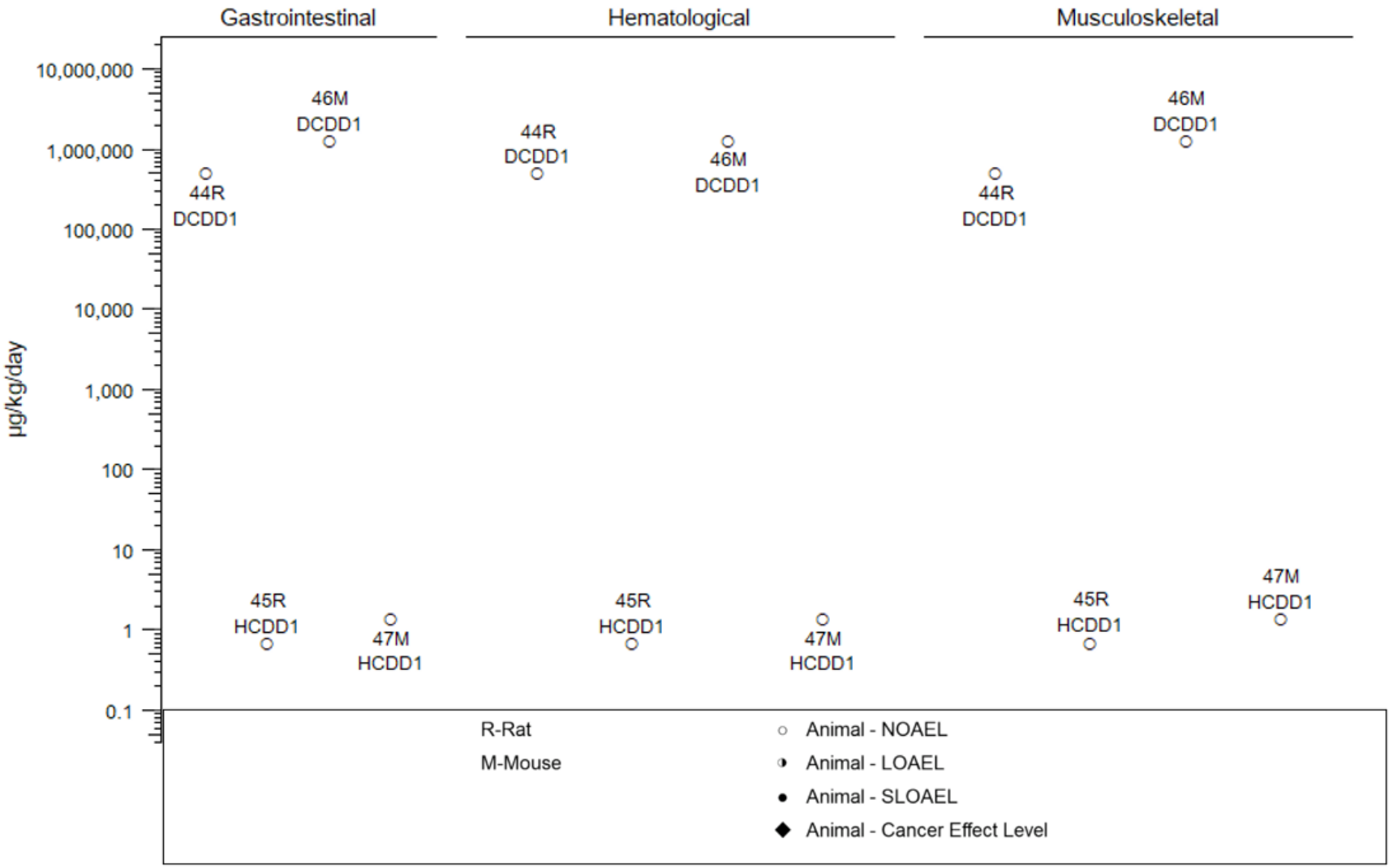


Figure 2-5. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral
Chronic (≥365 days)

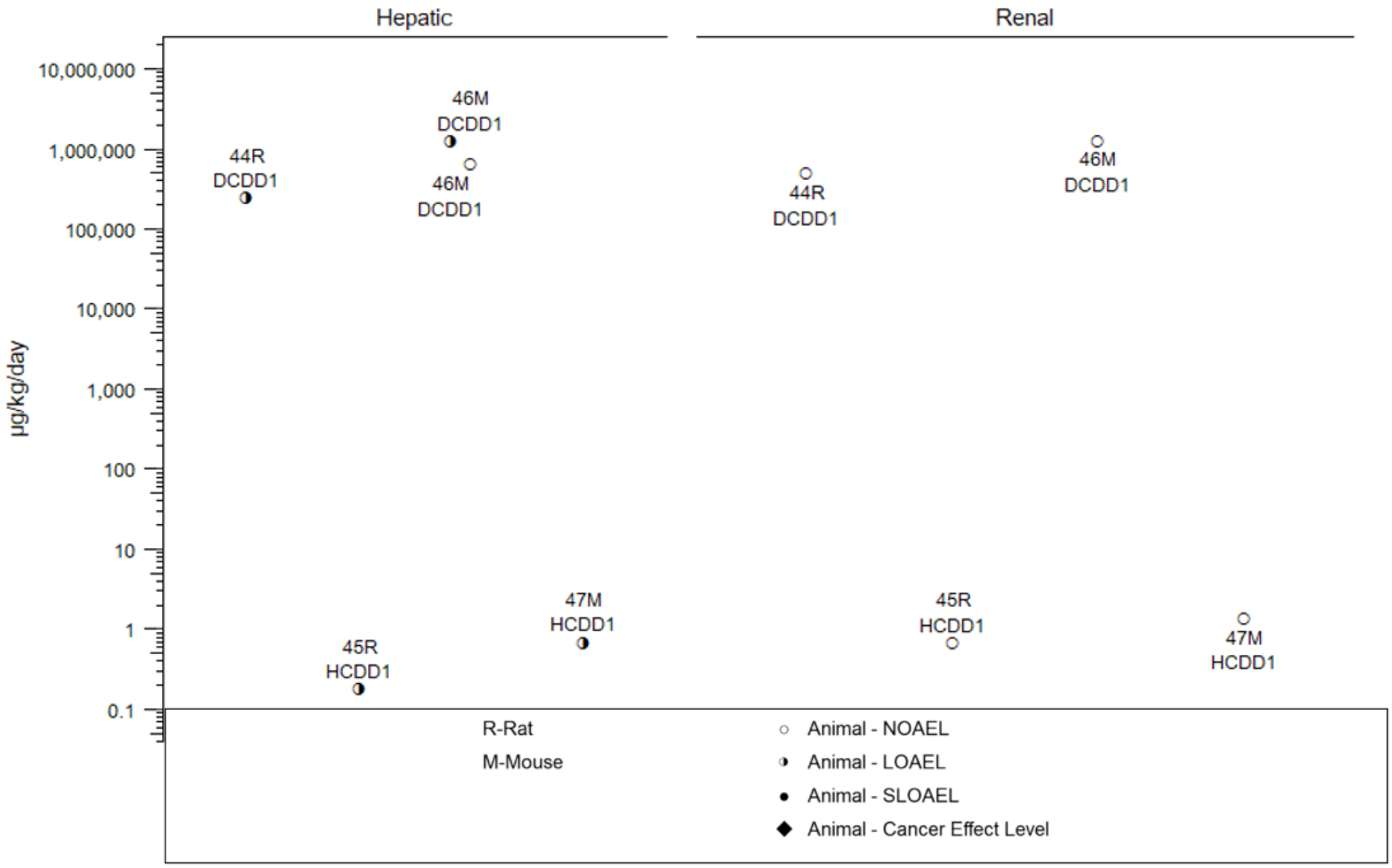


Figure 2-5. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Oral
Chronic (≥365 days)

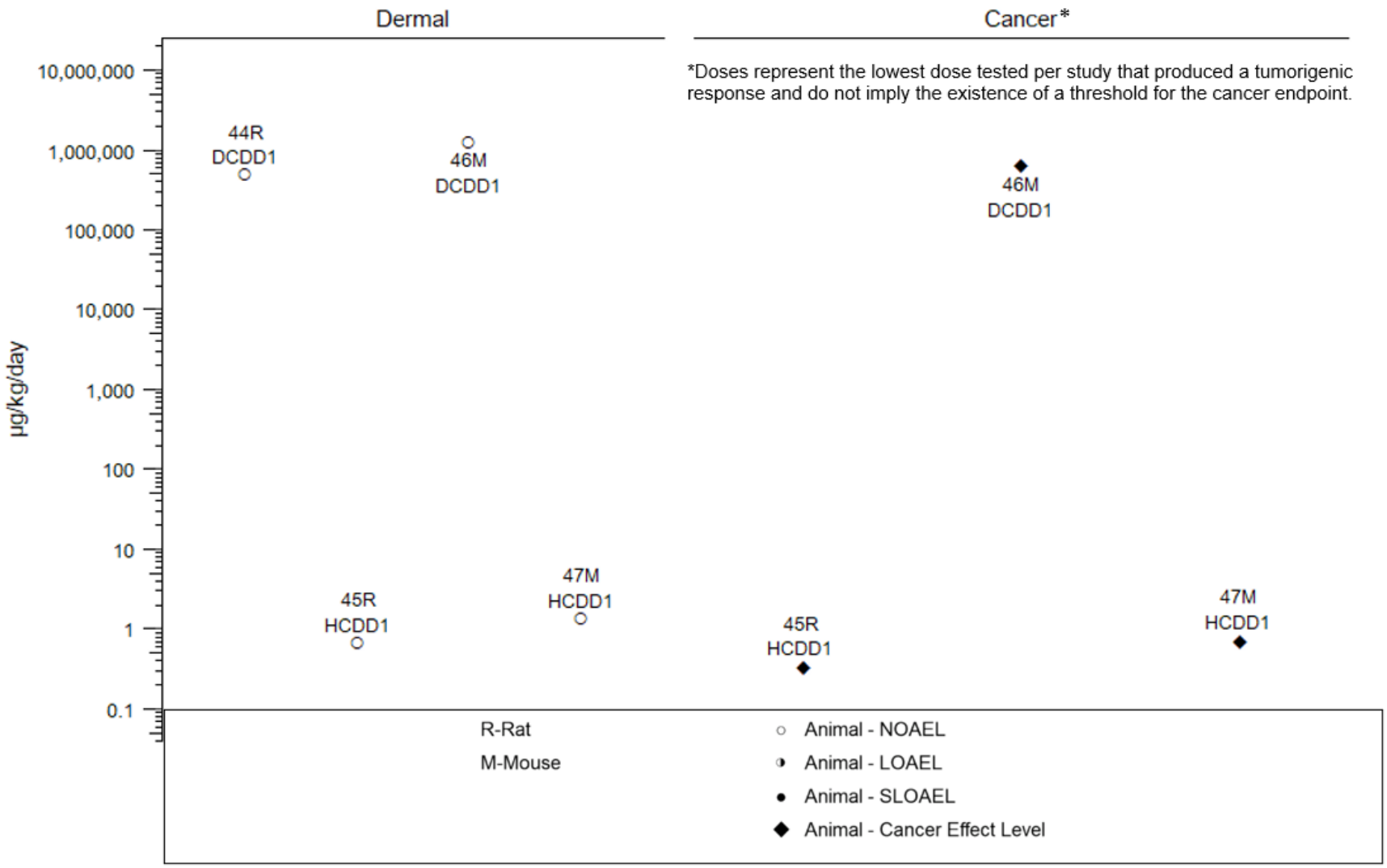


Table 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Puhvel and Sakamoto 1988								**2,3,7,8-TCDD**
Mouse (HRS/J) 5 F	2 weeks, 3 days/week	0, 0.01, 0.1 µg	HP, CS, BI	Dermal		0.01		LOAEL: Epidermal hyperkeratosis and hyperplasia and involution of sebaceous glands in newborns LOAEL: Epidermal hyperkeratosis and hyperplasia and involution of sebaceous glands in adults
Schwetz et al. 1973								**2,3,7,8-TCDD**
Rabbit (NS) NS B	Once	31.6, 63, 126, 252, 500 µg/kg	CS, LE	Death			275	LD50
Schwetz et al. 1973								**2,3,7,8-TCDD**
Rabbit (NS) NS	Once	2,000 µg	CS	Ocular		2,000		Transient inflammation of conjunctiva
INTERMEDIATE EXPOSURE								
Berry et al. 1978, 1979								**2,3,7,8-TCDD**
Mouse (CD-1) 30 F	30 weeks, 2 days/week	0.1 µg	HP	Dermal		0.1		Acne-like lesion
Hebert et al. 1990								**2,3,7,8-TCDD**
Mouse (HRS/J hairless) 20 F	20 weeks, 2 days/week	0, 0.0025, 0.005, 0.010 µg	BW, OW, HP, CS	Bd wt		0.01		16% decreased body weight gain
				Hepatic		0.0025		Increased relative liver weight
				Immuno	0.005	0.01		Decreased thymus/ body weight ratio in non-initiated mice
				Cancer			0.0025	Increased number of skin squamous cell papilloma and hyperproliferative nodules

Table 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Hebert et al. 1990								**2,3,7,8-TCDD**
Mouse (HRS/J) 20 F	20 weeks, 2 days/week	0, 0.010 µg	BW, OW, HP	Hepatic		0.01		Hypertrophy
NTP 1982a								**2,3,7,8-TCDD**
Mouse (Swiss-Webster) 10 M, 10 F	13 weeks, 3 days/week	0, 0.005, 0.01, 0.05, 0.1, 0.625, 1.25, 2.5, 5, 10 µg	BW, GN, HP, CS, LE	Death			0.625	50% died in both sexes
				Resp	0.01	0.05		Bronchiolar adenomatoid changes with hyperplasia
				Hepatic		0.005 M		Fatty degeneration
Poland et al. 1982								**2,3,7,8-TCDD**
Mouse (HRS/J hairless) 20 F	20 weeks, 2 days/week	0, 0.00375, 0.0075, 0.015, 0.030 µg	HP, CS	Cancer			0.00375	Skin papilloma following initiation
Poland et al. 1984								**2,3,7,8-TCDD**
Mouse (Hybrid) NS B	4 weeks, 1 day/week	0.3 µg	HP, CS	Dermal		0.3		Epidermal hyperplasia, hyperkeratosis and keratinized cyst formation in hairless mutants
Poland et al. 1984								**2,3,7,8-TCDD**
Mouse (DBA/2J) NS B	4 weeks, 1 day/week	1.0 µg	HP, CS	Dermal		1		Epidermal hyperplasia, hyperkeratosis and keratinized cyst formation in hairless mutants
Puhvel et al. 1982								**2,3,7,8-TCDD**
Mouse (HRS/J, Skh:HR-1) 3 F	4 weeks, 3 days/week	0, 0.1 µg	BW, HP, CS	Hepatic		0.1		Increased microsomal enzyme-activity
				Dermal		0.1		Hyperkeratosis absence of sebaceous glands

Table 2-4. Levels of Significant Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
CHRONIC EXPOSURE								
NTP 1982a								**2,3,7,8-TCDD**
Mouse (Swiss-Webster) 30–45 M	99–104 weeks, 5 days/week	0, 0.001 µg (M), 0.005 µg (F)	BW, OW, GN, HP, CS, LE	Death			0.001	Decreased probability of survival
				Bd wt	0.005			
				Resp	0.005			
				Cardio	0.005			
				Gastro	0.005			
				Hemato	0.005			
				Hepatic	0.005			
					0.001			
				Renal	0.005			
				Dermal	0.005			
				Repro	0.005			
				Cancer			0.005	CEL: fibrosarcoma without initiation

B = both males and females; Bd wt or BW = body weight; BI = biochemical changes; CEL = cancer effect level; Cardio = cardiovascular; CS = clinical signs; F = female(s); Gastro = gastrointestinal; GN = gross necropsy; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = median lethal dose; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; Repro = reproductive; Resp = respiratory

Table 2-5. Levels of Significant Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Schwetz et al. 1973								**HxCDD, unspecified mixture**
Rabbit (NS) NS	Once	2,000 µg	CS	Ocular		2,000		Transient inflammation of conjunctiva
Schwetz et al. 1973								**OCDD**
Rabbit (NS) NS	Once	2,000 µg	CS	Ocular		2,000		Transient inflammation of conjunctiva
Schwetz et al. 1973								**2,7-DCDD**
Rabbit (NS) NS	Once	2,000 µg	CS	Ocular		2,000		Transient inflammation of conjunctiva

CS = clinical signs; DCDD = dichlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; OCDD = octachlorodibenzo-*p*-dioxin

2.2 DEATH

Overview. Epidemiological studies evaluating possible associations between dioxin exposure and cause-specific deaths are discussed in subsequent sections of Chapter 2; this section reviews studies examining all-cause mortality. Studies have evaluated all-cause mortality in several populations, including workers at phenoxy herbicide or chlorophenol manufacturing facilities, workers exposed to 2,3,7,8-TCDD as a result of an accident, the Seveso population, and Vietnam veterans. Most studies have not found increases in all-cause mortality.

Oral exposure studies have estimated LD_{50} (lethal dose, kill for 50% of dosed animals during a certain time interval) values in several species (and strains) of animals exposed to 2,3,7,8-TCDD and several other congeners. The oral LD_{50} values for 2,3,7,8-TCDD differ between species and strains, and range from 0.6 µg/kg in Hartley guinea pigs to >3,000 µg/kg in DBA/2J mice and 5,051 µg/kg in Syrian hamsters. In all species tested, a pronounced wasting syndrome was the major contributor to death. Increases in mortality or decreased survival have also been reported in animals following intermediate- or chronic-duration oral exposure to 2,3,7,8-TCDD. Dermal exposure studies with 2,3,7,8-TCDD have also reported increased mortality following acute-duration exposure in rats (LD_{50} value of 275 µg/kg) and intermediate- and chronic-duration exposures in mice.

LD_{50} values have also been estimated in rats, mice, and guinea pigs exposed to several different CDD congeners. Studies in Sprague-Dawley rats allow for a comparison of LD_{50} values for other CDD congeners; the LD_{50} values decreased as the number of chlorine atoms increased with 1,2,3,7,8-PeCDD being the most lethal and OCDD being the least lethal. A comparison of LD_{50} values provides evidence that 2,3,7,8-TCDD is the most lethal of all the congeners tested and OCDD was the least lethal as tested animals survived very high doses. For example, the LD_{50} values in Sprague-Dawley rats were 43 µg/kg for 2,3,7,8-TCDD, 206 µg/kg for 1,2,3,7,8-PeCDD, 887 µg/kg for 1,2,3,4,7,8-HxCDD, 6,325 µg/kg for 1,2,3,4,6,7,8-HpCDD, and >1,000,000 ($1x10^6$) µg/kg for OCDD. Studies in guinea pigs suggest that the 2,3,7,8-substituted congeners were more lethal; for example, the LD_{50} values were 3.1 µg/kg for 1,2,3,7,8-PeCDD and 1,125 µg/kg for 1,2,4,7,8-PeCDD. In an intermediate-duration oral study, the serious LOAELs for death were lowest for 1,2,3,7,8-PeCDD followed by 1,2,3,4,7,8-HxCDD and 1,2,3,4,6,7,8-HpCDD.

Epidemiological Studies. None of the studies examining humans acutely exposed to high concentrations of 2,3,7,8-TCDD or other CDD congeners (as contrasted with long-term studies) reported acute instances

of death. A number of epidemiology studies have investigated mortality in populations occupationally or environmentally exposed to 2,3,7,8-TCDD or chemicals contaminated with 2,3,7,8-TCDD or other CDD congeners. Several studies reported increased mortality following dioxin exposure linked to specific health effects; these are discussed in subsequent sections of this chapter. No significant increases in the number of all-cause deaths were observed in workers at phenoxy herbicide or chlorophenol manufacturing facilities (Collins et al. 2016; Cook et al. 1986, 1987; Fingerhut et al. 1991; McBride et al. 2009, 2018; Ott et al. 1980, 1987; Zack and Suskind 1980) or in workers exposed to 2,3,7,8-TCDD as a result of the accident at the BASF AG facility in Germany (Ott and Zober 1996; Thiess et al. 1982; Zober et al. 1990). Additionally, no increases in mortality were observed in the 10-year period after the Seveso accident (Bertazzi et al. 1989b) or in Vietnam veterans involved in Operation Ranch Hand (Ketchum and Michalek 2005; Wolfe et al. 1985). In a study of chemical manufacturing workers, an increase in the risk of all-cause mortality was observed in male workers, but not in female workers (Manuwald et al. 2012). The median cumulative job exposure to 2,3,7,8-TCDD was higher in males (77.4 ppt) than in females (19.5 ppt).

2,3,7,8-TCDD—Animal Studies. Numerous studies provided doses associated with death following exposure to 2,3,7,8-TCDD in animals. LD_{50} values varied not only across species, but also among different strains of the same species. A summary of the LD_{50} values following a single oral dose of 2,3,7,8-TCDD is presented in Table 2-6; these data are not presented in the LSE table or figure (Table 2-2 and Figure 2-4). These results suggest that guinea pigs were the most sensitive species, while hamsters were the most resistant (up to 5,000 times greater lethal doses). The animals died following a latency period of several days (mean values varied from 9 to 43 days). In almost all laboratory animals, a pronounced wasting syndrome appears to be a major contributor to lethality.

Table 2-6. LD_{50} Values in Laboratory Animals Following a Single Oral Dose of 2,3,7,8-TCDD

Species (strain)	LD_{50} (µg/kg)	Reference
Sherman rat	22 (M) 45 (F)	Schwetz et al. 1973
Sprague-Dawley rat	43 (M)	Stahl et al. 1992
Long-Evans rat	60 (M) 100 (F)	Fan and Rozman 1995
Fischer 344 rat	164–340 (M)	Walden and Schiller 1985
Osborne-Mendel rat	165 (M) 125 (F)	NTP 1982b
C57BL mouse	146 (M)	Smith et al. 1981

Table 2-6. LD_{50} Values in Laboratory Animals Following a Single Oral Dose of 2,3,7,8-TCDD

Species (strain)	LD_{50} (µg/kg)	Reference
DBA/2J mouse	>3,000 (M)	Weber et al. 1995
New Zealand rabbit	115	Schwetz et al. 1973
Hartley guinea pig	0.6 (M) 2.1 (F)	Schwetz et al. 1973
Hartley guinea pig	1.75 (M)	McConnell et al. 1984
Hartley guinea pig	2.5 (F)	Silkworth et al. 1982
Syrian hamster	1,157 (M and F)	Olson et al. 1980a
Syrian hamster	5,051 (M)	Henck et al. 1981
Mink	4.2 (M)	Hochstein et al. 1988

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; F = females; LD_{50} = dose calculated to cause death in 50% of animals; M = males

Increases in mortality or decreased survival have been also observed in repeated exposure studies. Increased incidences of early deaths were observed in rats exposed to 1–3 µg/kg/day 2,3,7,8-TCDD for 3–13 weeks (Li and Rozman 1995; NTP 1982b; Van Miller et al. 1977) and in mice exposed to 1.3 µg/kg/day for 25 weeks (Umbreit et al. 1987). As with acute lethality studies, deaths occurred at lower doses in guinea pigs (0.03 µg/kg/day) (DeCaprio et al. 1986) than in rats or mice. Studies in monkeys reported deaths at 0.6 µg/kg/day in pregnant monkeys exposed for 3 weeks (McNulty 1984) and in monkeys exposed to 0.011 µg/kg/day for 9 months (Allen et al. 1977). In chronic-duration studies, increased cumulative mortality was observed in female rats exposed to 0.1 µg/kg/day for 2 years (Kociba et al. 1978) and decreased survival was observed in mice exposed to 0.1 or 1.0 µg/kg/day for 1 year (Della Porta et al. 1987; Toth et al. 1979). No alterations in survival were observed in 2-year studies of male and female rats exposed to 0.071 µg/kg/day or female mice exposed to 0.3 µg/kg/day (NTP 1982b). In all species, severe weight loss and body fat depletion were experienced prior to death, but other overt toxic signs were not typically observed.

Information regarding mortality following dermal exposure to 2,3,7,8-TCDD in animals is limited. A dermal LD_{50} value of 275 µg/kg was estimated in rabbits (Schwetz et al. 1973). Deaths occurred within 12–22 days, but the cause of death was not specifically indicated. Increased mortality was observed in mice exposed 3 days/week to 2,3,7,8-TCDD at 0.6255 µg for 13 weeks (NTP 1982a) and decreased survival was observed in male and female mice exposed to 0.001 µg or 0.005 µg, respectively, for 2 years (NTP 1982a). Increased mortality was observed in male ICR mice exposed twice weekly to 0.125 µg

2,3,7,8-TCDD for 20 weeks (Chang et al. 2005). No increase in lethality was reported in HRS/J hairless mice dermally exposed to 0.0025 µg, 2 days/week for 20 weeks (Hebert et al. 1990).

Other CDD Congeners—Animal Studies. Several studies have evaluated the acute lethality of other CDD congeners in rats, mice, and guinea pigs. The results of these studies are presented in Table 2-7; these data are not summarized in the LSE table or figure (Table 2-3 or Figure 2-5). The LD_{50} values for other CDD congeners increased with the degree of chlorination for PeCDD, HxCDD, and HpCDD. No deaths were observed in rats or mice exposed to at least 1,000,000 µg/kg 2,7-DCDD or OCDD.

Table 2-7. LD_{50} Values in Laboratory Animals Following a Single Oral Dose of Other CDD Congeners

Congener	Species	LD_{50} (µg/kg)	Reference
1,2,3,7,8-PeCDD	Sprague-Dawley rat	206 (M)	Stahl et al. 1992
1,2,3,7,8,9-HxCDD and 1,2,3,6,7,8-HxCDD mixture	Osborne-Mendel rat	1,800 (M) 800 (F)	NCI/NTP 1980
HxCDD (mixture of isomers)	Sprague-Dawley rat	>10,000 (M)	Schwetz et al. 1978
1,2,3,4,7,8-HxCDD	Sprague-Dawley rat	887(M)	Stahl et al. 1992
1,2,3,4,6,7,8-HpCDD	Sprague-Dawley rat	6,325 (M)	Stahl et al. 1992
OCDD	Sprague-Dawley rat	>1,000,000 (F)	Schwetz et al. 1978
2,7-DCDD	Swiss Webster mouse	>2,000,000 (M)	Schwetz et al. 1978
2,3,7-TrCDD	C57BL/6 mouse	>3,000 (M)	McConnell et al. 1978b
1,2,4,7,8-PeCDD	C57BL/6 mouse	>5,000 (M)	McConnell et al. 1978b
1,2,3,7,8-PeCDD	C57BL/6 mouse	337.5 (M)	McConnell et al. 1978b
1,2,3,7,8,9-HxCDD and 1,2,3,6,7,8-HxCDD mixture	B6C3F1 mouse	750 (M) 500 (F)	NCI/NTP 1980
1,2,3,6,7,8-HxCDD	C57BL/6 mouse	1,250 (M)	McConnell et al. 1978b
1,2,3,7,8,9-HxCDD	C57BL/6 mouse	>1,440 (M)	McConnell et al. 1978b
1,2,3,4,7,8-HxCDD	C57BL/6 mouse	825 (M)	McConnell et al. 1978b
OCDD	Swiss Webster mouse	>4,000,000 (M)	Schwetz et al. 1978
2,8-DCDD	Hartley guinea pig	>300,000 (M)	McConnell et al. 1978b
2,3,7-TrCDD	Hartley guinea pig	29,444 (M)	McConnell et al. 1978b
1,2,4,7,8-PeCDD	Hartley guinea pig	1,125 (M)	McConnell et al. 1978b
1,2,3,7,8-PeCDD	Hartley guinea pig	3.1 (M)	McConnell et al. 1978b
1,2,3,6,7,8-HxCDD	Hartley guinea pig	70–100 (M)	McConnell et al. 1978b
1,2,3,7,8,9-HxCDD	Hartley guinea pig	60–100 (M)	McConnell et al. 1978b

Table 2-7. LD_{50} Values in Laboratory Animals Following a Single Oral Dose of Other CDD Congeners

Congener	Species	LD_{50} (µg/kg)	Reference
1,2,3,4,7,8-HxCDD	Hartley guinea pig	72.5 (M)	McConnell et al. 1978b
1,2,3,4,7,8-HpCDD	Hartley guinea pig	>600 (M)	McConnell et al. 1978b

DCDD = dichlorodibenzo-*p*-dioxin; F = females; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; LD_{50} = dose calculated to cause death in 50% of animals; M = males; OCDD = octachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin; TrCDD = trichlorodibenzo-*p*-dioxin

A series of studies conducted by Viluksela et al. (1994, 1998a) allow for a comparison of the lethality of three CDD congeners in Sprague-Dawley rats administered 10 doses of CDDs in a 13-week period. Increases in mortality were observed at 2.6 µg/kg/day 1,2,3,7,8-PeCDD (75%), 10.3 µg/kg/day 1,2,3,4,7,8-HxCDD (25%), and 110 µg/kg/day (50%) 1,2,3,4,6,7,8-HpCDD. The main causes of death were wasting syndrome, hemorrhage, and anemia (Viluksela et al. 1994, 1998a). No effects on survival were observed following chronic dietary exposure of Osborne-Mendel rats and B6C3F1 mice to $5x10^5$ and $1.3x10^6$ µg/kg/day of 2,7-DCDD, respectively (NCI/NTP 1979), or following chronic gavage dosing with a mixture of 1,2,3,7,8,9-HxCDD and 1,2,3,6,7,8-HxCDD at 0.34 and 0.7 µg/kg/day, respectively (NCI/NTP 1980).

2.3 BODY WEIGHT

Overview. There are limited epidemiological studies evaluating associations between CDD exposure and body weight effects. Weight loss has been reported in a couple of cases of exposure to high levels of exposure and a general population study found an association between serum OCDD levels and body mass index (BMI).

In contrast, a large number of animal studies have reported decreases in body weight following oral or dermal exposure to 2,3,7,8-TCDD or oral exposure to several other CDD congeners. Body weight effects have been consistently observed in animal oral exposure studies in all species evaluated. At high doses, a wasting syndrome characterized as weight loss or lack of weight gain have been observed in monkeys, rats, mice, and mink; this is typically observed at lethal doses. Exposure to lower doses of 2,3,7,8-TCDD results in decreases in body weight gain or terminal body weights. A species comparison of the dose associated with a 50% decrease in body weight gain following a single dose exposure to 2,3,7,8-TCDD found that Hartley guinea pigs were the most sensitive followed by Sprague-Dawley rats, C57BL/6 mice,

and Golden Syrian hamsters. In long-term studies, body weight effects were observed at ≥0.047 µg/kg/day in rats, ≥2.8 µg/kg/day in mice, and 0.005 µg/kg/day in guinea pigs following intermediate-duration oral exposure and at ≥0.071 µg/kg/day in rats and 0.36 µg/kg/day in mice following chronic-duration oral exposure. Body weight effects have also been observed in repeated-exposure dermal studies at doses of 0.1 and 0.005 µg/kg/day following intermediate- and chronic-duration exposure, respectively.

Body weight effects have also been observed following acute-, intermediate-, or chronic-duration oral exposure to other CDD congeners. The lowest LOAELs were 0.18 µg/kg/day for a mixture of HxCDD congeners in Osborne-Mendel rats following intermediate- or chronic-duration exposure and 2.6 µg/kg/day for 1,2,3,7,8-PeCDD in Sprague-Dawley rats following intermediate-duration exposure.

Epidemiological Studies. Limited information was located regarding body weight effects in humans following exposure to CDDs. A transient weight loss was reported in a laboratory worker following an acute-duration exposure to 2,3,7,8-TCDD (Oliver 1975). Weight loss associated with severe cases of chloracne was mentioned in a study among herbicide-manufacturing workers (Jirasek et al. 1976), but further information regarding weight loss was not provided.

In a prospective study of boys (8–9 years of age at enrollment) living in Chapevsk, Russia, serum CDD/CDF/PCB TEQ levels were inversely associated with BMI at age 11–12 years (Burns et al. 2011) and age 19 years (Burns et al. 2020). Inverse associations between serum TEQs and height-adjusted fat and fat-free mass indices were also found at age 19 years (Burns et al. 2020). The median serum TEQ was 21.1 pg/g lipid (Burns et al. 2011, 2020). In a study utilizing National Health and Nutrition Examination Survey (NHANES) 1999–2002 data, associations between serum OCDD levels and BMI and waist circumference were observed (Elobeid et al. 2010).

2,3,7,8-TCDD—Animal studies. A characteristic effect of exposure to high doses of 2,3,7,8-TCDD in animals is wasting syndrome. Numerous studies have reported weight loss or a lack of weight gain in rats following a single, lethal 2,3,7,8-TCDD exposure. For example, these effects have been observed in rats (Christian et al. 1986; Kelling et al. 1985; Seefeld and Peterson 1984; Seefeld et al. 1984a; Walden and Schiller 1985), mice (Kelling et al. 1985), monkeys (McConnell et al. 1978a), and mink (Hochstein et al. 1988). Several studies have investigated the basis for this significant decrease in body weight gain. The initial decrease in body weight gain or weight loss appears to be associated with hypophagia rather than malabsorption (Kelling et al. 1985; Moore et al. 1985; Seefeld and Peterson 1984). At sublethal

2,3,7,8-TCDD doses, there appears to be a reduction in the regulation level for body weight; long term, the rats can maintain body weight but at a subnormal body weight (Seefeld and Peterson 1984).

Decreases in body weight gain or terminal body weights of at least 10% have been observed in rats administered a single oral dose of 2,3,7,8-TCDD. LOAEL values were >10 µg/kg in Sprague-Dawley rats (Boverhof et al. 2006; Fletcher et al. 2001; Lu et al. 2010; Moore et al. 1985; Seefeld et al. 1984a; Thunberg et al. 1979); no alteration in body weight gain was observed in Long-Evans rats administered 40 µg/kg (Raasmaja et al. 1996). Decreases in body weight gain or terminal body weights were infrequently reported in mice exposed to a single, nonlethal dose of 2,3,7,8-TCDD. Decreases ≥10% have been reported in C57BL/6 mice at ≥40 µg/kg (Fletcher et al. 2001; Pohjanvirta et al. 2012) and in DBA/2 mice at 1,500 µg/kg (Weber et al. 1995). No alterations in body weight were observed in B6C3F1 mice at ≤10 µg/kg (Diliberto et al. 1995; Frawley et al. 2014) or BALB/c mice at 20 µg/kg (Chen et al. 2013). A 15% decrease in body weight was observed in Golden Syrian hamsters at 40 µg/kg (Fletcher et al. 2001). Greater than 20% decreases in body weight gain or terminal body weights following acute-duration oral exposure have been observed in rats at doses ≥0.66 µg/kg (Boverhof et al. 2006; Fletcher et al. 2001; Roth et al. 1988; Seefeld et al. 1984b; Viluksela et al. 2004), monkeys at 70 µg/kg/day (McConnell et al. 1978a), mice at 200 µg/kg (Fletcher et al. 2001), hamsters at 200 µg/kg (Fletcher et al. 2001), and mink at 5 µg/kg/day (Hochstein et al. 1988). A species comparison of the dose resulting in a 50% reduction in body weight gain following administration of a single dose of 2,3,7,8-TCDD was conducted by Hanberg et al. (1989). The median effective dose (ED_{50}) values were 1.8 µg/kg in Hartley guinea pigs, 89 µg/kg in Sprague-Dawley rats, 890 µg/kg in C57BL/6 mice, and 1,000 µg/kg in Golden Syrian hamsters.

Decreases in body weight gain or body weight loss have been consistently reported in animals following intermediate-duration exposures to 2,3,7,8-TCDD. Decreased body weight was observed in Osborne-Mendel rats exposed for 13 weeks to 0.56 µg/kg/day (NTP 1982b), Sprague-Dawley rats treated with ≥0.047 µg/kg/day for 10–29 weeks (Chen et al. 2009; Li and Rozman 1995; Ma et al. 2010; NTP 2006; Van Birgelen et al. 1995; Viluksela et al. 1994), Wistar rats administered 0.14 µg/kg/day (Gül et al. 2018), in guinea pigs exposed to 0.005 µg/kg/day in the feed (DeCaprio et al. 1986), and mice exposed to ≥2.8 µg/kg/day (Fader et al. 2017a, 2017b; Thigpen et al. 1975; Vos et al. 1973). Weight loss was recorded in Rhesus monkeys exposed to 0.011 µg/kg/day for 9 months (Allen et al. 1977). In contrast to these findings, a study of C57BL/6J mice exposed to a high-fat diet (60% calorie intake from saturated fat) and administered via gavage 1 µg/kg 2,3,7,8-TCDD once a week (0.14 µg/kg/day) for 32 weeks found significant increases in body weight gain (Brulport et al. 2017).

In chronic-duration experiments with 2,3,7,8-TCDD, decreased body weight gain was reported in Osborne-Mendel and Sprague-Dawley rats exposed via gavage to 0.071 µg/kg/day (NTP 1982b, 2006) and in B6C3 mice exposed to 0.36 µg/kg/day by gavage for 52 weeks (Della Porta et al. 1987), but not in C57BL/6 mice gavaged once per week for 14–15 months with 0.03 µg/kg/day 2,3,7,8-TCDD (Oughton et al. 1995).

Decreased maternal weight gain has been reported in Rhesus monkeys at 0.1 µg/kg/day (McNulty 1984), Holtzman rats at 6 µg/kg/day (Kransler et al. 2007), CRCD rats at 0.5 µg/kg (Giavini et al. 1983), Sprague-Dawley rats at 0.5 µg/kg (Sparschu et al. 1971b), CD-1 mice at 100 µg/kg/day (Courtney 1976), and New Zealand rabbits at 0.25 µg/kg/day (Giavini et al. 1982).

In animal studies, decreased body weight was observed in HRS/J and Skjh:HR-1 mice following intermediate-duration dermal exposure to 0.1 µg 2,3,7,8-TCDD (Puhvel et al. 1982) and in Swiss Webster mice following chronic-duration exposure to 0.005 µg 2,3,7,8-TCDD 3 days/week (NTP 1982a).

Other CDD Congeners—Animal Studies. A small number of studies have evaluated the effect of other CDD congeners on body weight in animals; these data are summarized in Table 2-8. The data suggest that the degree of chlorination affects the toxicity, with the most toxic other CDD congener being PeCDD, and that toxicity decreases with increasing number of carbons for the higher chlorinated compounds. Simanainen et al. (2002) conducted a comparison of the ED_{50} (50% reduction in body weight measured 8 days post-exposure) for several CDDs and in two rat strains. In both rat strains, the ED_{50} values for 1,2,3,4,7,8-HxCDD were approximately 10 times higher than for 1,2,3,7,8-PeCDD and 6–7 times lower than 1,2,3,4,6,7,8-HpCDD. As a comparison, the ED_{50} values for 2,3,7,8-TCDD were 6.3 µg/kg in Long-Evans rats and 19 µg/kg in Han/Wistar rats (Simanainen et al. 2002). A decrease in maternal body weight gain of 39% was observed in Sprague-Dawley rats exposed to 10 µg/kg/day HxCDD mixture on gestation days (GDs) 6–15 (Schwetz et al. 1973).

Table 2-8. Alterations in Body Weight in Animals Orally Exposed to Other CDD Congeners

CDD congener	Duration	Species	Lowest LOAEL (µg/kg/day)	Reference
10–19% Decrease in body weight gain or terminal body weights				
2,7-DCDD	14 days	CD-1 mouse	>1,000	Courtney 1976
	110 weeks	Osborne-Mendel rat	250,000	NCI/NTP 1979
	90 weeks	B6C3F1 mouse	650,000	NCI/NTP 1979
1,2,3,7,8-PeCDD	13 weeks	Sprague-Dawley rat	2.6	Viluksela et al. 1998a, 1998b
HxCDD mixture	13 weeks	Osborne-Mendel rat	0.71	NCI/NTP 1980
	13 weeks	B6C3F1 mouse	0.18	NCI/NTP 1980
OCDD	14 days	CD-1 mouse	>1,000	Courtney 1976
≥20% Decrease in body weight gain or terminal body weight				
1,2,3,7,8-PeCDD	Once	Long-Evans rat Hans/Wistar rat	14 32	Simanainen et al. 2002
	13 weeks	Sprague-Dawley rat	3.8	Viluksela et al. 1998a, 1998b
1,2,3,4,7,8-HxCDD	Once	Long-Evans rat Hans/Wistar rat	140 390	Simanainen et al. 2002
	13 weeks	Sprague-Dawley rat	15.4	Viluksela et al. 1998a, 1998b
HxCDD mixture	104 weeks	Osborne-Mendel rat	0.18	NCI/NTP 1980
1,2,3,4,6,7,8-HpCDD	Once	Long-Evans rat Hans/Wistar rat	980 2,500	Simanainen et al. 2002
	13 weeks	Sprague-Dawley rat	110	Viluksela et al. 1994

CDD = chlorinated dibenzo-*p*-dioxin; DCDD = dichlorodibenzo-*p*-dioxin; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; LOAEL = lowest-observed-adverse-effect level; OCDD = octachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin

No effect on the body weight of CD-1 mice was observed after 14 daily doses of OCDD at 1 µg/kg/day or 2,7-DCDD at 1,000 µg/kg/day (Courtney 1976). Chronic-duration exposure induced decreased weight gain in Osborne-Mendel rats and in B6C3F1 mice exposed to $2.5x10^5$ and $6.5x10^5$ µg/kg/day of 2,7-DCDD, respectively, in the feed (NCI/NTP 1979).

2.4 RESPIRATORY

Overview. There are limited data on CDD-induced respiratory effects. Several occupational exposure, Seveso cohort, and Vietnam War veteran studies have examined respiratory tract effects. Symptoms of respiratory tract irritation were observed in workers exposed to 2,3,7,8-TCDD as a result of an industrial

accident. Conflicting results for lung function have been reported in studies of workers and Vietnam War veterans.

A small number of animal studies have examined potential respiratory effects in animals orally exposed to 2,3,7,8-TCDD. Lung damage has been reported in monkeys and rats following intermediate- or chronic-duration oral exposure. Lung lesions have been observed in rats chronically exposed to a mixture of HxCDD congeners but were not observed in similarly exposed mice. No respiratory effects were observed in rats or mice chronically exposed to 2,7-DCDD.

Epidemiological Studies. Information regarding respiratory effects of CDDs in humans is limited. Effects of acute, massive exposure in workers exposed to 2,3,7,8-TCDD in an industrial accident in Germany included bronchitis and laryngitis a few days after exposure and hemorrhagic pleuritis 11 months after exposure (Goldman 1972). In an occupationally exposed group, decreased pulmonary function was found in smokers 10 years after the cessation of manufacture of herbicides contaminated with 2,3,7,8-TCDD as compared with nonexposed smokers (Suskind and Hertzberg 1984). Similarly, inverse associations have been found between CDD/CDF TEQs intake (estimated from dietary intake and air monitoring data) and forced vital capacity (FVC) or forced expiratory volume in 1 second (FEV_1) in workers at an automobile foundry facility (Zhang et al. 2020). When workers were grouped by smoking status, the inverse associations were observed in the smokers and nonsmokers. Calvert et al. (1991) found no significant differences in ventilatory function between a group of workers employed 15 years earlier in the production of sodium trichlorophenol (NaTCP), 2,4,5-T ester, or hexachlorophene and referents. At the time of the examination, the lipid-adjusted mean serum 2,3,7,8-TCDD concentration was 220 ppt in the exposed workers compared to 7 ppt in the referents. In addition, there was no association between previous occupational exposure to 2,3,7,8-TCDD contamination and elevation in the incidence of chronic bronchitis or in the prevalence of chronic obstructive respiratory disease. Calvert et al. (1991) suggested that the disparity between their results and those of Suskind and Hertzberg (1984) may have been due to the potential exposure to 2,4,5-T acid dust in that study. The 2,4,5-T acid was finished as a liquid as opposed to a powder in the plant studied by Suskind and Hertzberg (1984), thus limiting inhalation exposure.

No respiratory effects were associated with exposure to 2,3,7,8-TCDD-contaminated herbicides in a group of Vietnam Air Force veterans involved in Operation Ranch Hand examined more than 10 years after the war (Wolfe et al. 1985). In the 1987 follow-up (USAF 1991), no association was found between the initial or current serum level of 2,3,7,8-TCDD and incidences of asthma, bronchitis, pleurisy,

pneumonia, or tuberculosis; abnormal spirometric measurements were often associated with CDD blood levels, but according to the study authors (USAF 1991), the differences in the mean level between high- and low-exposure subjects were not clinically important. The study authors suggested that these findings may have been related to the association between 2,3,7,8-TCDD and body fat because obesity is known to cause a reduction in vital capacity. In contrast, a study of Korean Vietnam veterans exposed to Agent Orange found higher incidences of diseases of the respiratory tract among veterans with higher Agent Orange exposure (Yi et al. 2014). Specific diseases included pneumonia not due to influenza, chronic bronchitis, bronchiectasis, and asthma.

A follow-up of the cohort involved in the Seveso accident reported a significant increase in deaths (four deaths) from chronic obstructive pulmonary disease in males from zone A and in females from zone B (Pesatori et al. 1998). The excess found among zone A males was mainly detected in the first 5 years after the accident and mainly affected elderly men. As mentioned in Section 2.5, Cardiovascular, Pesatori et al. (1998) stated that stress related to the disaster experience among this cohort could have precipitated early deaths among people with pre-existing chronic respiratory disease. The investigators also speculated that 2,3,7,8-TCDD, through immunotoxic action, may have impaired protection and defense against episodes of respiratory infection, which play a major role in the natural history of chronic obstructive respiratory disease.

2,3,7,8-TCDD—Animal Studies. Few studies have examined the respiratory system in animals following oral exposure to CDDs. However, serious respiratory effects have been observed in monkeys that died from 2,3,7,8-TCDD exposure.

One study evaluated potential respiratory effects following acute-duration oral exposure and found no histological alterations in B6C3F1 mice exposed to 1 μg/kg/day for 14 days (Holsapple et al. 1986). Respiratory tract damage has been observed in longer-term studies. Epistaxis (bleeding from the nose) was reported in Rhesus monkeys exposed via gavage to 0.1 μg/kg/day, 3 days/week for 3 weeks (McNulty 1984). Hemorrhage, hyperplasia, and metaplasia of the bronchial epithelium (as well as at other organ sites that had mucous-secreting cells) developed in monkeys exposed to diets providing 0.011 μg/kg/day for 9 months (Allen et al. 1977); five of eight monkeys died at this dose level.

Bronchiolar metaplasia of the alveolar epithelium was observed in the lungs of female Harlan Sprague-Dawley rats administered gavage doses ≥0.002 μg/kg/day 2,3,7,8-TCDD for 2 years; histiocytic infiltration was observed at ≥0.016 μg/kg/day (NTP 2006). Bronchiolar metaplasia was also observed in

a 0.071 µg/kg/day stop-exposure group (30-week exposure followed by vehicle administration until the end of the 2-year study), but the incidence was significantly lower than the 0.071 µg/kg/day continuous exposure group (NTP 2006). No significant increases in respiratory tract lesions were observed in rats exposed to ≤0.071 µg/kg/day for 14 or 31 weeks (NTP 2006). Tritscher et al. (2000) also reported alveolar epithelial metaplasia in female Sprague-Dawley rats administered 2,3,7,8-TCDD biweekly for 60 weeks (average daily dose of 0.125 µg/kg/day) (Tritscher et al. 2000); exposure for 14 or 30 weeks did not result in lung lesions. A third chronic-duration study in female Sprague-Dawley rats reported focal alveolar hyperplasia at 0.01 µg/kg/day 2,3,7,8-TCDD in the feed (Kociba et al. 1978). At 0.1 µg/kg/day, lung effects included pulmonary edema, focal interstitial inflammation and fibrosis, and squamous metaplasia (Kociba et al. 1978); the investigators noted that the observed effects were more extensive in females, as compared to the males. In contrast, no respiratory effects were observed in Osborne-Mendel rats chronically administered 0.071 µg/kg/day for 2 years (NTP 1982b) or in B6C3F1 mice exposed to 0.3 µg/kg/day 2 days/week for 2 years (NTP 1982b).

Dermal exposure of Swiss Webster mice to 0.05 µg 2,3,7,8-TCDD 3 days/week for 13 weeks resulted in bronchiolar adenomatoid changes; the NOAEL was 0.01 µg (NTP 1982a). No respiratory effects were observed in Swiss Webster mice following chronic-duration exposure to 0.005 µg (NTP 1982a).

Other CDD Congeners—Animal Studies. No respiratory effects were found in rats and mice chronically exposed by diet to $5x10^5$ and $1.3x10^6$ µg/kg/day of 2,7-DCDD, respectively (NCI/NTP 1979). In contrast, rats exposed chronically by gavage to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD at ≥0.18 µg/kg/day had a dose-related increased incidence of adenomatous hyperplastic lesions in terminal bronchioles and adjacent alveoli of both males and females; no such effects were found in mice exposed chronically to 0.7 µg/kg/day of that same mixture (NCI/NTP 1980). The existing information suggests that in animals, the respiratory system is not a sensitive target for CDDs toxicity via oral exposure.

2.5 CARDIOVASCULAR

Overview. Cardiovascular outcomes have been evaluated in several populations including workers, Vietnam War veterans, Seveso cohort, communities living in areas with contaminated soil, and the general population. These studies have found inconsistent results. Several studies of phenoxy herbicide production workers or applicators have reported increased mortality from cardiovascular disease, particularly ischemic heart disease. However, many of these studies did not control for potential

confounding variables such as smoking. Other studies of workers have not found associations with cardiovascular deaths or the incidence of several cardiovascular outcomes. Studies in the Seveso cohort have found increases in deaths from cardiovascular deaths; however, several investigators attributed this to post-accident stress. Inconsistent results have been observed in studies evaluating possible associations between CDD exposure and cerebrovascular disease, hypertension, and arteriosclerosis and vascular function.

Animal studies have reported cardiovascular effects in animals orally exposed to 2,3,7,8-TCDD. A small number of animal studies have evaluated cardiovascular function; studies have found alterations in blood pressure; however, the direction of the change was not consistent. Chronic-duration oral exposure to ≥0.071 µg/kg/day 2,3,7,8-TCDD resulted in cardiomyopathy and arteritis in rats. No histopathological alterations were observed in the hearts of rats and mice exposed following chronic-duration oral exposure to 2,7-DCDD or a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-HxCDD.

Epidemiological Studies. Possible associations between CDD exposure and cardiovascular disease have been examined in several populations including production workers and applicators, Vietnam veterans with Agent Orange exposure, Seveso residents, residents in communities with contaminated soil, and the general population. A summary of the epidemiological studies is presented in Table 2-9.

Several occupational exposure studies evaluating mortality causes found increased risk of deaths due to cardiovascular disease. Flesch-Janys et al. (1995) found significant increases in mortality from heart and circulatory diseases in workers exposed to 2,3,7,8-TCDD and other CDD congeners during the accident at BASF AG. Increased risks for cardiovascular disease and ischemic heart disease mortality were found in workers with extrapolated serum lipid 2,3,7,8-TCDD levels ≥348 pg/g lipid (current 2,3,7,8-TCDD levels were used to estimate 2,3,7,8-TCDD levels at the end of exposure). Additionally, significant dose-response trends for increasing cardiovascular and ischemic heart disease deaths were found. The risk for cardiovascular and ischemic heart disease deaths also increased as the serum lipid CDD and CDF levels increased. However, the results from the Flesch-Janys et al. (1995) study are difficult to interpret since the percentage of chemical workers who died from cardiovascular disease was 38% compared to 49% for a referent group from a gas supply company with no known special exposure to CDDs/CDFs. An international study comprising workers in 36 cohorts from 12 countries exposed to phenoxyacid herbicides and chlorophenols from 1939 to 1992 detected an increased risk for death from cardiovascular disease, especially ischemic heart disease, among the exposed workers (Vena et al. 1998). Risks did not

Table 2-9. Cardiovascular Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Occupational			
Calvert et al. 1998 Cross-sectional study of former workers (n=281) at two 2,4,5-T production facilities in New Jersey and Missouri and unexposed workers (n=260)	Current 2,3,7,8-TCDD level: 220 pg/g lipid Half-life extrapolated 2,3,7,8-TCDD level to estimate TCDD concentration at the time of exposure cessation: 1,900 pg/g lipid	Myocardial infarction	↔
		Angina	↔
		Arrhythmia	↔
		Hypertension	↔
		Abnormal arterial flow	↔
Flesch-Janys et al. 1995 Retrospective cohort study of 1,189 male workers in a phenoxy herbicide, chlorophenols, and other pesticide facility in Germany	Estimated 2,3,7,8-TCDD levels using blood/adipose samples from 190 workers and work histories 4th quintile: 49.3–156.7 pg/g lipid 10th decile: 344.7–3,890.2 pg/g lipid	Cardiovascular disease deaths	↑, 4th quintile
		Ischemic heart disease deaths	↑, 10th decile
Moses et al. 1984 Cross-sectional study of 226 workers at a 2,4,5-T production facility	Chloracne used as a surrogate for exposure	Myocardial infarction	↔
		Angina	↔
Pelclova et al. 2007 2004 follow-up examination of 15 workers exposed more than 35 years earlier to TCDD in an industrial setting in herbicide production plant; 14 controls	1996 mean plasma level was 256 pg 2,3,7,8-TCDD/g lipid (range=14–760 pg/g lipid); estimated range at the time of exposure (1965–1968) was 3,300–74,000 pg 2,3,7,8-TCDD/g lipids	Impaired skin microvascular reactivity; presence of endothelial dysfunction	↑
Steenland et al. 1999 A 6-year extended follow-up of the large NIOSH cohort of workers (n=5,132) from 12 factories exposed during 1960s–1983	Blood samples from workers (n=253) suggested estimated mean serum level of 2,000 ppt in lipids at the time of exposure; exposure categories were created based on points obtained by attributed job-exposure matrix	Ischemic heart disease deaths	↔
Suskind and Hertzberg 1984 Cross-sectional study of 204 exposed and 163 unexposed workers at a 2,4,5-T manufacturing facility in West Virginia	Not measured	Coronary artery disease	↔
		Hypertension	↔
		Angina	↔

Table 2-9. Cardiovascular Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Mannetje et al. 2005 Cross-sectional study of a total of 813 producers and 699 sprayers classified as exposed to dioxin and phenoxy herbicides in a New Zealand study	Job codes were used for exposure evaluation	Ischemic heart disease deaths	↔
		Cardiovascular disease deaths	↔
Vena et al. 1998 Cross-sectional study of 21,863 workers in the IARC International cohort study of phenoxy herbicide and chlorophenol production workers and sprayers	Exposure to 2,3,7,8-TCDD and higher CDDs estimated from blood levels, job records, and levels in workplace environment	All circulatory disease deaths	↑
		Ischemic heart disease deaths	↑
		Cerebrovascular disease deaths	↔
Vietnam War Veterans and Operation Ranch Hand Veterans			
Kang et al. 2006 Cross-sectional study of 1,499 members of the U.S. Army Chemical Corp involved in handling and spraying Agent Orange during the Vietnam War and 1,428 non-Vietnam veterans	Mean serum 2,3,7,8-TCDD levels in Vietnam veteran group: 4.3 ng/g lipid	Heart disease among herbicide sprayers	↑
		Hypertension among herbicide sprayers	↑
Ketchum and Michalek 2005 Cross-sectional study of 1,262 deceased Operation Ranch Hand veterans	Job history used as a surrogate for exposure	Atherosclerotic heart disease deaths among ground crew	↑
		Cardiomyopathy deaths among ground crew	↔
		Cerebrovascular disease deaths among ground crew	↔
		Hypertensive disease deaths among ground crew	↔

Table 2-9. Cardiovascular Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Kim et al. 2012 Cross-sectional study of Korean men undergoing coronary angiograms due acute coronary syndrome divided into two groups: veterans (n=121) exposed to Agent Orange and a group (n=130) with no exposure to 2,3,7,8-TCDD	Self-reported exposure	Hypertension (comparison between two groups)	↑
		Severity of coronary lesions (comparison between two groups)	↔
		Major adverse cardiovascular events (comparison between two groups)	↔
Kim et al. 2014 Cross-sectional study of two groups of patients undergoing coronary angiograms; 1,245 Korean veterans exposed to Agent Orange in the Vietnam war and 506 patients with no history of exposure to 2,3,7,8-TCDD	Self-reported exposure	Hypertension (comparison between two groups)	↑
		Myocardial infarction (comparison between two groups)	↑
		Coronary artery lesions (comparison between two groups)	↑
USAF 1991 Cross-sectional report of 866 Operation Ranch Hand personnel and a comparison group of 1,198	Not measured	Essential hypertension	↔
		Arrhythmias	↔
Wolfe et al. 1985 Retrospective study of 1,278 Operation Ranch Hand personnel	Not reported	Blood pressure	↔
		EKG	↔
Yi et al. 2013 Group of 114,562 Korean veterans of the Vietnam War exposed to Agent Orange	Exposure based on military record	Circulatory diseases	↑
		Hypertension	↔
		Myocardial infarction	↑
		Angina pectoris	↔
		Heart failure	↔
		Arrhythmia	↔
		Cerebral hemorrhage	↔

Table 2-9. Cardiovascular Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Cerebral infarction	↑
		Arteriosclerosis	↔
Yi et al. 2014 Group of 111,726 Korean veterans of the Vietnam War exposed to Agent Orange	Self-reported exposure	Hypertension	↔
		Ischemic heart diseases	↑
		Stroke	↑
		Cerebral infarction	↑
		Arteriosclerosis	↔
Seveso, Italy			
Bertazzi et al. 1989a Retrospective cohort study of 30,703 residents living in the Seveso area at the time of the accident	Not measured	Chronic ischemic heart disease deaths	↑, men ↔, women
		Acute myocardial infarction deaths	↔
		Cerebrovascular disease deaths	↔
Bertazzi et al. 1989b Retrospective cohort study of 1,559 deaths of residents of Seveso	Not measured	Acute myocardial infarction deaths	↑, men ↔, women
Pesatori et al. 1998 Retrospective cohort study 15-year follow-up of the Seveso cohort (n=3,987 deaths)	Soil contamination levels (not reported) in three zones used as a biomarker of exposure	Hypertension deaths	↔, men ↑, women
		Ischemic heart disease deaths	↔, men and women
		Myocardial infarction deaths	↔, men and women
		Chronic ischemic heart disease deaths	↑, men ↔, women
		Cerebrovascular disease deaths	↔, men and women
Communities with contaminated soil			
Chang et al. 2010b Cross-sectional study of 1,490 residents living near a deserted PCP factory in Taiwan	Blood CDD/CDF TEQ levels not reported	Systolic blood pressure	↔
		Diastolic blood pressure	↑

Table 2-9. Cardiovascular Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Chang et al. 2011a Cross-sectional study of 914 residents living near a deserted PCP factory in Taiwan	Mean serum CDD/CDF level: 18.3 pg TEQ/g lipid	Cardiovascular disease	↑
General population			
Donat-Vargas et al. 2020 Cross-sectional study of male participants (n=1844) in the Aragon Worker's Health Study in Spain	Total dioxin (no additional information provided) levels consumed in the diet: 519 pg/day for the 1st quartile and 809 pg/day in the 4th quartile	Coronary artery calcium score (indicator of subclinical atherosclerosis)	↔
Lind et al. 2012 Participants (n=1,016) in the Prospective Investigation of the Vasculature in Uppsala Seniors study in Sweden; participants were 70 years of age	Serum median OCDD level: 2.6 pg/mL	Carotid artery plaques	↑
		Carotid artery intima media thickness	↔
		Carotid artery intima media complex	↔
Nakamoto et al. 2013 Cross-sectional study of 1,063 men and 1,201 women in Japan	Median serum total CDDs/CDFs: 9.8 pg TEQ/g lipid	Hypertension	↑, 4th quartile

↑ = association; ↔ = no association; 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid; CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; EKG = electrocardiogram; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; OCDD = octachlorodibenzo-*p*-dioxin; PCP = pentachlorophenol; TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ = toxic equivalency

differ across latency categories or by year of first exposure but increased slightly by duration of exposure except for those with ≥20 years of exposure. Vena et al. (1998) indicated, however, that the study was hampered by the reliance on mortality and the crudeness and inaccuracies of death certificate diagnoses. Furthermore, they noted that possible confounding effects from important risk factors for ischemic heart disease such as cigarette smoking, high fat diet, blood pressure, obesity, physical inactivity, and serum lipids cannot be ruled out. A 6-year follow-up study was conducted on the original National Institute for Occupational Safety and Health (NIOSH) cohort of workers exposed to 2,3,7,8-TCDD in occupational settings during production of phenoxy herbicide and chlorophenol (Steenland et al. 1999). No associations between blood CDD levels and ischemic heart disease deaths were found. However, internal analyses using Cox regression found statistically significant exposure-response trends. Only a small subset of workers in the original cohort had dioxin serum levels analyzed. The mean TCDD serum level was back-estimated to be 2,000 pg/g lipid at the time of exposure (1960s–1983). A study of phenoxy herbicides producers and sprayers in New Zealand study did not find increases in the risk of deaths from ischemic heart disease and all cardiovascular diseases (Mannetje et al. 2005). Studies evaluating alterations in the incidence of cardiovascular disease have not found associations between 2,3,7,8-TCDD occupational exposure and the incidence of myocardial infarction (Calvert et al. 1998; Moses et al. 1984) or angina (Calvert et al. 1998; Moses et al. 1984; Suskind and Hertzberg 1984).

In the 10-year period following the Seveso accident, there was an association between the risk of death from chronic ischemic heart disease in men, which was predominantly due to the increased risk during the first 5-year period (Bertazzi et al. 1989a). When the residents were divided into contamination zones, there were associations with the risk of death from chronic heart disease in zones A and R, but not in zone B, for the first 5-year period and only in zone R for the 10-year period (Bertazzi et al. 1989b). Bertazzi et al. (1989b) noted that increased risk of cardiovascular disease deaths may have been due to post-accident stress rather than to 2,3,7,8-TCDD exposure. A 5-year follow-up found increased risk of chronic ischemic heart disease in males, deaths from chronic rheumatic heart disease in females, and deaths from hypertensive vascular disease in females, all from zone A, the most severely affected area (Pesatori et al. 1998). Although these observations suggest an association between exposure to 2,3,7,8-TCDD and incidence of cardiovascular effects, they do not necessarily show that the effects were caused by 2,3,7,8-TCDD. As previously suggested by Bertazzi et al. (1989a), Pesatori et al. (1998) also indicated that the disaster experience with its burden of psychosocial stressors may have played a major role in the increased deaths found. An association between serum CDD/CDF levels and cardiovascular disease was found in a cross-sectional study of residents living near a deserted PCP factory (Chang et al. 2011a). Increased risk of cardiovascular disease has been inconsistently reported in studies of Vietnam

War veterans. Increases in the risk of myocardial infarctions (Kim et al. 2014; Yi et al. 2013), cerebrovascular infarction (Yi et al. 2014), ischemic heart disease (Yi et al. 2014), and atherosclerotic heart disease (Ketchum and Michalek 2005) have been reported in some studies, whereas other studies have not reported cardiovascular disease risk increases (Ketchum and Michalek 2005; Kim et al. 2012).

Studies evaluating possible associations between CDD exposure and cerebrovascular disease have not found associations in workers (Vena et al. 1998), Vietnam War veterans (Ketchum and Michalek 2005), or Seveso residents (Bertazzi et al. 1989a; Pesatori et al. 1998). An increased risk of cerebral infarction was observed in two studies of Vietnam War veterans (Yi et al. 2013, 2014); one of the studies also found an increased risk of stroke (Yi et al. 2014).

A number of studies have evaluated the potential association between CDDs exposure and hypertension. Two studies of workers involved in the production of 2,4,5-T did not find increased risks of hypertension (Calvert et al. 1998; Suskind and Hertzberg 1984). Increases in the risk of hypertension were found in studies of Vietnam War veterans involved in herbicide spraying (Kang et al. 2006) or self-reporting exposure to Agent Orange (Kim et al. 2012, 2014). However, other studies of Operation Ranch Hand personnel (Ketchum and Michalek 2005; USAF 1991; Wolfe et al. 1985) or other veterans (Yi et al. 2013, 2014) did not find associations with hypertension. An increased risk of hypertension deaths was found among female Seveso residents, but not among males (Pesatori et al. 1998). Chang et al. (2010b) found an association between serum CDD/CDF TEQ levels and diastolic blood pressure in residents living near a deserted PCP facility; no association was found for systolic blood pressure.

A small number of studies have evaluated arteriosclerosis and vascular function. Ketchum and Michalek (2005) reported increased risk of atherosclerotic heart disease deaths among Operation Ranch Hand ground crew personnel. In contrast, Yi and associates did not find increased risks of arteriosclerosis among Vietnam War veterans (Yi et al. 2013, 2014). Pelclova et al. (2007) reported impaired vascular function, as measured by skin microvascular reactivity, in workers previously exposed to high levels of 2,3,7,8-TCDD in an herbicide production facility. A general population study found an association between serum OCDD levels and carotid artery plaques, but no association with carotid artery intima media thickness or complex (Lind et al. 2012). Another general population study (Donat-Vargas et al. 2020) found no association between total dioxin levels in the diet and coronary artery calcium score, which is an indicator of subclinical atherosclerosis.

2,3,7,8-TCDD—Animal Studies. Cardiovascular effects, including impaired cardiovascular function and histopathological alterations, have been detected in animals following acute-, intermediate-, and chronic-duration oral exposure to 2,3,7,8-TCDD.

Several studies have evaluated potential alterations in blood pressure. Three daily oral doses of 40 µg/kg/day 2,3,7,8-TCDD resulted in depressed mean arterial blood pressure (34%), measured 6 days post-exposure, in Sprague-Dawley rats (Hermansky et al. 1988). Decreased mean arterial blood pressure (31%) was also observed in Sprague-Dawley rats administered via gavage 0.28 µg/kg/day 2,3,7,8-TCDD for 45 days (Sarihan et al. 2015). In contrast, a time-course study in C57BL/6 mice administered 0.18 µg/kg 2,3,7,8-TCDD via capsule, 5 days/week for 35 days reported increased mean arterial blood pressure (approximately 20%) (Kopf et al. 2010). The increased blood pressure began on day 15 and plateaued at 25 days. Gavage administration of 0.5 µg/kg/day for 28 days resulted in a significant increase in systolic blood pressure (25%) in Sprague-Dawley rats (İlhan et al. 2015). The limited number of studies precludes assessing whether the inconsistent results are due to differences in dose-response or duration of exposure.

Other studies of cardiovascular function reported an increased sensitivity to the inotropic (left atrium) and chronotropic (right atrium) effects of isoproterenol in Sprague-Dawley rats administered a single dose of 100 µg/kg 2,3,7,8-TCDD (Kelling et al. 1987). Electrocardiograms revealed atrial fibrillation, ST depression, T wave and P wave negativity, QTS prolongation, bundle branch block, and biphasic P waves in Sprague-Dawley rats administered 0.28 µg/kg/day for 45 days (Sarihan et al. 2015). In C57BL/6 mice, 0.18 µg/kg 2,3,7,8-TCDD administered 5 days/week for 35 days resulted in increased acetylcholine-dependent vasorelaxation of the aortic rings (Kopf et al. 2010).

Longer-term oral exposure to lethal doses resulted in histopathological lesions. Hemorrhages in the epicardial, myocardial, and endocardial tissues were observed in monkeys that died after exposure to diets providing 0.011 µg/kg/day of 2,3,7,8-TCDD for 9 months (Allen et al. 1977). Myocardial degenerative changes and periarteritis were reported in Sprague-Dawley rats exposed to a diet providing 0.1 µg/kg/day of 2,3,7,8-TCDD for 2 years (Kociba et al. 1978); no histological alterations were observed at the highest nonlethal dose (0.01 µg/kg/day). In contrast, minimal to mild cardiomyopathy was observed in another chronic-duration exposure study in which female Harlan Sprague-Dawley rats were gavaged with 0.0071 µg/kg/day for 2 years (Jokinen et al. 2003; NTP 2006). The investigators noted that the cardiomyopathy, which was characterized as multiple foci of myocardial degeneration scattered within the ventricular walls, was similar to lesions observed in aging rats. A significant increase in the incidence

of cardiomyopathy was also observed in rats administered 0.071 µg/kg/day for 30 weeks and allowed to recover for the remainder of the 2-year study; however, the incidence was significantly lower than in the rats administered 0.071 µg/kg/day for 2 years (NTP 2006). Additionally, significant increases in the incidence of arteritis (characterized as circumferential fibrinoid necrosis of the tunica media, proliferation of adventitial connective tissue with adventitial thickening, and infiltration of the adventitia) were observed in the arteries in the mesentery and pancreas in rats exposed to 0.071 µg/kg (Jokinen et al. 2003).

Information regarding cardiovascular effects in animals after dermal exposure to CDDs is limited. Chronic-duration dermal exposure of Swiss Webster mice to 2,3,7,8-TCDD at 0.005 µg, 3 days/week, did not induce any cardiovascular changes observable under histopathological examination (NTP 1982a).

Other CDD Congeners—Animal Studies. No histopathological lesions were observed in the hearts of rats and mice chronically exposed in the diet to $5x10^5$ and $1.3x10^6$ µg/kg/day 2,7-DCDD, respectively (NCI/NTP 1979a), or by gavage for 104 weeks to approximately 0.34 and 0.7 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD, respectively (NCI/NTP 1980).

2.6 GASTROINTESTINAL

Overview. A small number of epidemiological studies have examined gastrointestinal outcomes. Inconsistent results for associations between CDD exposure and the incidence of ulcers have been reported in studies of workers and Vietnam War veterans potentially exposed to Agent Orange.

Gastrointestinal lesions have been observed in the stomachs and small intestines of several animal species orally exposed to 2,3,7,8-TCDD. Administration of a single lethal oral dose of 2,3,7,8-TCDD resulted in gastrointestinal tract ulceration, ileitis, and hyperplasia. Repeated oral exposure to nonlethal doses resulted in gastric mucosal metaplasia and gastric ulcers in monkeys and forestomach hyperplasia in mice. Gingival mucosal lesions have also been observed in rats following gavage administration of 2,3,7,8-TCDD. Chronic-duration oral studies have not found gastrointestinal lesions in rats or mice exposed to 2,7-DCDD or a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD congeners.

Epidemiological Studies. A small number of epidemiological studies evaluated gastrointestinal effects resulting from occupational exposure or exposure to Agent Orange during the Vietnam War; the results of these studies are summarized in Table 2-10.

Table 2-10. Gastrointestinal Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Occupational			
Bond et al. 1983 Cross-sectional study of workers exposed at a 2,4,5-T production facility (n=87) or workers involved in a chloracne incident in an area of trichlorophenol production (n=22); medical surveillance results were compared to unexposed workers	Not measured	Ulcer	↑
		Digestive system diseases	↑
Calvert et al. 1992 Cross-sectional study of former workers (n=281) at two 2,4,5-T production facilities in New Jersey and Missouri and unexposed workers (n=260)	Current 2,3,7,8-TCDD level: 220 pg/g lipid Half-life extrapolated 2,3,7,8-TCDD level to estimate TCDD concentration at the time of exposure cessation: 1,900 pg/g lipid	Ulcer	↔
		Gastritis	↔
		Gastrointestinal hemorrhage	↔
Suskind and Hertzberg 1984 Cross-sectional study of 204 exposed and 163 unexposed workers at a 2,4,5-T manufacturing facility in West Virginia	Not measured	Ulcer	↑
Vietnam War veterans and Operation Ranch Hand veterans			
USAF 1991 Cross-sectional report of 866 Operation Ranch Hand personnel and a comparison group of 1,198	Not measured	Ulcer	↔
Yi et al. 2013 Group of 114,562 Korean veterans of the Vietnam War exposed to Agent Orange	Exposure based on military record	Gastritis	↔
		Peptic ulcer	↔
		Enterocolitis	↔

Table 2-10. Gastrointestinal Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Yi et al. 2014 Group of 111,726 Korean veterans of the Vietnam War exposed to Agent Orange	Self-reported exposure	Gastritis and duodenitis	↔
		Peptic ulcer	↑
		Ulcerative colitis	↔
		Crohn's disease	↔

↑ = association; ↔ = no association; 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid; CDD = chlorinated dibenzo-*p*-dioxin; TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

Two occupational exposure studies of workers exposed to substances contaminated with 2,3,7,8-TCDD ≥15 years prior reported an increase in ulcers (Bond et al. 1983; Suskind and Hertzberg 1984); no alterations in ulcer prevalence were observed in a third occupational exposure study (Calvert et al. 1992). Ulcers were also reported in two studies of Korean Vietnam Veterans self-reporting exposure to Agent Orange (Yi et al. 2013, 2014). However, in the Yi et al. (2013) study, the association was not increased when Agent Orange exposure was based on battalion/company level proximity. No alterations in ulcer prevalence were observed in Operation Ranch Hand personnel (USAF 1991). No consistent alterations in other gastrointestinal diseases were found (Calvert et al. 1992; Yi et al. 2013, 2014).

2,3,7,8-TCDD—Animal Studies. Major 2,3,7,8-TCDD-induced effects in various animal species include the wasting syndrome and hypophagia that occur after a single near-lethal dose or after repeated dosing (discussed in Section 2.3, Body Weight). Studies of effects on the gastrointestinal system have been carried out to investigate the mechanism of this starvation-like syndrome. The response of the antral mucosa of the rat stomach to 2,3,7,8-TCDD has been studied by Theobald et al. (1991). In Sprague-Dawley rats, a single oral dose of 100 µg 2,3,7,8-TCDD/kg caused a 7–10-fold increase in serum gastrin (secreted by G-cells in the antrum) that was not detected until 14 days after dosing, whereas control rats fed a restricted diet had atrophic changes in the antral mucosa and no increase in gastrin (Theobald et al. 1991). The number of G-cells in the antral mucosa was not affected by treatment with 2,3,7,8-TCDD or paired-feed restriction, indicating that hypergastrinemia in treated rats is not due to reduced feed intake or antral G-cell hyperplasia. In 2,3,7,8-TCDD-treated rats, both gastrin and somatostatin (which inhibits gastrin release) levels in the antral mucosa were significantly decreased, and these changes were observed a week earlier than the hypergastrinemia. Moreover, the ED_{50} values (half maximum effect level of 2,3,7,8-TCDD) for the decrease in antral mucosa content and concentration of gastrin (29 and 22 µg/kg, respectively) and somatostatin (24 and 19 µg/kg, respectively) were less than that for hypergastrinemia (46 µg/kg). This suggested that hypergastrinemia in 2,3,7,8-TCDD-treated rats is not a consequence of reduced antral levels of gastrin or somatostatin.

Several studies have reported histological alterations in the gastrointestinal tract. Observed effects in animals receiving a single lethal oral dose of 2,3,7,8-TCDD include epithelial hyperplasia in the stomach of Rhesus monkeys exposed to 70 µg/kg (McConnell et al. 1978a), gastrointestinal tract ulceration and bloody stools in minks at 5 µg/kg (Hochstein et al. 1988), and moderate to severe ileitis (characterized by hyperplasia of the mucosal epithelium with hemorrhaging and necrosis) and peritonitis in hamsters at ≥1,000 µg/kg 2,3,7,8-TCDD (Olson et al. 1980a); hypertrophy, hyperplasia, and metaplasia were observed in Rhesus monkeys exposed to 0.011 µg/kg/day for 9 months (Allen et al. 1977).

Gastrointestinal lesions were also observed in animals following repeated oral exposure to nonlethal doses: gastric mucosal metaplasia in Rhesus monkeys at 0.1 µg/kg/day for 3 weeks (McNulty 1984) and minimal to mild squamous hyperplasia of the forestomach in female Harlan Sprague-Dawley rats at 0.071 µg/kg/day 2,3,7,8-TCDD for 2 years (NTP 2006). No gastrointestinal effects were observed in Sprague-Dawley or Osborne-Mendel rats exposed to 0.1 or 0.071 µg/kg/day, respectively, for 2 years (Kociba et al. 1978; NTP 1982b) or in B6C3F1 mice exposed to 0.3 µg/kg/day (NTP 1982b).

No histopathological changes were observed in the gastrointestinal tract of Swiss Webster mice dermally exposed to 0.005 µg 2,3,7,8-TCDD 3 days/week for 99–104 weeks (NTP 1982a).

NTP (2006) also reported significant increases in the incidence of gingival squamous hyperplasia of the oral mucosa in female rats exposed to all tested doses of 2,3,7,8-TCDD (≥0.002 µg/kg). The lesion was characterized as a focal lesion occurring in the gingival oral mucosa adjacent to molars; the ends of hair shafts and/or inflammation were often present in the same area as the hyperplasia.

Other CDD congeners—Animal Studies. Gastrointestinal lesions were not observed following exposure of rats and mice to $5x10^5$ and $1.3x10^6$ µg/kg/day of 2,7-DCDD, respectively, in the diet (NCI/NTP 1979a) or to 0.34 and 0.7 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD, respectively, by gavage for 104 weeks (NCI/NTP 1980).

2.7 HEMATOLOGICAL

Overview. A small number of epidemiological studies have evaluated hematological endpoints; in general, most of the studies did not find alterations in hematological parameters. In studies that did find effects, the magnitudes of the alteration were small and not likely to be clinically significant.

Hematological effects, such as alterations (increases and decreases) in erythrocyte and leukocyte levels, have been reported in 2,3,7,8-TCDD oral exposure animal studies; however, the results are not consistent across studies. These nonspecific changes were probably due to the broad systemic toxicity of 2,3,7,8-TCDD rather than a direct effect on the hematological system. Hematological effects have been observed at lethal doses of 1,2,3,7,8-PeCDD and 1,2,3,4,7,8-HxCDD and splenic hyperplasia was observed in mice exposed to 2,7,-DCDD. These data were not considered adequate to establish a relationship between exposure to other CDD congeners and hematological toxicity.

Epidemiological Studies. A small number of epidemiological studies evaluated potential hematological effects resulting from exposure to 2,3,7,8-TCDD. Contact with 2,3,7,8-TCDD-contaminated soil in Missouri by physical or recreational activities for 6 months at 100 ppb or for 2 years at 20–100 ppb resulted in a slight, but statistically significant, increase in total white blood cell (WBC) counts using a prevalence test (5.3% were increased above 10,000 WBC/mm^3 compared to 0.7% for controls, but the increase was slight) (Hoffman et al. 1986). A follow-up study of the same population found no differences in the number of red blood cells, WBCs, or platelets between exposed and nonexposed individuals (Evans et al. 1988). In a similar cohort, Stehr et al. (1986) found no consistent differences in hematology parameters in a high-risk group (68 persons) compared to a low-risk group (36 persons) except a slightly elevated platelet count. No alterations in hematological parameters were observed in children living near a municipal waste incinerator in China (Xu et al. 2019a). No significant differences in total leukocyte, granulocyte, or lymphocyte levels were observed between workers with high serum lipid CDD and CDF levels and workers with lower serum CDD and CDF levels (Neubert et al. 1993).

A health study of Vietnam veterans involved in Operation Ranch Hand indicated an association between high initial and current serum 2,3,7,8-TCDD levels and increased erythrocyte sedimentation (Wolfe et al. 1995) and an earlier study by Wolfe et al. (1985) indicated an increase in mean corpuscular volume; however, these changes were minor and were not observed in the 1991 follow-up (USAF 1991). Higher serum 2,3,7,8-TCDD levels were also associated with positive dose-response trends for increases in WBC and platelet levels.

2,3,7,8-TCDD—Animal Studies. A number of hematological effects have been observed in animals following oral exposure to 2,3,7,8-TCDD, although effects have not been consistently observed across studies. Increased levels of erythrocytes have been observed in CD rats exposed to 10 µg/kg/day for 14 days (Weissberg and Zinkl 1973) and Sprague-Dawley rats exposed to 0.1 µg/kg/day for 4 weeks (Harrill et al. 2015); a 2-year study in Sprague-Dawley rats reported decreased erythrocyte levels at 0.1 µg/kg/day (Kociba et al. 1978). No alterations in erythrocyte levels were observed in C57BL/6N mice exposed to 0.03 µg/kg/day for 14–15 months (Oughton et al. 1995) or guinea pigs exposed to 0.03 µg/kg/day for 90 days (DeCaprio et al. 1986). Total and differential leukocyte levels have also been affected by oral exposure to 2,3,7,8-TCDD. Increased total leukocyte levels have been observed in Golden Syrian hamsters exposed to 1.5 µg/kg during pregnancy (Kransler et al. 2007), but not in Hartley guinea pigs or Holtzman rats similarly exposed to 1.5 or 18 µg/kg, respectively (Kransler et al. 2007). No alterations in total leukocyte levels were observed in CD rats administered 0.71 µg/kg/day for 6 weeks

(Vos et al. 1973), C57BL/6N mice at 0.03 µg/kg/day for 14–15 months (Oughton et al. 1995), or guinea pigs administered 0.03 µg/kg/day for 90 days (DeCaprio et al. 1986). Zinkl et al. (1973) reported a decrease in leukocyte levels in CD-1 mice administered a single dose of 1 µg/kg. Decreased lymphocyte levels were observed in CD-1 mice administered 1 µg/kg once (Zinkl et al. 1973) and in Hartley guinea pigs administered 0.001 µg/kg/day for 8 weeks (Vos et al. 1973). In contrast, increased lymphocyte levels, as well as neutrophil and monocyte levels, were observed in CD rats exposed to 10 µg/kg for 10–14 days (Weissberg and Zinkl 1973). Other hematological effects that have been observed include decreased platelet counts in rats at ≥0.1 µg/kg/day (Viluksela et al. 1994; Weissberg and Zinkl 1973; Zinkl et al. 1973) and a decrease in the vitamin-K-dependent blood coagulation factor VII in rats administered a single dose of 96 µg/kg (Bouwman et al. 1999). Bone marrow hypoplasia was observed in Rhesus monkeys at ≥0.011 µg/kg/day (Allen et al. 1977; McNulty 1984) and CD rats at 10 µg/kg/day for 10–14 days (Weissberg and Zinkl 1973); no bone marrow alterations were observed following chronic-duration exposure of Osborne-Mendel rats or B6C3F1 mice exposed to 0.071 or 0.3 µg/kg/day, respectively (NTP 1982b). No hematological alterations were observed in Swiss Webster mice dermally exposed to 0.005 µg 2,3,7,8-TCDD (NTP 1982a) for a chronic duration.

Other CDD Congeners—Animal Studies. Hematological effects have been reported in some animals following exposure to other CDDs. No hematological effects were observed in rats after 2 weeks of intermittent exposure to 50 µg/kg/day OCDD (Couture et al. 1988), but increased neutrophils, decreased mean cell volume, and hemoglobin (Couture et al. 1988), and mild anemia were observed at the same exposure level after 13 weeks of intermittent exposure (Birnbaum et al. 1989a). A dose-dependent decrease in platelet counts was observed in male Sprague-Dawley rats following administration by gavage of doses equivalent to 73 or 110 µg 1,2,3,4,6,7,8-HpCDD/kg/day for 13 weeks (Viluksela et al. 1994); no such effect was observed with doses ≤24 µg/kg/day. Some rats administered the highest dose also showed increased prothrombin times. Administration of doses equivalent to 2.6 µg 1,2,3,7,8-PeCDD/kg/day or 10.3 µg 1,2,3,4,7,8-HxCDD/kg/day for 13 weeks resulted in decreased hematocrit and reduced platelet count in female Sprague-Dawley rats (Viluksela et al. 1998a); these doses also caused mortality. Splenic hyperplasia was observed in rats exposed by gavage to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD at 7.1 µg/kg/day, but not at 1.4 µg/kg/day, for 13 weeks (NCI/NTP 1980). No hematological effects were observed in Osborne-Mendel rats or B6C3F1 mice chronically exposed to $5x10^5$ and $1.3x10^6$ µg/kg/day of 2,7-DCDD, respectively, in feed (NCI/NTP 1979a) or to 0.34 and 0.7 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD, respectively, 2 days/week for 104 weeks by gavage (NCI/NTP 1980).

2.8 MUSCULOSKELETAL

Overview. A very small number of epidemiological studies have evaluated the possible association between CDD exposure and musculoskeletal effects. General population studies examined possible associations between CDD congeners and bone mineral density and walking speed, and a study of the Seveso cohort examined dental defects.

Potential musculoskeletal effects have been poorly studied in animals. Increases in bone mass have been observed in two intermediate-duration oral studies of 2,3,7,8-TCDD in mice. Tooth defects have been observed in rats exposed to 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, or 1,2,3,4,6,7,8-HpCDD. Chronic-duration oral exposure studies with 2,3,7,8-TCDD, 2,7-DCDD, or a mixture of HxCDD congeners have not found histological alterations in muscles or bones.

Epidemiological Studies. There is limited information on the effect of CDD exposure in humans on the musculoskeletal system. Some information comes from two anecdotal reports. In one of them, two individuals exposed to 2,3,7,8-TCDD in a horse arena that was sprayed with waste oil for dust control complained of painful joints (arthralgia) (Kimbrough et al. 1977). In the second case, a chemist exposed to 2,3,7,8-TCDD and 2,3,7,8-tetrabromo-*p*-dibenzo dioxin (2,3,7,8-TBDD) complained of muscle pain in the lower extremities and back (Schecter and Ryan 1991). The role that 2,3,7,8-TCDD played in these cases, if any, is unknown. No further information was located.

Cho et al. (2011) examined the possible association between 1,2,3,4,6,7,8-HpCDD and OCDD levels and bone mineral density using NHANES (1999–2004) data. No associations were found for either congener in men or women less than 50 years of age or older than 50 years. In another study utilizing NHANES (1999–2000 and 2001–2002) data, Xu et al. (2019b) examined possible associations between CDD body burden and walking speed. No associations were found for 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, or OCDD.

Potential dental defects were examined in 48 Seveso residents and 65 controls (Alaluusua et al. 2004); mean serum 2,3,7,8-TCDD levels were 130, 383, and 1,830 ppt, for residents in zones R, B, and A, respectively, and 15 ppt in controls. Ninety-three percent (25 of 27) of children who were <5 years old at the time of the incident in 1976 had developmental enamel defects as adults. For the 38 children who were >5 years old, only 2 developed enamel defects. The data suggest that a window of susceptibility exists in early childhood for the effect to manifest itself later in life. Hypodontia was found in 6 of

48 exposed individuals and 3 of 65 controls. In contrast, dental caries and periodontal disease did not increase with exposure. The incidence of all dental effects for the exposed groups was 10% (zone R), 45% (zone B), and 60% (zone A). The reference group had a 26% incidence.

2,3,7,8-TCDD—Animal Studies. The musculoskeletal system does not appear to be a major target of toxicity in animals exposed to 2,3,7,8-TCDD. Focal areas of hemorrhaging and edema were observed in the musculoskeletal system of severely debilitated monkeys following dietary exposure to 0.011 µg/kg/day of 2,3,7,8-TCDD for 9 months (Allen et al. 1977). No histological alterations were observed in the musculoskeletal system in Sprague-Dawley rats exposed to 0.1 µg/kg/day in the diet for 2 years (Kociba et al. 1978) or in Osborne-Mendel rats and B6C3F1 mice chronically exposed 2 days a week by gavage to 0.071 or 0.3 µg/kg/day of 2,3,7,8-TCDD, respectively (NTP 1982b).

Increased trabecular bone mass (bone mineral density and content, thickness, and bone volume fraction) and decreased trabecular spacing were observed in juvenile C57BL/6 mice administered 3 and 0.30 µg/kg/day for 28-days (Fader et al. 2018). Administration of a single dose of 8 µg/kg/day, resulted in increased bone mineral fraction, increased trabecular thickness, decreased trabecular spacing, increased mineral content, and increased trabecular mineral density 7 days post exposure (Fader et al. 2018). The observed reductions in bone resorption biomarker and osteoclast surface to bone surface ratio are suggestive of impaired bone resorption. Similar results have been found in adult C57BL/6J mice administered 2.9 µg/kg/day 2,3,7,8-TCDD for 10 weeks (Herlin et al. 2013). The observed effects included increased trabecular bone mass (increased bone volume fraction, bone mineral deposits, and decreased spacing), decreased cortical bone thickness, imbalance of bone remodeling markers, and mechanically weaker bones.

Kiukkonen et al. (2002) examined the effect of intermediate-duration exposure to 2,3,7,8-TCDD on the lower incisor teeth in two strains of female rats (Han/Wistar and Long-Evans). Exposure to 0.12 or 1.2 µg/kg/day for 20 weeks resulted in discoloration, an opening of the pulp chamber to the lingual dental surface, and pulpal perforation to the lingual dental surface in both strains. Histological examination of the teeth showed larger-than-normal pulp chamber, pulpal cell death, and arrested dentin formation. The severity of the effects was dose-related, and no significant differences were found between the rat strains. ED_{50} values were estimated for incisor tooth defects in Han/Wistar and Long-Evans rats administered a single dose of 2,3,7,8-TCDD; the ED_{50} values were 57 and 22 µg/kg, respectively (Simanainen et al. 2002).

Other CDD Congeners—Animal Studies. Chronic-duration experiments with other congeners showed no musculoskeletal effects in Osborne-Mendel rats and B6C3F1 mice exposed in the diet to $5x10^5$ and $1.3x10^6$ µg/kg/day of 2,7-DCDD, respectively (NCI/NTP 1979a) or by gavage to approximately 0.34 and 0.7 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD, respectively (NCI/NTP 1980).

Simanainen et al. (2002) estimated ED_{50} values of 27, 64, and 760 µg/kg for incisor tooth defects in Han/Wistar rats administered a single dose of 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, or 1,2,3,4,6,7,8-HpCDD, respectively. In Long-Evans rats, the ED_{50} values were 24, 130, or 630 µg/kg, respectively.

2.9 HEPATIC

Overview. The potential hepatotoxicity of CDDs has been investigated in studies of workers, Seveso residents, residents living in areas with contaminated soil, Vietnam War veterans, the general population, and a large number of studies in laboratory animals. Results of a small number of studies examining the association between CDD exposure and liver diseases are inconsistent. Inconsistent results have also been reported in studies examining serum liver enzymes and lipid levels, with some studies reporting increases and other studies finding no alterations. In studies reporting alterations, the magnitudes of the alteration were small.

Although the results in humans are inconsistent, the results from animal studies provide strong evidence that the liver is a primary target of CDD toxicity; 2,3,7,8-TCDD was the most toxic congener, but other congeners were also capable of inducing hepatic effects. The induced effects were dose-related and species- and strain-related. Liver effects have been observed in numerous oral exposure studies of 2,3,7,8-TCDD at all exposure durations and in all species tested. The observed effects include increases in relative liver weight, increases in serum ALT levels, alterations in serum lipid levels, decreases in liver vitamin A levels, and histopathological alterations. Acute-duration oral exposures to 2,3,7,8-TCDD resulted in hepatocellular hypertrophy and vacuolization at doses ≥0.1 µg/kg/day. In intermediate-duration studies, liver effects were observed at ≥0.016 µg/kg/day and included hepatocellular hypertrophy, vacuolization, necrosis, and inflammation; similar effects were observed following chronic-duration exposure with the lowest LOAELs of ≥0.002 µg/kg/day. Long-term oral studies of 2,3,7,8-TCDD also reported biliary hyperplasia at ≥0.01 µg/kg/day. Toxic hepatitis was observed in rats exposed to 250,000 µg/kg/day 2,7-DCDD or 0.18 µg/kg/day mixture of 1,2,3,6,7,8-HxCDD and

1,2,3,7,8,9-HxCDD; cytoplasmic fatty vacuolization was observed in rats exposed to 36 µg/kg/day OCDD.

Epidemiological Studies. Several epidemiological studies have evaluated associations between CDD exposure, primarily 2,3,7,8-TCDD, and hepatic effects in workers, Seveso residents, residents living in areas with contaminated soil, Vietnam War veterans, and the general population. A summary of these studies is presented in Table 2-11. Most of these studies evaluated possible associations with liver enzyme levels and dyslipidemias; three studies examined possible associations with liver disease.

A medical survey of workers at two sodium trichlorophenol production facilities found no evidence of an elevated risk of clinical liver disease (hepatitis, cirrhosis, or fatty liver) (Calvert et al. 1992). An examination of children in Seveso found no increases in the risk of liver enlargement or scleral jaundice (Caramaschi et al. 1981). An increased risk of fatty liver was found in a study of residents living near a closed PCP facility in Taiwan (Lee et al. 2006); the association was found among residents with serum CDD/CDF TEQs in the fourth quartile. Among Vietnam War veterans with self-reported exposure to Agent Orange, there was no association with chronic hepatitis and an association for liver cirrhosis (Yi et al. 2014).

Studies examining liver enzymes primarily examined serum/plasma ALT, aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase activities; some studies evaluated serum activity levels while other studies examined the risk of abnormal levels. The results of these studies of workers, Seveso residents, residents living in areas with contaminated soil, and the general population are inconsistent. Increases in serum ALT levels were observed in two studies (Hoffman et al. 1986; Neuberger et al. 1999) but not in other studies (Yorita Christensen et al. 2013; Lee et al. 2006; Mocarelli et al. 1986; Ott et al. 1994). A study of Seveso children found an increased risk of abnormal serum ALT levels (Caramaschi et al. 1981) and two studies of workers did not find associations (Calvert et al. 1992; Moses et al. 1984). Increased serum AST levels have been reported (Hoffman et al. 1986; Lee et al. 2006; Mocarelli et al. 1986; Neuberger et al. 1999). However, Ott et al. (1994) did not find alterations in serum AST levels among workers, and no studies found an increased risk of abnormal AST levels (Calvert et al. 1992; Caramaschi et al. 1981; Moses et al. 1984). Several studies of workers (Calvert et al. 1992; Moses et al. 1984) and Seveso children (Caramaschi et al. 1981; Mocarelli et al. 1986) reported increased risk of abnormal serum GGT levels; Neuberger et al. (1999) also reported elevated serum GGT levels in workers. However, no association between CDD exposure and serum GGT

Table 2-11. Hepatic Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Occupational			
Calvert et al. 1992 Cross-sectional study of former workers (n=281) at two 2,4,5-T production facilities in New Jersey and Missouri and unexposed workers (n=260)	Current 2,3,7,8-TCDD level: 220 pg/g lipid Half-life extrapolated 2,3,7,8-TCDD level to estimate TCDD concentration at the time of exposure cessation: 1,900 pg/g lipid	Hepatitis	↔
		Cirrhosis	↔
		Fatty liver	↔
		Abnormal serum ALT	↔
		Abnormal serum AST	↔
		Abnormal serum GGT	↑
Calvert et al. 1996 Cross-sectional study of former workers (n=281) at two 2,4,5-T production facilities in New Jersey and Missouri and unexposed workers (n=260)	Current median 2,3,7,8-TCDD level: 0.406 pg/g serum in workers and 0.0369 pg/g serum in referents	Abnormal total cholesterol	↔
		Abnormal HDL cholesterol	↑, among workers with serum 2,3,7,8-TCDD levels of 1.516–19.717 pg/g lipid
		Abnormal triglyceride	↔
Mannetje et al. 2018 Cross-sectional study in former employees (n=245) of a phenoxy herbicide production facility in New Zealand	Work history and 2007–2008 serum 2,3,7,8-TCDD levels ≥10 pg/g lipid	Abnormal serum total cholesterol	↔, highly exposed job
		Abnormal serum triglyceride	↑, highly exposed job
		Abnormal HDL cholesterol	↑, highly exposed job
		Abnormal LDL cholesterol	↔, highly exposed job
Moses et al. 1984 Cross-sectional study of 206 workers at a 2,4,5-T production facility in the United States	Comparisons between workers with and without chloracne	Abnormal serum γ-glutamyl transferase	↑
		Abnormal serum triglycerides	↔
		Abnormal serum ALT	↔
		Abnormal serum AST	↔
Neuberger et al. 1999 Cross-sectional study of 56 workers with chloracne involved in the production of 2,4,5-trichlorophenol and 2,4,5-T at a facility in Austria; a matched control group was also examined	Median serum 2,3,7,8-TCDD level: 280.0 pg TEQ/g lipid (workers)	Serum ALT (compared to controls)	↑
		Serum AST (compared to controls)	↑
		Serum GGT (compared to controls)	↑

Table 2-11. Hepatic Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Ott et al. 1994 Retrospective cohort study of 138 workers exposed to 2,3,7,8-TCDD due to an accident at a trichlorophenol facility in Germany	Current 2,3,7,8-TCDD serum levels: <1–553 ppt Back calculated 2,3,7,8-TCDD serum levels: 3.3–12,000 ppt	Serum AST	↔
		Serum ALT	↔
		Serum GGT	↔
		Serum alkaline phosphatase	↑, using back calculated TCDD levels or chloracne status as biomarker
Pazderova-Vejlupková et al. 1981 Case series of 55 workers at a 2,4,5-T production facility in Czechoslovakia with signs of 2,3,7,8-TCDD toxicity (95% of workers had chloracne)	Not measured	Serum cholesterol	↑
Pelclova et al. 2001 Case series of 13 workers at a trichlorophenoxyacetic acid production facility in Czechoslovakia exposed to high levels of 2,3,7,8-TCDD during an accident 30 years ago	Mean serum 2,3,7,8-TCDD level in 1996: 256 pg/g lipid	Plasma cholesterol	↑
		Plasma triglycerides	↑
		Plasma lipids	↑
Suskind and Hertzberg 1984 Cross-sectional study of 204 exposed and 163 unexposed workers at a 2,4,5-T manufacturing facility in West Virginia	Not measured; comparisons between exposed and unexposed workers	Plasma cholesterol	↔
		Plasma triglycerides	↔
		Plasma LDL cholesterol	↔
		Plasma HDL cholesterol	↔
Seveso, Italy			
Assennato et al. 1989 Retrospective cohort study of 193 Seveso residents (88% were children <15 years of age) with chloracne and 182 controls from a neighboring region	Not measured	Serum GGT	↔
		Serum triglycerides	↔
		Serum cholesterol	↔
		Serum HDL cholesterol	↔

Table 2-11. Hepatic Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Caramaschi et al. 1981 Retrospective cohort study of 164 children with chloracne living in Seveso at the time of the accident and 182 children from the same area without chloracne	Not measured	Liver enlargement and/or scleral jaundice	↔
		Abnormal serum GGT	↑
		Abnormal serum AST	↔
		Abnormal serum ALT	↑
		Abnormal serum cholesterol	↔
		Abnormal serum alkaline phosphatase	↔
Mocarelli et al. 1986 Retrospective cohort study of 6–10-year-old children in zone A (n=69), zone B (n=83), and zone R (n=241, served as control group)	Not measured	Serum ALT	↔
		Serum AST	↑, boys
		Serum GGT	↑, boys
		Serum alkaline phosphatase	↔
		Serum triglycerides	↔
		Serum cholesterol	↔
Vietnam War veterans and Operation Ranch Hand veterans			
Yi et al. 2014 Group of 111,726 Korean veterans of the Vietnam War exposed to Agent Orange	Self-reported exposure	Chronic hepatitis	↔
		Liver cirrhosis	↑
Communities living in areas with contaminated soil			
Hoffman et al. 1986 Cross-sectional study of 154 people living in Quail Run Mobile Home Park and exposed to 2,3,7,8-TCDD in soil and 155 control subjects	Years of residence in the park used as surrogate for exposure	Serum triglycerides	↔
		Serum total cholesterol	↔
		Serum AST	↑
		Serum ALT	↑
		Serum GGT	↔
		Serum alkaline phosphatase	↑

Table 2-11. Hepatic Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Lee et al. 2006 Cross-sectional study of 52 residents living in the vicinity of a closed PCP manufacturing facility in Taiwan and 33 residents in a nearby control facility	Serum CDD/CDF TEQs: 80.1 pg TEQ/g lipid in residents and 50.9 pg TEQ/g lipid in controls Serum CDD/CDF TEQs (pg TEQ/g lipid): • 1st quartile: <22.93 • 4th quartile: ≥78.42	Fatty liver	↑, 4th quartile
		Serum cholesterol	↔, 4th quartile
		Serum triglyceride	↔, 4th quartile
		Serum AST	↑, 4th quartile
		Serum ALT	↔, 4th quartile
General population			
Yorita Christensen et al. 2013 Cross-sectional study using NHANES (2003–2004) data	Quartiles concentrations not reported	Serum ALT	↔, 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, or OCDD
Nakamoto et al. 2013 Cross-sectional study of 1,063 men and 1,201 women in Japan	Median serum total CDDs/CDFs: 9.8 pg TEQ/g lipid	Hyperlipidemia	↑, 2nd quartile and trend

↑ = association; ↔ = no association; 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; GGT = gamma-glutamyl transferase; HDL = high-density lipoprotein; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; LDL = low-density lipoprotein; NHANES = National Health and Nutrition Examination Survey; OCDD = octachlorodibenzo-*p*-dioxin; PCP = pentachlorophenol; TCDD = tetrachlorodibenzo-*p*-dioxin; TEQ = toxic equivalency

levels were observed in other studies of workers (Ott et al. 1994), Seveso children (Assennato et al. 1989), or residents living in an area with contaminated soil (Hoffman et al. 1986). Four studies evaluated possible associations with serum alkaline phosphatase levels; a study of workers (Ott et al. 1994) and residents living in an area with contaminated soil (Hoffman et al. 1986) found increased levels and two studies of Seveso children found no association (Caramaschi et al. 1981; Mocarelli et al. 1986).

As with the findings on serum liver enzyme levels, inconsistent results have been reported for serum lipids. Pelclova et al. (2001) reported increased serum triglycerides in workers, but other studies have not found increases in serum triglycerides (Assennato et al. 1989; Hoffman et al. 1986; Mocarelli et al. 1986; Suskind and Hertzberg 1984) or in the risk of abnormal triglycerides (Calvert et al. 1996; Moses et al. 1984). With the exception of a study of workers by Pelclova et al. (2001), studies of workers (Suskind and Hertzberg 1984), Seveso children (Assennato et al. 1989; Mocarelli et al. 1986), and communities living in areas with contaminated soil (Hoffman et al. 1986; Lee et al. 2006) did not find associations between CDD exposure and increased serum cholesterol levels. Calvert et al. (1996) found associations with an increased risk of abnormal total cholesterol levels and abnormal high-density lipoprotein (HDL) cholesterol in workers. However, HDL cholesterol and low-density lipoprotein (LDL) cholesterol levels were not elevated in studies of workers (Suskind and Hertzberg 1984) or Seveso children (Assennato et al. 1989).

2,3,7,8-TCDD—Animal Studies. Effects on the liver have been seen after acute-, intermediate-, and chronic-duration oral exposure and intermediate-duration dermal exposure to 2,3,7,8-TCDD. The observed effects include increases in liver weight, alterations in serum liver enzymes, alterations in liver and serum lipid levels, and histological alterations. Increased relative liver weights were observed in rats, mice, and hamsters at doses of ≥0.12, 3, and 14 µg/kg, respectively, following a single-dose oral exposure (Fletcher et al. 2001; Hanberg et al. 1989; Weber et al. 1995) and in rats and mice at ≥0.022 and 0.08 µg/kg/day, respectively (Fader et al. 2017b; Harrill et al. 2015), following intermediate-duration oral exposure.

As shown in Table 2-12, increases in serum ALT levels have been observed at doses ≥1 µg/kg; the magnitude of change is typically >250%. A number of studies have demonstrated alterations in serum lipid levels, in particular serum triglyceride and cholesterol levels. Inconsistent results have been found for serum triglyceride levels, with some studies reporting increases and others reporting decreases; however, this may be related to the amount of time lapse between dosing and sample collection. A study in rats reported increased serum triglyceride levels 24 hours post-exposure to 40 µg/kg 2,3,7,8-TCDD and

decreased levels 7 days post-exposure (Fletcher et al. 2005). Similarly, Boverhof et al. (2006) reported peak serum triglyceride levels 24 hours post-exposure, followed by a marked decrease in levels by 72 hours post-exposure. This time course could explain why Kakizuka et al. (2015) reported decreased serum triglyceride levels; rats were sacrificed 7 days post-exposure. Studies in rats have consistently found increased serum cholesterol levels following acute-duration oral exposure to 2,3,7,8-TCDD (see Table 2-12). A time-course study in rats administered a single dose of 40 µg/kg 2,3,7,8-TCDD demonstrated an initial decrease in serum cholesterol levels followed by increased levels 24 hours and 7 days post-exposure (Fletcher et al. 2005). Increases in free fatty acid levels have also been observed following single-dose administration (Boverhof et al. 2005, 2006; Kakizuka et al. 2015). Several studies have reported a depletion of vitamin A levels in the liver; decreases in hepatic retinoids and retinol levels have also been reported (see Table 2-12).

Table 2-12. Hepatic Clinical Chemistry in Rats and Mice Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, duration	Dose[a] (µg/kg)	Serum ALT	Serum triglycerides	Serum cholesterol	Other effects	Reference
Sprague-Dawley rat, once	10	↔	↑ (185%)	↑ (30%)	↑ FFA (87%)	Boverhof et al. 2006
Sprague-Dawley rat, once	40		↑ 24 hours (74%) ↓ 7 days (47%)	↑ (61%)	↓ hepatic retinoids	Fletcher et al. 2005
Sprague-Dawley rat, once	6.25				Altered vitamin A storage	Håkansson et al. 1989
Wistar rat, once	60		↓ (40%)	↑ (30%)	↔ hepatic cholesterol, ↔ FFA, ↑ serum bile acids	Kakizuka et al. 2015
Sprague-Dawley rat, 12 days	10	↔	↔	↔	↑ total bilirubin	Lu et al. 2010
Sprague-Dawley rat, once	10				↓ retinol storage	Thunberg et al. 1984
Fischer 344 rat, once	45		↑ (55%)	↑ (146%)		Walden and Schiller 1985
C57BL/6 mouse, once	30	↑ (260%)	↑ (40%)	↓ (28%)	↑ FFA (28%)	Boverhof et al. 2005, 2006
A2G-hr/+ mouse, once	75	↑ (412%)				Greig et al. 1987

Table 2-12. Hepatic Clinical Chemistry in Rats and Mice Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, duration	Dose[a] (µg/kg)	Serum ALT	Serum triglycerides	Serum cholesterol	Other effects	Reference
C57BL/6 mouse, 2 weeks (1 time/week)	2.9	↑ (629%)				Lamb et al. 2016
C57BL/6 mouse, once	125	↑ (300%, males)				Pohjanvirta et al. 2012
Sprague-Dawley rat, 13 weeks	0.01				↓ hepatic retinol	Van Birgelen et al. 1995
CD rat, 30 days	1			↑ (70%)		Zinkl et al. 1973

[a]Doses were duration-adjusted for continuous exposure.

↑ = association; ↓ = inverse association; ↔ = no association; ALT = alanine aminotransferase; FFA = free fatty acid

A variety of histopathological alterations have been observed in the liver following acute-, intermediate-, or chronic-duration oral exposure to 2,3,7,8-TCDD; see Table 2-13. Single-dose exposure to 10–40 µg/kg resulted in hypertrophy in rats. Other effects observed in acutely exposed rats include cytoplasmic vacuolization at 10 µg/kg and necrosis and inflammation at 40 µg/kg. In mice, the lowest LOAEL for histological alterations was 30 µg/kg; at this dose, cytoplasmic vacuolization and necrosis were observed. Fatty changes were observed at 75 µg/kg and inflammation was observed at 500 µg/kg. Guinea pigs were more sensitive than rats and mice, with necrosis occurring following a single dose of 0.1 µg/kg. Long-term oral exposure resulted in hypertrophy, necrosis, inflammation, and fatty changes in rats at doses ≥0.013 µg/kg/day and cytoplasmic vacuolization and necrosis in mice at ≥0.09 µg/kg/day. Biliary hyperplasia has been observed in monkeys following intermediate-duration exposure to ≥0.01 µg/kg/day and in rats following chronic-duration oral exposure to ≥0.01 µg/kg/day. Other hepatic lesions observed in rats exposed to 2,3,7,8-TCDD for 2 years included bile duct cysts at 0.016 µg/kg/day and cholangiofibrosis, portal fibrosis, and nodular hyperplasia at 0.032 µg/kg/day (NTP 2006). Another 2-year study found toxic hepatitis in rats and mice administered 0.02 µg/kg/day (NTP 1982b).

Table 2-13. Histopathological Alterations in the Liver of Experimental Animals Resulting From Oral Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	Oral doses[a] (µg/kg/day) resulting in histopathological alterations							
Species, duration	Hypertrophy	Necrosis	Inflammation	Fatty changes	Cytoplasmic vacuolization	Hepatocytes with pyknotic nuclei	Biliary hyperplasia	Reference
Sprague-Dawley rat, once	10							Boverhof et al. 2006
Sprague-Dawley rat, once	10							Boverhof et al. 2006
Sprague-Dawley rat, once	25							Christian et al. 1986
Sprague-Dawley rat, once	40							Fletcher et al. 2005
Sprague-Dawley rat, 3 days		40	40					Hermansky et al. 1988
Sprague-Dawley rat, 12 days					10			Lu et al. 2010
C57BL/6 mouse, once					30			Boverhof et al. 2005
C57BL/6 mouse, once					1			Boverhof et al. 2005
C57BL/6 mouse, once					0.1			Boverhof et al. 2006
C57BL/6 mouse, once	30				30			Boverhof et al. 2006
A2G-jr/+ mouse, once		75		75				Greig 1984, 1987
C57BL/6 mouse, once					30			Kopec et al. 2010
C57BL/6 mouse, once		30			30			Kopec et al. 2008

Table 2-13. Histopathological Alterations in the Liver of Experimental Animals Resulting From Oral Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	Oral doses[a] (µg/kg/day) resulting in histopathological alterations							
Species, duration	Hypertrophy	Necrosis	Inflammation	Fatty changes	Cytoplasmic vacuolization	Hepatocytes with pyknotic nuclei	Biliary hyperplasia	Reference
C57BL/6 mouse, once		500	500		500			Pohjanvirta et al. 2012
Hartley guinea pig, once		0.1						Turner and Collins 1983
Rhesus monkey, 9 months							0.011	Allen et al. 1977
Rhesus monkey, 3 weeks, 3 days/week							0.1	McNulty 1984
Sprague-Dawley rat, 4 weeks (19 doses)	0.022							Harrill et al. 2015
Sprague-Dawley rat, 14 weeks, 5 days/week	0.016							NTP 2006
Sprague-Dawley rat, 31 weeks	0.016			0.071				NTP 2006
C57BL/6 mouse, 28 days					0.8			Fader et al. 2015
C57BL/6 mouse, 28 days (seven doses)		0.8			0.3			Fader et al. 2017b
BALB/c mouse, 28 days						0.09		Maranghi et al. 2013
BALB/c mouse, 28 days			0.0009					Rasinger et al. 2018
Sprague-Dawley rat, 2 years		0.01	0.01	0.01			0.01	Kociba et al. 1978

Table 2-13. Histopathological Alterations in the Liver of Experimental Animals Resulting From Oral Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	Oral doses[a] (µg/kg/day) resulting in histopathological alterations							
Species, duration	Hypertrophy	Necrosis	Inflammation	Fatty changes	Cytoplasmic vacuolization	Hepatocytes with pyknotic nuclei	Biliary hyperplasia	Reference
Sprague-Dawley rat, 2 years	0.002	0.002	0.002				0.016	NTP 2006

[a]Doses were adjusted for continuous exposure.

The National Toxicology Program (NTP) 2-year study in female rats grouped all non-neoplastic liver changes together (termed toxic hepatopathy) in order to evaluate the incidence and severity dose-response (NTP 2006). The incidences of toxic hepatopathy increased with dose; 15, 57, 85, and 100% at 0.0071, 0.016, 0.032, and 0.071 µg/kg/day, respectively. The respective severity scores were 1.3, 1.2, 1.8, and 3.5 (a severity score of 1 was considered minimal and 4 considered marked). The NOAEL of toxic hepatopathy was 0.002 µg/kg/day; note that there were significant increases in specific types of lesions at this dose level. The NTP (2006) study also demonstrated duration-dependent increases in the severity of effects and the pattern of hepatotoxicity. Hepatocellular hypertrophy and diffuse fatty changes were observed at 14 weeks; hepatocellular hypertrophy, diffuse fatty changes, and inflammation were observed after 31 weeks of exposure; hepatocellular hypertrophy, diffuse fatty changes, inflammation, and bile duct hyperplasia were observed after 53 weeks of exposure; and hepatocellular hypertrophy, diffuse fatty changes, inflammation, bile duct hyperplasia, bile duct cysts, necrosis, cholangiofibrosis, portal fibrosis, and nodular hyperplasia were observed after 2 years of exposure.

In dermal exposure studies, liver hypertrophy was observed in mice administered 0.01 µg 2 times/week for 20 weeks (Hebert et al. 1990) and fatty changes were observed in male mice administered 0.005 µg 3 times/week for 13 weeks (NTP 1982a). No hepatic effects were observed in male mice chronically exposed to 0.001 µg 3 times/week for 2 years.

Other CDD Congeners—Animal Studies. A small number of studies have evaluated the hepatotoxicity of other CDD congeners. In acute-duration oral exposure studies, no histological alterations were observed in mice exposed to 10 µg/kg/day 2,7-DCDD for 14 days (Holsapple et al. 1986), 1,000 µg/kg 1,2,3,4-TCDD once (Courtney 1976), or 20 µg/kg/day OCDD for 10 days (Courtney 1976). Liver effects were reported following longer-term oral exposure. Toxic hepatitis (characterized as centrilobular fatty metamorphosis and/or necrosis) was observed in rats and mice exposed to 250,000 or 1,300,000 µg/kg/day, respectively, 2,7-DCDD for 110 weeks (NCI/NTP 1979a). Toxic hepatitis (characterized as degenerative hepatocellular changes, mild fibrosis, and bile duct hyperplasia) was also observed in rats and mice exposed to 0.18 or 0.7 µg/kg/day mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD 2 days/week for 2 years (NCI/NTP 1980). Intermediate-duration exposure to 36 µg/kg/day OCDD resulted in cytoplasmic fatty vacuolization (Couture et al. 1988) in rats; no liver alterations were observed in rats exposed for 2 weeks (Couture et al. 1988).

2.10 RENAL

Overview. A few epidemiological studies evaluated potential renal effects with mixed results. Renal effects have been reported in animals following oral exposure to 2,3,7,8-TCDD or 1,2,3,4,6,7,8-HpCDD. Evidence of impaired renal function (increases in serum creatinine and urea nitrogen levels) and histological alterations have been reported in rats, mice, and monkeys orally exposed to 2,3,7,8-TCDD. The lowest LOAELs for renal effects were 10 µg/kg/day for increased serum creatinine and urea nitrogen levels and proximal tubular damage in rats following acute-duration exposure, 0.01 µg/kg/day for tubular epithelial hyperplasia in monkeys following intermediate-duration exposure, and 0.032 µg/kg/day for transitional epithelial hyperplasia in rats following chronic-duration exposure. Renal lesions were also observed in rats administered 1,2,3,4,6,7,8-HpCDD over a lifetime but not in rats exposed to 2,7-DCDD or a mixture of HxCDD congeners for 2 years.

Epidemiological Studies. A child who played in a sand box contaminated with waste oils containing 2,3,7,8-TCDD developed hemorrhagic cystitis and focal pyelonephritis (Kimbrough et al. 1977). Since chloracne was not seen and levels of 2,3,7,8-TCDD in the sand were not provided, the effects cannot be definitely attributed to 2,3,7,8-TCDD exposure. No renal effects were reported in other individuals exposed at the same location. An early study in Missouri residents chronically exposed to a 2,3,7,8-TCDD-contaminated environment found increased incidence of self-reported urinary problems, leukocyturia, and microscopic hematuria (Webb et al. 1984). However, the results of urinalysis on this group did not indicate any kidney effects (Hoffman et al. 1986; Stehr et al. 1986). A study of a community near a production facility with serum dioxin levels found an association between high dioxin levels (CDD/CDF TEQ ≥20 pg TEQ/g lipid) and chronic kidney disease (Huang et al. 2016). No renal effects were found in a group of Vietnam veterans exposed to 2,3,7,8-TCDD in Agent Orange based on case histories and evaluation of five laboratory variables comparing Ranch Hand veterans and the various comparison groups (USAF 1991; Wolfe et al. 1985). Using NHANES 1999–2004 data, Everett and Thompson (2016) found an association between serum 1,2,3,6,7,8-HxCDD levels of ≥0.299 pg/g lipid and the risk of nephropathy among adults.

2,3,7,8-TCDD—Animal Studies. Mild-to-moderate renal effects have been reported in some mature animals exposed to lethal or near-lethal levels of 2,3,7,8-TCDD. Acute-duration exposure to 2,3,7,8-TCDD caused dilation of convoluted tubules and Bowman's spaces at 10 µg/kg/day or 25 µg/kg in Sprague-Dawley rats (Christian et al. 1986; Lu et al. 2009). Similar findings were reported in monkeys exposed to 0.011 µg/kg/day of 2,3,7,8-TCDD for 9 months (Allen et al. 1977) and Wistar rats exposed to

1 µg/kg/day for 1 month (Erdemli et al. 2020). Increased serum creatinine and urea levels were also observed in rats exposed to 10 µg/kg/day for 12 days (Lu et al. 2009) or 1 µg/kg/day for 1 month (Erdemli et al. 2020). No renal effects were observed in rats exposed to ≤0.071 µg/kg/day for 14 or 31 weeks (NTP 2006). Chronic-duration exposure to 0.032 or 0.071 µg/kg/day 2,3,7,8-TCDD for 2 years resulted in increases in the incidence of transitional epithelial hyperplasia in the kidneys of female Sprague-Dawley rats (NTP 2006). Mild nephropathy was also observed in rats exposed to 0.071 µg/kg/day for 2 years or for 30 weeks followed by a 16.5-month recovery period (NTP 2006); the incidence in the stop-exposure group was significantly lower than the continuous exposure group. Chronic-duration exposure of B6C3F1 mice by gavage to approximately 0.071 µg/kg/day of 2,3,7,8-TCDD induced renal inflammatory changes; no effects were found at 0.0071 µg/kg/day (NTP 1982b). In contrast, no renal effects were found in Osborne-Mendel rats exposed to 0.071 µg/kg/day of 2,3,7,8-TCDD for 104 weeks (NTP 1982b) or in Sprague-Dawley rats exposed to 0.1 µg/kg/day of 2,3,7,8-TCDD in the feed for 2 years (Kociba et al. 1978).

Information regarding renal effects in animals after dermal exposure to 2,3,7,8-TCDD is limited. No histopathological changes were found in Swiss Webster mice exposed to 0.005 µg 2,3,7,8-TCDD 3 days/week for 99–104 weeks (NTP 1982a).

Other CDD Congeners—Animal Studies. An increase in the prevalence of non-malignant kidney lesions were observed in female Sprague-Dawley rats administered 4 µg/kg/day 1,2,3,4,6,7,8-HpCDD over a lifetime; the lesions were described as glomerulonephritis, nephritis, nephropathy, hydronephrosis, and proteinuria; however, the incidences for specific lesions were not reported (Rozman et al. 2005). Studies with other congeners reported no renal effects following chronic-duration exposure to 0.34 or 0.7 µg/kg/day of a mixture of 1,2,3,7,8,9-HxCDD and 1,2,3,6,7,8-HxCDD by gavage in rats and mice, respectively (NCI/NTP 1980) or $5x10^5$ and $1.3x10^6$ µg/kg/day of 2,7-DCDD in the feed in rats and mice, respectively (NCI/NTP 1979a).

2.11 DERMAL

Overview. Epidemiological and animal studies provide evidence that the skin is a target tissue following exposure to high doses of CDDs. Dermal effects, particularly chloracne, are the most commonly reported effects of 2,3,7,8-TCDD exposure in humans because they are easy to identify. Chloracne may persist 20–30 years postexposure. Interindividual differences in susceptibility do exist and may be linked to

genetic polymorphism. Other dermal conditions reported include hypertrichosis, hyperpigmentation, and solar elastosis.

Dermal effects have been observed in animals following oral exposure to 2,3,7,8-TCDD or other congeners. The most commonly reported effects include hair loss and dermatitis in monkeys and mice exposed to 2,3,7,8-TCDD and hair loss in rats exposed to 1,2,3,7,8-PeCDD or 1,2,3,4,7,8-HxCDD. Dermal exposure to 2,3,7,8-TCDD can result in damage to sebaceous glands in mice.

Epidemiological Studies. The most observed effect of 2,3,7,8-TCDD exposure in humans is chloracne (Jirasek et al. 1976; Kimbrough et al. 1977; May 1973; Oliver 1975; Reggiani 1980). Chloracne is characterized by follicular hyperkeratosis (comedones) occurring with or without cysts and pustules (Crow 1978). Unlike adolescent acne, chloracne may involve almost every follicle in an involved area and may be more disfiguring than adolescent acne (Worobec and DiBeneditto 1984). Chloracne usually occurs on the face and neck, but may extend to the upper arms, back, chest, abdomen, outer thighs, and genitalia. In mild cases, the lesions may clear several months after exposure ceases, but in severe cases, they may still be present 30 years after initial onset (Crow 1978; Moses and Prioleau 1985). In some cases, lesions may resolve temporarily and reappear later. Scarring may result from the healing process. Other chlorinated organic chemicals can also cause chloracne.

Acute-duration exposure to 2,3,7,8-TCDD in a chemical laboratory induced the development of chloracne in two of three individuals within 8 weeks of the exposure (Oliver 1975). Chloracne occurred in workers occupationally exposed to 2,3,7,8-TCDD during the manufacture of herbicides (Bond et al. 1989; Moses and Prioleau 1985; Poland et al. 1971) and after industrial accidents in several locations throughout the world (Goldman 1972; May 1973; Moses et al. 1984; Pocchiari et al. 1979; Suskind and Hertzberg 1984).

Accidental exposure to 2,3,7,8-TCDD in a 1949 explosion in a trichlorophenol plant in Nitro, West Virginia, resulted in an outbreak of severe chloracne. Moses et al. (1984) conducted a cross-sectional survey of workers in this plant in 1979. In reviewing the impact of the accident, the study authors indicated that 117 workers had severe chloracne as a result of the explosion; however, 111 additional workers were found to have had chloracne prior to the explosion. A cross-sectional study of 226 workers in 1979 indicated that 52% had chloracne that persisted for 26 years, and in 29 subjects, it was still present after 30 years. Blood levels were not measured, but the air dust in the plant was suspected to have contained 2,4,5-T contaminated with 6 ppm 2,3,7,8-TCDD compared to 0.1 ppm in later years. Similarly, high incidences of chloracne were also found in other facilities (Jirasek et al. 1976; May 1973; Poland et

al. 1971). Appearance of chloracne after accidental occupational exposure may be immediate or delayed; since workers may not always be removed from the work environment, the duration of exposure and total exposure is difficult to assess.

Skin lesions from environmental exposures to 2,3,7,8-TCDD have been most thoroughly studied in the population exposed in Seveso, Italy. Reggiani (1980) described dermal lesions for 17 persons (primarily children) hospitalized shortly after the accidental release in Seveso. Acute lesions probably due to alkali and burns were observed immediately and had a duration of up to 2 months; chloracne in children occurred within 2 weeks (earliest occurrence was 3 days) and usually persisted for 8–26 months. Irritative lesions (characterized by erythema and edema of exposed areas, vesiculobullous and necrotic lesions, and papulonodular lesions) were observed in 447 people in Seveso 20–40 days after the accident, and 34 of these individuals later developed chloracne (Caputo et al. 1988). In 1976 and 1978, there were 193 childhood cases of chloracne and 17 of the most severe were in zone A where soil levels were the highest. Bisanti et al. (1980) reported that in zone A, 46 early cases (within 3–6 months of exposure) and 15 late cases (within 7–10 months of exposure) of chloracne were seen, and in zone B, 9 delayed cases were observed. In all zones, 50 early-appearing and 143 late-appearing cases of chloracne were reported (Caputo et al. 1988). In the 193 people with chloracne, the comedones and cysts progressively decreased in the 2 years following the accident (Caputo et al. 1988). In the most severe cases, regression of the lesions began at the end of 1978. All affected children were clear of lesions by 1982. Histological examination of the lesions from the limbs of severe chloracne patients revealed orthokeratotic hyperkeratosis with loss of adhesiveness, particularly near the follicular ostia; dilated follicular ostia filled with cornified lamellae; acanthosis; horny metaplasia with possible acrosyringeal cyst formation in the dermal and intradermal eccrine duct; and foreign body granulomas around the detached wall of the excretory ducts of some eccrine sweat glands (Caputo et al. 1988). Thirty of the 30,000 samples of serum collected and frozen in 1976 (10 zone A residents with the most severe cases of chloracne types 3 and 4 [chloracne was rated as type 1 for the mildest form to type 4 for the most severe cases], 10 former zone A residents who did not develop chloracne, and 10 controls from non-contaminated zones) were analyzed by Mocarelli et al. (1991). 2,3,7,8-TCDD blood levels (lipid adjusted) of 12,100–56,000 ppt were observed in six children with type 4 chloracne and levels of 828, 1,690, and 7,420 ppt were found in three children with type 3 chloracne. In adults, levels of 1,770–10,400 ppt were associated with no chloracne. No chloracne was observed in Missouri residents who had adipose 2,3,7,8-TCDD levels of 5.2–59.1 ppt 16 years after exposure (using a half-life of 8.5 years, peak tissue levels of 6–204 ppt can be estimated) (Needham et al. 1991). While there is a higher incidence of this disorder in those with higher

serum 2,3,7,8-TCDD levels, interindividual variability makes it difficult to specify a dose that will result in chloracne.

The results of a further examination of Operation Ranch Hand veterans were published (Burton et al. 1998). The cohort consisted of 930 exposed subjects and 1,200 comparison individuals who served in Southeast Asia (SEA) during the same period, but who were not involved with spraying herbicides. The study authors examined the associations between serum dioxin levels and: (1) chloracne; (2) occurrence of acne relative to the tour of duty in SEA; and (3) anatomical location of acne after service in SEA. Initial dioxin levels were computed using a first-order pharmacokinetic model with a constant half-life of 8.7 years. Four exposure categories were defined: (1) comparisons, with current dioxin levels of ≤10 ppt; (2) background Operation Ranch Hand veterans, with current dioxin levels of ≤10 ppt; (3) low category, with current dioxin levels exceeding 10 ppt but ≤94.2 ppt; and (4) high category, with dioxin levels >92.4 ppt. Adjustments were made for age, race, and military occupation. The ranges of initial dioxin levels in the low and high categories were 27.7–94.1 and 94.2–3,290 ppt, respectively. Because physicians did not find any cases of chloracne among Operation Ranch Hand veterans at any physical examination and no cases were found via medical record review, the analysis was restricted to cases of acne. The results showed that among Operation Ranch Hand veterans who had acne only after their service in SEA, the prevalence of acne at any location was increased in the high-exposure category, but the adjusted odds ratio (OR) relating acne in the eye-ear-temple location and dioxin category was increased for all three Operation Ranch Hand exposure categories. The increase was greatest in the background exposure category (OR: 1.3; 95% confidence interval [CI]: 0.8–2.2). According to Burton et al. (1998), the results suggest that the Operation Ranch Hand exposure to dioxin, which was much lower than the Seveso exposure, was insufficient for the production of chloracne or that the exposure may have caused chloracne that resolved and was currently undetectable.

The incidence of chloracne was examined in a group of 3 men and 4 women who were among 231 workers exposed to dioxins at a chemical factory in Ufa, Russia, approximately 25 years prior to blood collection in 1991 and 1992 (Schecter et al. 1993). Five of the seven (three males and two females) were diagnosed with chloracne after working in the manufacture of 2,4,5-T contaminated with 2,3,7,8-TCDD between 1965 and 1967. Blood analysis showed 2,3,7,8-TCDD levels (on a lipid basis) ranging from 36 to 291 ppt (mean 185 ppt) in 1991 and 1992 compared with a mean of 4.4 ppt from a sample of 68 subjects from the general Russian population. Polychlorinated dibenzofurans and "dioxin-like" PCBs were also detected, but it was estimated that in the workers, 2,3,7,8-TCDD contributed >60% of the total dioxin equivalents (2,3,7,8-TCDD plus "dioxin-like" CDDs and PCBs). One of the workers

diagnosed with chloracne had the lowest 2,3,7,8-TCDD blood concentration of the group, whereas two workers with higher levels did not display chloracne. This suggested that the presence of chloracne indicates exposure to dioxin (or similar chlorinated chemical), but its absence does not preclude such exposure, as noted by others (Mocarelli et al. 1991). Schecter et al. (1993) estimated that in the workers, the dioxin TEQs in 1967 were 226–1,707 ppt, assuming a 10-year half-life and 1,173–9,366 ppt assuming a 5-year half-life. They also estimated the total 2,3,7,8-TCDD body burden for the workers to have been between 22 and 172 μg using a 5-year half-life and 4–30 μg using a 10-year half-life (mean present body burden was 3.2 μg versus 0.072 μg for general population). According to Schecter et al. (1993), this is the first reported incidence of chloracne in females with elevated dioxin blood levels from occupational exposure.

A group of eight individuals who had contracted chloracne between 1973 and 1976 while working in the manufacture of TCP or in the maintenance of a TCP plant were examined 15 years after the exposure (Jansing and Korff 1994). Slight residual chloracne was diagnosed in two subjects, but otherwise, the workers were healthy. 2,3,7,8-TCDD levels in blood were 163–1,935 ppt (lipid basis), and by assuming a half-life of 7 years, the study authors estimated that the blood concentrations during the exposure were 545–9,894 ppt. It was found that the concentration of 2,3,7,8-TCDD in blood correlated well (r=0.93) with duration of chloracne if two subjects with a disposition to hypersensitive skin reactions were not included in the analysis.

Two follow-up studies were located regarding dermal effects in humans following exposure to dioxins. The first follow-up was on a case-control study that originally included 159 cases of chloracne reported during the time period of 1969–1975 in TCDD-contaminated production of the herbicide, 2,4,5-T (Kogevinas et al. 1993, 1997). Only 50 survivors remained in 1996 and constituted the follow-up study cohort (Neuberger et al. 1999). Chloracne was found in 15 males and 1 female out of the surviving 50 cases originally diagnosed with chloracne. Similarly, a follow-up examination of 13 workers exposed 30 years ago (Jirasek et al. 1976) to TCDD in an industrial incident in an herbicide production plant was conducted (Pelclova et al. 2001). The current mean plasma level was 256 pg TCDD/g lipid (range: 14–760 pg/g lipid) in the follow-up study. Chloracne persisted in two individuals with their respective current TCDD levels of 760 and 420 pg/g lipids. In contrast, no chloracne was found in one individual with 600 pg TCDD/g lipids body burden.

Some insights regarding differences in individual susceptibility may be inferred from a genetic polymorphism study in CYP1A1 and GSTM1 in human populations exposed to PCB/CDF-contaminated

oil in Taiwan in 1979 (Tsai et al. 2006). About 2,000 people consumed the contaminated oil in the Yu-Cheng incident (see ATSDR 2023 for more details). Predominant dermal effects included chloracne, abnormal nails, hyperkeratosis, and skin allergies. In the genetic polymorphism study, 393 exposed and 181 control individuals were examined (Tsai et al. 2006). Among highly exposed individuals (>51 ppb PCB), combined CYP1A1-MspI mutant genotype and GSTM1-null genotype were linked to increased risk of chloracne (OR: 2.8). Among individuals with intermediate-duration exposures (≤51 ppb PCB), GSTM1-null genotype was linked to dermal allergies in both CYP1A1 genotypic groups.

Other effects manifested as dermal changes have also been noted to accompany chloracne. In addition to chloracne, hyperpigmentation and hirsutism (also known as hypertrichosis or abnormal distribution of hair) were also reported in 2,3,7,8-TCDD-exposed workers (Jirasek et al. 1976; Oliver 1975; Poland et al. 1971; Suskind and Hertzberg 1984). In the cohort examined by Suskind and Hertzberg (1984), hypertrichosis was observed 25 years after exposure, particularly among workers with persistent chloracne upon clinical examination. In contrast, Moses et al. (1984) found no evidence of hypertrichosis, even though 31% of the exposed workers had evidence of residual chloracne. Webb et al. (1989) observed three cases of hypertrichosis, but not hyperpigmentation, among Missouri residents, one with serum levels of <20 pg/g and two with levels between 20 and 60 pg/g. However, neither condition was noted on examination among residents of the Quail Run Mobile Home Park (Hoffman et al. 1986). Actinic or solar elastosis was also observed among a group of workers diagnosed with active chloracne at the time of their examinations in 1979 (Suskind and Hertzberg 1984).

2,3,7,8-TCDD—Animal Studies. A number of changes in the skin have been observed in rodents and monkeys following oral exposure to 2,3,7,8-TCDD. In monkeys, skin lesions seen after a single oral dose or repeated dosing resemble the chloracne observed in humans. Nail loss and facial hair loss with acneiform lesions were observed in Rhesus monkeys following acute-duration exposure to a single dose of 70 µg/kg (McConnell et al. 1978a). Monkeys had hair loss due to squamous metaplasia and keratinization of the sebaceous glands and hair follicles following intermediate-duration exposure to 0.011 µg/kg/day of 2,3,7,8-TCDD in the diet (Allen et al. 1977) or exposure to 0.1 µg/day, 3 days/week for 3 weeks (McNulty 1984). Skin thickening was observed in A2G-hr/+ mice exposed to a single dose of 75 µg/kg 2,3,7,8-TCDD (Greig 1984). A 10-week exposure to 1.3 µg/kg/day resulted in alopecia and edema in Swiss-Webster mouse dams (Thomas and Hinsdill 1979). No alteration in scratching behavior was observed in hairless mice administered via gavage 0.001 µg/kg/day TCDD for 54 days (Ono et al. 2010); however, dermal application of an external stimuli (distilled water or acetone/olive oil) resulted in increased scratching behavior at 0.0003 µg/kg/day. Chronic-duration exposure by gavage to

2,3,7,8-TCDD induced dermatitis in B6C3F1 mice at 0.36 µg/kg/day (Della Porta et al. 1987) and amyloidosis in Swiss mice at 0.001 µg/kg/day (Toth et al. 1979). In the B6C3F1 mice, dermatitis regressed after discontinuation of treatment (Della Porta et al. 1987). In contrast, no dermal effects were observed in Osborne-Mendel rats and B6C3F1 mice following chronic-duration exposure to 0.071 and 0.3 µg/kg/day of 2,3,7,8-TCDD, respectively, by gavage for 104 weeks (NTP 1982b).

The dermal toxicity to 2,3,7,8-TCDD following dermal exposure has been investigated. Epidermal hyperplasia and hyperkeratosis and involution of sebaceous glands were observed in newborn and adult hairless HRS/J mice dermally exposed 3 days/week for 2 weeks to 0.01 µg (newborns) or 0.1 µg (adults) (Puhvel and Sakamoto 1988); the reactions were similar in the adults and newborns. A similar exposure of haired HRS/J mice only resulted in involution of sebaceous glands (Puhvel and Sakamoto 1988). A 4-week exposure of HRS/J mice resulted in hyperkeratinization of the stratum corneum, epidermal hyperplasia, and an absence of sebaceous glands and follicles (Puhvel et al. 1982). Acne-like lesions in the ears were found in CD-1 mice following exposure to 0.1 µg 2,3,7,8-TCDD applied on the pre-shaved back 2 days/week for 30 weeks (Berry et al. 1978, 1979). In contrast, no dermal effects were observed in Swiss Webster mice exposed to 0.005 µg 2,3,7,8-TCDD/application, 3 days/week for up to 104 weeks (NTP 1982a). Poland et al. (1984) evaluated the toxicity of 2,3,7,8-TCDD in several strains of mice. A once-a-week exposure of 0.3 µg 2,3,7,8-TCDD for 4 weeks resulted in sebaceous gland metaplasia, and epidermal hyperplasia, hyperkeratosis, and keratinized cyst formation in the hairless mutants of HRS/J, C57BL/6J, and C3H/HeN strains; no dermal lesions were observed in the haired mutants. Similar results were observed in hairless DBA/2J mice administered 1 µg 2,3,7,8-TCDD once a week for 4 weeks (Poland et al. 1984). There are a number of limitations in the reporting of the study, including lack of information on the number of animals tested and incidence data and the lack of a control group, which makes it difficult to compare across strains. Based on the severity scores, it appears that HRS/J mice may be more sensitive than the other strains.

Other CDD Congeners—Animal Studies. No dermal effects were found in Osborne-Mendel rats and B6C3F1 mice gavaged with approximately 0.34 and 0.7 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD, respectively, for 104 weeks (NCI/NTP 1980). However, male and female Sprague-Dawley rats treated with doses equivalent to 2.6–3.8 µg 1,2,3,7,8-PeCDD/kg/day or 10.3–15.4 µg 1,2,3,4,7,8-HxCDD/kg/day for 13 weeks exhibited occasional hair loss and sores in the ears, nose, neck, tail, and feet (Viluksela et al. 1998a). No effects were observed following chronic-duration exposure of Osborne-Mendel rats and B6C3F1 mice to $5x10^5$ and $1.3x10^6$ µg/kg/day of 2,7-DCDD, respectively, in the feed (NCI/NTP 1979a).

2.12 OCULAR

Overview. One epidemiological study reported eye irritation in workers with chloracne. Ocular effects (swelling and inflamed eye lids) have been reported in monkeys orally exposed to 2,3,7,8-TCDD. Ocular application of 2,3,7,8-TCDD, 2,7-DCDD, mixed HxCDD, or OCDD resulted in conjunctival inflammation in rabbits.

Epidemiological Studies. Eye irritation, which correlated with severity of chloracne, was reported by Poland et al. (1971) among workers employed in a 2,4,5-T factory; however, the role of 2,3,7,8-TCDD, if any, cannot be determined.

2,3,7,8-TCDD—Animal Studies. Ocular effects have been observed in Rhesus monkeys following acute- or intermediate-duration oral exposure to 2,3,7,8-TCDD. Swelling and inflamed eyelids were observed following a single-dose exposure of 70 µg/kg (McConnell et al. 1978a). Intermediate-duration exposure to 0.011 µg/kg/day in the diet or 0.1 µg/kg/day via gavage resulted in periorbital edema (Allen et al. 1977) and gavage administration of 0.1 µg/kg/day resulted in thickening and reddening of the eyelids (McNulty 1984). No ocular effects were observed in Osborne-Mendel or Sprague-Dawley rats following chronic-duration exposure to 0.071 µg/kg/day 2,3,7,8-TCDD by gavage for 104 weeks (NTP 1982b, 2006) or B6C3F1 mice administered 0.3 µg/kg/day for 2 years (NTP 1982b).

A single application of 2,000 µg 2,3,7,8-TCDD into the conjunctival sac of rabbits caused transient pain and conjunctival inflammation and delayed conjunctival chemosis (Schwetz et al. 1973); no corneal injury or iritis were observed.

Other CDD Congeners—Animal Studies. No ocular effects were found in Osborne-Mendel rats and B6C3F1 mice gavaged with approximately 0.34 and 0.7 µg/kg/day of a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD, respectively, for 104 weeks (NCI/NTP 1980). Similarly, no effects were observed following chronic-duration exposure of Osborne-Mendel rats and B6C3F1 mice to $5x10^5$ and $1.3x10^6$ µg/kg/day of 2,7-DCDD, respectively, in the feed (NCI/NTP 1979a).

Transient pain and conjunctival inflammation, but no corneal injury or iritis, were observed in rabbits following a single application of 2,000 µg 2,7-DCDD, mixed HxCDD, or OCDD into the conjunctival sac of rabbits (Schwetz et al. 1973).

2.13 ENDOCRINE

Overview. Potential endocrine effects have been reported in studies of workers, Vietnam War veterans, Seveso cohort, communities living in areas with contaminated soil, and the general population. These studies have primarily focused on thyroid alterations and diabetes. Epidemiological studies have not found consistent alterations in thyroid hormone levels or thyroid disease. A number of studies have found associations between CDD exposure and an increased risk of diabetes.

CDDs were shown to alter endocrine parameters mostly in oral exposure rodent studies of 2,3,7,8-TCDD. One of the better characterized effects was a decrease in serum thyroxine (T4), caused apparently by CDD-induced T4 metabolism and excretion. A number of studies have evaluated thyroid hormone levels in animals orally exposed to 2,3,7,8-TCDD. Decreases in serum T4 levels have been observed in acute-duration studies at doses ≥5 µg/kg and in intermediate-duration studies at doses ≥0.016 µg/kg/day. Results for serum triiodothyronine (T3) levels are less consistent across studies, and TSH levels are increased following high-dose, acute-duration exposure but has not been observed at lower intermediate- or chronic-duration exposures. Some studies in rodents have also reported thyroid gland follicular cell hypertrophy. Decreases in serum T4 levels have also been observed following a single dose exposure to other congeners. A study comparing ED_{50} values across congeners found that 2,3,7,8-TCDD was the most potent, followed by 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, and 1,2,3,4,6,7,8-HpCDD; the ED_{50} for 1,2,3,4,6,7,8-HpCDD was 3 orders of magnitude higher than for 2,3,7,8-TCDD.

Epidemiological Studies. Most epidemiological studies have not found consistent alterations in thyroid hormone levels or thyroid disease associated with 2,3,7,8-TCDD or CDD/CDF exposure; see Table 2-14 for study summaries. Elevated free or total serum T4 levels were observed in workers in highly exposed jobs (Mannetje et al. 2018), women who were premenarchal at the time of the Seveso accident (Chevrier et al. 2014); and one study found an inverse association between CDD/CDF/dioxin-like PCBs and free T4 in a study of anglers (Bloom et al. 2006). Other studies did not find alterations in serum T4 levels (Darnerud et al. 2010; Foster et al. 2005; Jennings et al. 1988; Lignell et al. 2016; Pavuk et al. 2003; Xu et al. 2019a; Zhang et al. 2010). Two studies found alterations in serum T3 levels; an association between CDD/CDF levels and free T3, but not total T3, was found in children living near a municipal waste incinerator (Xu et al. 2019a) and an inverse association between human milk CDD/CDF levels and total T3 was found in a general population study (Lignell et al. 2016). Occupational (Jennings et al. 1988), Seveso (Chevrier et al. 2014), or general population (Bloom et al. 2006; Darnerud et al. 2010) studies

Table 2-14. Endocrine Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Thyroid effects		
Occupational			
Jennings et al. 1988 Cross-sectional study of 18 workers at a 2,4,5-T production facility exposed to 2,3,7,8-TCDD as a result of an industrial accident and 15 workers not exposed	Not measured	T4	↔
		T3	↔
		TSH	↔
Mannetje et al. 2018 Cross-sectional study in former employees (n=245) of a phenoxy herbicide production facility in New Zealand	Work history and 2007–2008 serum 2,3,7,8-TCDD levels ≥10 pg/g lipid	Hypothyroid	↔, highly exposed job ↔, TCDD concentration
		Free T4	↑, highly exposed job ↔, TCDD concentration
		TSH	↔, highly exposed job ↔, TCDD concentration
Zober et al. 1994 Cohort morbidity study of 175 2,4,5-T production workers accidently exposed to 2,3,7,8-TCDD; referents were workers with no known 2,3,7,8-TCDD exposure	Geometric mean 2,3,7,8-TCDD levels back-calculated to the time of the accident: 148 ppt in workers without chloracne and 1,118 ppt in workers with severe chloracne	Thyroid diseases	↑, as compared to referents
Vietnam War veterans and Operation Ranch Hand veterans			
Pavuk et al. 2003 Cross-sectional study of U.S. Air Force veterans of Operation Ranch Hand (n=1,009) and veteran controls (n=1,429)	Groups: high (>94 ppt), low (>10 and <94 ppt), background (<10 ppt), controls (4.6 ppt)	Total T4	↔
		Free T4	↔
		T3 uptake	↔
		TSH	↑, high exposure
		Hyperthyroidism	↔
		Hypothyroidism	↔

Table 2-14. Endocrine Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Yi et al. 2014 Group of 111,726 Korean veterans of the Vietnam War exposed to Agent Orange	Self-reported exposure	Hypothyroidism	↑
		Nontoxic goiter	↑
		Hyperthyroidism	↔
		Thyroiditis	↔
		Autoimmune thyroiditis	↑
Seveso, Italy			
Chevrier et al. 2014 Prospective cohort study of participants in the Seveso Women's Health study (n=909 in 1976 and 260 in 1996); thyroid hormone levels measured in 1996 and 2008	Median serum 2,3,7,8-TCDD levels: 60.2 ppt in 1976 and 7.0 ppt in 1996	1996 total T4 levels 2008 total T4 levels	↑, 1976 TCDD ↔, 1996 TCDD
		1996 free T4 levels 2008 free T4 levels	↔, 1976 TCDD ↔, 1996 TCDD
		1996 free T3 levels 2008 free T3 levels	↔, 1976 TCDD ↔, 1996 TCDD
		1996 TSH levels 2008 TSH levels	↔, 1976 TCDD ↔, 1996 TCDD
Communities with contaminated soil			
Xu et al. 2019a Cross-sectional study of 10-year-old children (n=82) living near a municipal waste incinerator and children (n=49) living in an uncontaminated area in China	Mean blood CDD/CDF levels: 3.40 pg TEQ/g lipid for exposed group and 2.77 pg TEQ/g lipid for controls	Free T3	↑
		T3	↔
		Free T4	↔
		T4	↔
		TSH	↔
Zhang et al. 2010 Cross-sectional study of 25 pregnant women living in an e-waste area and 25 pregnant women living in an uncontaminated area in China	Median CDD/CDF cord blood levels: 0.041 pg TEQ/g lipid	Total T4	↔
		TSH	↔

Table 2-14. Endocrine Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
General population			
Bloom et al. 2006 Prospective study of 38 anglers participating in the New York Angler Cohort study	Median CDD/CDF/dioxin-like PCBs serum concentration: 5.963 pg TEQ/g	Total T4	↔
		Free T4	↓
		T3	↔
		TSH	↔
Darnerud et al. 2010 Prospective study of 180 mother-infant pairs living in Sweden	Median CDD/CDF human milk level: 9 pg TEQ/g lipid	Free T4	↔
		Total T3	↔
		TSH	↔
Foster et al. 2005 Cross-sectional examination; pregnant women (n=150) attending a prenatal diagnosis clinic	Mean serum lipid-adjusted dioxin-like activity TEQs: 0.34 pg/g	T4	↔
		TSH	↔
Lignell et al. 2016 Prospective study of 91 mother infant pairs living in Sweden; same population as Darnerud et al. (2010)	Median CDD/CDF human milk level: 9 pg TEQ/g lipid	Total T3	↓
		Free T4	↔
		TSH	↔
Diabetes			
Occupational			
Calvert et al. 1999 Cross-sectional study in workers (n=281 exposed and 260 controls) exposed >15 years before in the production of 2,4,5-trichlorophenol in the United States	Mean TCDD level in exposed: 220 pg/g lipid; in controls: 7 pg/g; the half-life extrapolated concentrations to the time exposure stopped averaged 1,900 pg/g	Diabetes	↔

Table 2-14. Endocrine Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Mannetje et al. 2018 Cross-sectional study in former employees (n=245) of a phenoxy herbicide production facility in New Zealand	Work history and 2007–2008 serum 2,3,7,8-TCDD levels ≥10 pg/g lipid	Diabetes	↑, highly exposed job ↔, TCDD concentration
		Glucose	↑, highly exposed job ↔, TCDD concentration
Pelcl et al. 2018 Cross-sectional study of eight former workers at a 2,4,5-T production facility and eight controls	Median 2,3,7,8-TCDD levels: 112 pg/g lipid in workers and 12 pg/g lipid in controls	Prevalence of diabetes	↑
Yamamoto et al. 2015a Cross-sectional study of 678 male workers at 36 municipal and private waste incineration plants in Japan	4th quartile CDDs levels: ≥8.98 pg TEQ/g lipid	Diabetes mellitus	↑, 4th quartile
Vietnam War veterans and Operation Ranch Hand veterans			
Henriksen et al. 1997 Cross-sectional study of Operation Ranch Hand veterans (n=989) and a comparison group of (1,276)	Median serum 2,3,7,8-TCDD levels: background 5.7 ppt, low 52.7 ppt, high 197.5 ppt, control ≤4.0 ppt	Risk of diabetes mellitus	↑, high exposure
Kang et al. 2006 Health survey of 1,499 Vietnam veterans and 1,428 non-Vietnam veterans assigned to chemical operations jobs conducted using a computer-assisted telephone interview system	Serum TCDD analyzed on subgroups; a self-reported history of spraying Agent Orange used to categorize exposed	Diabetes	↑
Longnecker and Michalek 2000 Cross-section study of 1,197 veterans in the Air Force Health Study who never had contact with dioxin-contaminated herbicides	4th quartile TCDD level: ≥5.2 pg/g lipid	Diabetes	↑

Table 2-14. Endocrine Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Michalek et al. 1999a Cross-sectional study of Air Force Ranch Hand veterans exposed to TCDD in Vietnam (1962–1971) and veteran controls not exposed; 1992 follow-up High Ranch Hand exposure Diabetics (n=43) Nondiabetics (n=205) Low Ranch Hand exposure Diabetics (n=36) Nondiabetics (n=211) Background Ranch Hand exposure Diabetics (n=32) Nondiabetics (n=344) Controls Diabetics (n=125) Nondiabetics (n=996)	Median current serum 2,3,7,8-TCDD in background, low-, and high-exposure groups: 5.7, 15, and 45.8 ppt, respectively	Fasting glucose	↔
		Insulin	↑, high exposure, non-diabetics
USAF 1991 Cross-sectional report of 866 Operation Ranch Hand personnel and a comparison group of 1,198	Not measured	Glucose intolerance	↑
		Risk of diabetes	↑
Yi et al. 2014 Group of 111,726 Korean veterans of the Vietnam War exposed to Agent Orange	Self-reported exposure	Diabetes	↑
Seveso, Italy			
Bertazzi et al. 2001 Retrospective cohort mortality study of Seveso residents (n=804 in zone A and n=5,941 in zone B); follow-up to the Bertazzi et al. (1993, 1997) studies	Not reported	Diabetes deaths	↔

Table 2-14. Endocrine Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Pesatori et al. 1998 Retrospective cohort study of the 15-year follow-up of the Seveso cohort (n=3,987 deaths)	Soil contamination levels in three zones used as a biomarker of exposure	Diabetes deaths	↔, males ↑, females
Warner et al. 2013 Retrospective cohort study of female residents of Seveso at the time of the accident	4th quartile serum 2,3,7,8-TCDD: >135 ppt	Diabetes	↔
Communities with contaminated soil			
Chang et al. 2010a Cross-sectional study of 1,234 people living near a former PCP production facility in Taiwan	Median CDD/CDF concentration: 20.5 pg TEQ/g lipid	Fasting blood glucose	↑
		Insulin resistance	↑
		Pancreatic β-cell function	↔
Chang et al. 2011b Cross-sectional study of 1,449 people living near a former PCP production facility in Taiwan	Median CDD/CDF concentration: 33.2 pg TEQ/g lipid	HOMA-IR	↑
		HOMA-β-cell	↔
Chang et al. 2016 Cross-sectional study of 2,876 people living near a former PCP production facility in Taiwan	Mean CDD/CDF concentration: 21.9–44.8 pg TEQ/g lipid	Blood glucose	↑
		HOMA-IR	↑
Cranmer et al. 2000 Cross-sectional study of 69 individuals living within 25 miles of a Superfund site	TCDD levels ranged from 2 to 94 ppt Lower serum levels 2–15 ppt (n=62); higher levels >15 ppt (n=7)	Plasma insulin concentrations after a 75-g glucose load	↑

Table 2-14. Endocrine Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Huang et al. 2015 Cross-sectional study of 2,898 adults living near a former PCP production facility in Taiwan	2nd tertile CDD/CDF serum level: 20–63 pg TEQ/g lipid	Diabetes	↑, 2nd tertile
General population			
Fierens et al. 2003 Volunteer-case study in Belgium; environmental exposure to CDDs, CDFs, PCBs+12 marker PCB (not TEQs)	Total TEQs (geometric mean): Cases (n=9) 64.2 pg/g Controls (n=248) 32.8 pg/g	Diabetes	↑, with higher dioxins

↑ = association; ↓ = inverse association; ↔ = no association; 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid; CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; HOMA-IR = homeostatic model assessment of insulin resistance; HOMA-β-cell = homeostatic model assessment of pancreatic beta-cell function; PCB = polychlorinated biphenyl; PCP = pentachlorophenol; T3 = triiodothyronine; T4 = thyroxine; TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ = toxic equivalency; TSH = thyroid-stimulating hormone

have not found associations between CDDs and serum T3 levels. Apart from a study of Operation Ranch Hand veterans, which found increased serum TSH levels in a high-exposure group (Pavuk et al. 2003), no associations between CDDs and TSH levels have been found (Bloom et al. 2006; Chevrier et al. 2014; Darnerud et al. 2010; Foster et al. 2005; Jennings et al. 1988; Lignell et al. 2016; Mannetje et al. 2018; Xu et al. 2019a; Zhang et al. 2010).

Several studies have evaluated the possible associations between CDD exposure and thyroid diseases. A 35-year follow-up study of workers exposed to 2,3,7,8-TCDD during the BASF accident found an increase in the incidence of thyroid disease, as compared to an age-matched referent group (Zober et al. 1994). The workers were divided into two groups based on back-calculated (using a 7-year half-life) serum lipid 2,3,7,8-TCDD levels of ≥1,000 and <1,000 ppt; the incidence did not differ between the groups. Among Korean Vietnam War veterans who self-reported exposure to Agent Orange, there was an increase in the prevalence of hypothyroidism, nontoxic goiter, and autoimmune thyroiditis, but no effect of hyperthyroidism or thyroiditis prevalence (Yi et al. 2014). Another study of Vietnam veterans did not find associations between serum 2,3,7,8-TCDD and the prevalence of hyperthyroidism or hypothyroidism (Pavuk et al. 2003).

Epidemiological studies have also evaluated possible associations between CDD exposure and the risk of diabetes; see Table 2-14 for study summaries. A number of studies have found associations between 2,3,7,8-TCDD or CDD blood levels and increased risk of diabetes among workers (Mannetje et al. 2018; Pelcl et al. 2018; Yamamoto et al. 2015a), Vietnam War veterans (Henriksen et al. 1997; Kang et al. 2006; Longnecker and Michalek 2000; USAF 1991; Yi et al. 2014), communities with contaminated soil (Huang et al. 2015), and the general population (Fierens et al. 2003). Two studies evaluating the Seveso cohort did not find an increased risk of diabetes or diabetes deaths (Bertazzi et al. 2001; Warner et al. 2013), although one study found an increased risk of diabetes deaths in women, but not in men (Pesatori et al. 1998).

2,3,7,8-TCDD—Animal Studies. Animal studies evaluating endocrine outcomes have primarily focused on the thyroid. A number of studies have reported significant decreases in serum T4 levels in rats following acute- or intermediate-duration exposure to 2,3,7,8-TCDD; a summary of these studies is presented in Table 2-15. The magnitude of the decrease was 21–65% and effective doses were as low as 5 µg/kg following a single dose (Viluksela et al. 2004) and 0.016 µg/kg/day following a 13-week exposure (NTP 2006). Results for serum T3 levels were less consistent across studies with some studies reporting 9–43% increases (Bastomsky 1977; Hermansky et al. 1988; Potter et al. 1986) and other studies

not finding significant alterations at doses associated with T4 level decreases (Fan and Rozman 1995; Raasmaja et al. 1996; Sewall et al. 1995; Van Birgelen et al. 1995; Viluksela et al. 2004). At higher doses, increases in TSH levels were observed in rats acutely exposed to 2,3,7,8-TCDD (Bastomsky 1977; Potter et al. 1986), but not at lower intermediate- or chronic-duration doses (NTP 2006). Bastomsky (1977) suggested that the decrease in T4 appeared to be the result of an increased biliary excretion of T4-glucuronide, and this was attributed to induction of uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronyltransferase) by 2,3,7,8-TCDD; UDP-glucuronyltransferase catalyzes glucuronidation of T4 and clearance. The increase in T3 was consistent with increased thyroid secretion from thyrotropin (TSH) stimulation. A small number of studies have evaluated potential histopathological alterations. Thyroid gland follicular cell hypertrophy was observed in female Sprague-Dawley rats exposed to 0.016 µg/kg/day for 14 weeks, 0.032 µg/kg/day for 31 weeks, 0.071 µg/kg/day for 53 weeks, or 0.032 µg/kg/day for 2 years (NTP 2006) and in BALB/c mice exposed to 0.09 µg/kg/day for 28 days (Maranghi et al. 2013). Thyroid gland follicular cysts were observed in male Sprague-Dawley rats exposed to 0.1 µg/kg/day for 2 years (Kociba et al. 1978). Other studies have not found histological alterations following acute-duration (Potter et al. 1986) or chronic-duration exposure (NTP 1982b).

Table 2-15. Results of Studies Evaluating Thyroid Outcomes in Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, duration	Dose (µg/kg)	T3	T4	TSH	Histopathology	Reference
Sprague-Dawley rat, once	25	↑ (43%)	↓ (48%)	↑ (356%)		Bastomsky 1977
Long-Evans rat, once	0.15		↓ (30%)			Crofton et al. 2005
Long-Evans rat, once	12	↔	↓ (44%)			Fan and Rozman 1995
Sprague-Dawley rat, 3 days	40	↑ (9%)	↓ (65%)			Hermansky et al. 1988
Sprague-Dawley rat, once	6.25	↑ (12%)	↓ (50%)	↑ (138%)	↔	Potter et al. 1986
Long-Evans rat, once	10	↔	↓ (58%)			Raasmaja et al. 1996
Sprague-Dawley rat, once	5	↔	↓ (40%)			Viluksela et al. 2004
Sprague-Dawley rat, 4 weeks	1				↔	Harrill et al. 2015

Table 2-15. Results of Studies Evaluating Thyroid Outcomes in Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, duration	Dose (µg/kg)	T3	T4	TSH	Histopathology	Reference
Sprague-Dawley rat, 10 weeks	0.03		↓ (50%)			Li and Rozman 1995
BALB/c mouse, 28 days	0.09				Follicular cell hypertrophy	Maranghi et al. 2013
Sprague-Dawley rat, 14 or 31 weeks	0.022		↓ (25–34%)	↔	Follicular cell hypertrophy after 14 weeks	NTP 2006
Sprague-Dawley rat, 30 weeks	0.036	↔	↓ (25%)			Sewall et al. 1995
Sprague-Dawley rat, 13 weeks	0.047	↔	↓ (21%)			Van Birgelen et al. 1995
Sprague-Dawley rat, 13 weeks	0.8	↔	↓ (47%)			Viluksela et al. 1994
Sprague-Dawley rat, 2 years	0.1				↔	Kociba et al. 1978
Osborne-Mendel rat, 2 years	0.071				↔	NTP 1982b
B6C3F1 mouse, 2 years	0.3				↔	NTP 1982b
Sprague-Dawley rat, 53 weeks	0.0071	↑ (14%)	↔	↔		NTP 2006
Sprague-Dawley rat, 2 years	0.032				Follicular cell hypertrophy	NTP 2006

↑ = association; ↓ = inverse association; ↔ = no association; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone

Adverse effects have also been observed in other endocrine tissues of laboratory animals orally exposed to 2,3,7,8-TCDD. NTP (2006) found significant increases in the incidence of hyperplasia of the adrenal cortex in female rats administered ≥0.016 µg/kg/day 2,3,7,8-TCDD 5 days/week for 2 years; atrophy was observed at the highest dose tested (0.071 µg/kg/day). The cortical atrophy was characterized by the loss of cortical epithelial cells within the zona fasciculata and zona reticularis with a subsequent reduction in

cortical thickness. Pitt et al. (2000) examined the effect of a single dose gavage exposure to 10 µg/kg 2,3,7,8-TCDD on pituitary-adrenal gland function in male Sprague-Dawley rats. Ten days after exposure, no significant alterations in pituitary or plasma adrenocorticotropin levels, pituitary weight, adrenal or plasma corticosterone levels, or adrenal gland weight were observed. A 46% decrease in the ratio of adrenocorticotropin to corticosterone levels was observed; although the alteration was not statistically significant due to the low statistical power of the study, the investigators noted that the change was biological significant. In *ex vivo* studies, Pitt et al. (2000) also found no significant alterations in corticotrophin-releasing-hormone-stimulated adrenocorticotropin secretion from the pituitary gland or adrenocorticotropin-stimulated corticosterone secretion from the adrenal gland.

A series of studies conducted by Blackwell et al. (1998) examined the potential association between 2,3,7,8-TCDD exposure and type II diabetes. There were no alterations in serum glucose levels in male C57BL/6J mice maintained on a diabetic diet (high fat, high simple carbohydrate diet) or a normal diet for 2 weeks prior to a single gavage administration of 1–60 µg/kg. Similarly, repeated exposure to 0.0015 or 0.15 µg/kg/day 2,3,7,8-TCDD for 4, 8, or 12 weeks or 0.0015–0.15 µg/kg/day for 16 weeks did not alter serum glucose levels in resting or fasting mice on either diet. A decrease in serum glucose levels was observed in male Sprague-Dawley rats 7 days after receiving a single dose of 40 µg/kg 2,3,7,8-TCDD (Fletcher et al. 2005b); at earlier time points (6 or 24 hours after dosing), no changes in serum glucose levels were found. No significant alterations in serum glucose or insulin levels were observed in female Sprague-Dawley rats administered an initial loading dose of 3.2 µg/kg 2,3,7,8-TCDD followed by a maintenance dose of 0.32 µg/kg every third day for 20 weeks (Croutch et al. 2005). However, decreases in serum insulin-like growth factor-I and hepatic phosphoenolpyruvate carboxykinase (PEPCK) protein levels were observed and suggest an early effect on energy metabolism; decreases in PEPCK activity and messenger ribonucleic acid (mRNA) levels were found, but the changes were not statistically significant at most time points.

Significant decreases in plasma glucose levels and liver glycogen content were observed in female Long-Evans rats administered a single dose of ≥5 µg/kg, in male Long-Evans rats significant decreases were observed at ≥10 µg/kg (Viluksela et al. 1999). When a pair-fed control group was used as the comparison group rather than *ad-libitum*-fed controls, the only significant difference in plasma glucose level was in males exposed to 50 µg/kg. PEPCK activity in the liver was significantly decreased in male rats exposed to ≥5 µg/kg and female rats at ≥10 µg/kg. In the pair-fed controls, PEPCK was significantly higher than the *ad libitum* controls and 50 µg/kg 2,3,7,8-TCDD exposed rats. Additionally, significant increases in plasma glucogenic amino acids were observed in females (males were not examined) at ≥10 µg/kg and

plasma ketogenic amino acids were increased at ≥5 µg/kg. As compared to the pair-fed control group only, the increases in plasma glucogenic and ketogenic amino acids were significant only in the 50 µg/kg group. The investigators noted that the lack of change in plasma urea levels suggested decreased utilization of amino acids for gluconeogenesis, which is likely due to the decreased activity of PEPCK. Viluksela et al. (1999) similarly exposed Han/Wistar rats and found significant decreases in female rats administered ≥500 µg/kg; no significant alterations were observed in the male rats. No alterations in liver glycogen content or plasma amino acid levels were observed; however, a decrease in PEPCK activity was observed in the males exposed to ≥50 µg/kg. Similar to the findings for 2,3,7,8-TCDD, no alterations in serum glucose or insulin levels were observed in female Sprague-Dawley rats administered an initial loading dose of 80 µg/kg HxCDD followed by maintenance doses of 8 µg/kg every 9 days for 20 weeks (Croutch et al. 2005), but decreases in PEPCK protein levels and nonsignificant decreases in PEPCK mRNA and activity levels and insulin growth factor-I levels were observed.

Intermediate-duration exposure to 0.071 µg/kg/day 2,3,7,8-TCDD (5 days/week) resulted in a significant increase in minimal acinar cytoplasmic vacuolization in the pancreas of female Harlan Sprague-Dawley rats (NTP 2006); the lesions were observed after 31 weeks of exposure, but not after 14 weeks. A 2-year exposure to ≥0.032 µg/kg/day resulted in significant increases in the incidence of acinar cytoplasmic vacuolization (NTP 2006; Nyska et al. 2004). At 0.071 µg/kg/day, there were also significant increases in the incidence of chronic active inflammation and acinar atrophy.

Other CDD Congeners—Animal Studies. A small number of studies have examined potential endocrine effects in laboratory animals. An ED_{30} for serum T4 levels (30% reduction in serum levels, as compared to controls) of 1.51 µg/kg/day (95% CI of 1.10–1.92 µg/kg/day) was estimated in female Long-Evans rats administered 0.003–10 µg/kg/day 1,2,3,7,8-PeCDD in corn oil for 4 days (Crofton et al. 2005). Simanainen et al. (2002) estimated the ED_{50} values for decreases in serum T4 levels in male Han/Wistar and Long-Evans rats receiving a single gavage dose of several CDD congeners. The ED_{50} values were 1.4, 4.1, and 99 µg/kg in Han/Wistar rats administered 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, and 1,2,3,4,6,7,8-HpCDD, respectively. In Long-Evans rats, the ED_{50} values were 3.6, 21, and 47 µg/kg, respectively.

2.14 IMMUNOLOGICAL

Overview. The available data provide strong evidence that immunotoxicity is a sensitive target of CDD toxicity. Epidemiological studies of workers, Seveso cohort, Vietnam War veterans, communities living

in areas with contaminated soil, and the general population and experimental studies in monkeys, rats, mice, guinea pigs, and hamsters have evaluated immunological outcomes. The epidemiological studies provide suggestive evidence; however no consistent exposure-related immunological effects have been observed in human populations exposed to levels of CDDs several orders of magnitude higher than background exposure. This may in part be due to the limited number of studies evaluating immune competence in humans.

Studies in laboratory animals have reported effects on primary and secondary immune organs and adaptive immune function. Decreases in thymus weight and thymic atrophy are commonly reported in oral exposure studies, with respective LOAELs of ≥0.66 and ≥0.8 µg/kg for acute-duration exposure and ≥0.005 and 0.016 µg/kg/day for intermediate-duration exposure; the lowest LOAEL for thymic atrophy following chronic-duration exposure is 0.0071 µg/kg/day. The most well-studied alteration in immune function is impaired host resistance and impaired response to antigens. Impaired immune function has been observed at doses of 0.01 µg/kg following acute-duration oral exposure, 0.0011 µg/kg/day following intermediate-duration exposure, and 0.00012 µg/kg/day following chronic-duration exposure.

The immune system is also a sensitive target of toxicity for other CDD congeners. Decreases in thymus weights have been observed in animals orally exposed to 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, or 1,2,3,4,6,7,8-HpCDD. Impaired immune function has also been observed in animals orally exposed to 2,7-DCDD, 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, and 1,2,3,4,6,7,8-HpCDD.

Epidemiological Studies. A number of epidemiological studies have evaluated the potential immunotoxicity of 2,3,7,8-TCDD and other CDD congeners; the results of these studies are summarized in Table 2-16. These studies have evaluated a number of immune endpoints including immunoglobulin (Ig) levels, complement and cytokine levels, lymphocyte levels and phenotypes, natural killer (NK) cell levels, and tests of immune function (antibody responses, disease resistance, delayed hypersensitivity, and hypersensitivity). Consistent results have not been observed across studies, which likely reflects differences in exposures, differences in the populations, and the tests used to assess immunotoxicity.

Table 2-16. Immunological Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Occupational			
Jennings et al. 1988 Cross-sectional study of 18 workers at a 2,4,5-T production facility exposed to 2,3,7,8-TCDD released after an accident and 15 matched controls		Immunoglobulins: IgA, IgG, IgM, IgD, IgE	↔
		Total lymphocyte, T cell count, T-helper cells, T-suppressor cells	↔
		Natural killer cells	↑
		Lymphocyte proliferation test response to phytohemagglutinin A	↔
Jung et al. 1998 Cross-sectional study of 29 former workers at a German pesticide facility highly exposed to 2,3,7,8-TCDD and 28 external controls	Median serum 2,3,7,8-TCDD level: 217 pg/g lipid in exposed workers and 3.9 pg/g lipid in controls	Frequency of infectious diseases	↔
		Immunoglobulins: IgA, IgG, IgM	↔
		Tetanus antibodies 3 weeks after vaccination	↔
		Lymphocyte subgroups: activated T cells	↓
		Lymphocyte subgroups: B cells, activated B cells, T-helper cells, $CD3^+$ killer cells, natural killer cells	↔
		Lymphocyte proliferation test response to phytohemagglutinin, pokeweed mitogen, or tetanus toxoid	↔

Table 2-16. Immunological Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Halperin et al. 1998 Cross-sectional study of 259 workers at two 2,4,5-T production facilities in the United States and 243 unexposed referents	Serum 2,3,7,8-TCDD levels: Workers: 3rd quintile: 52–125 pg/g lipid 5th quintile: 298–3,389 pg/g lipid Referents: 6.4 pg/g lipid (random sample of referents)	Immune markers: CD3, CD4, CCD4/CDW29, CD4/CD45, CD8/CD11B+ Lymphocytes, neutrophils IgG Complement Proliferation in response to phytohemagglutinin	↔
		CD26 (activated T cells)	↓, 3rd quintile
		Lymphocyte proliferation test response to mitogens (concanavalin and pokeweed)	↑, 5th quintile
Hosnijeh et al. 2011 Cross-sectional study of 45 workers at a chlorophenoxy herbicide facility in the Netherlands; 108 non-exposed workers (39 from same facility and 69 from a comparable facility) were also examined	Current serum TCDD levels: 3.3 ppt in exposed workers and 1.2 and 0.4 ppt in control groups	Immunoglobulins: IgG, IgA, IgM, IgD, IgE	↔
		Complement 3 or Complement 4	↔
Hosnijeh et al. 2012a, 2012b Cross-sectional study of 85 workers at a chlorophenoxy herbicide facility in the Netherlands; 47 workers were exposed to high levels of 2,3,7,8-TCDD and 38 were exposed to low levels	Current serum TCDD levels: 3.25 ppt in high-exposed workers and 1.07 ppt in low-exposed workers	Cytokines: IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, granulocyte-macrophage colony stimulating factor, tumor necrosis factor-α, epidermal growth factor, eotaxin, granulocyte colony stimulating factor, melanoma growth stimulating activity/growth related oncogene, interferon gamma-induced protein 10, monocyte chemotactic protein-1, macrophage derived chemokine, macrophage inflammatory protein-1α, macrophage inflammatory protein-1β, soluble CD40 ligand	↔

Table 2-16. Immunological Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Cytokines: fibroblast growth factor 2, fractalkine, transforming growth factor-α	↓
		Leukocytes	↔
		B cells	↓
		IgG/IgA+ memory B cells	↓
		T cells	↔
		CD4/CD8 ratio	↔
Neubert et al. 1993, 1995 Cross-sectional study of 12 workers in Germany exposed to CDDs/CDFs and 77 referents	Median serum TCDD level of 41.5 ppt and total CDD/CDFs of 133.3 TEQ ppt Referents divided into three groups, median serum TCDD levels 2, 5, and 11 ppt in the low-, medium-, and high-level subgroups; median CDD/CDF levels of 18, 28, and 49 TEQ ppt, respectively	$CD4^{+}CD45R0$	↑
		Lymphocyte proliferation in response to pokeweed mitogen, phytohemagglutinin, concanavalin A	↔
Ott et al. 1994 Retrospective cohort study of 138 workers exposed to 2,3,7,8-TCDD due to an accident at a trichlorophenol facility in Germany	Current 2,3,7,8-TCDD serum levels: <1–553 ppt Back calculated 2,3,7,8-TCDD serum levels: 3.3–12,000 ppt	IgA IgG	↑, current TCDD, back-calculated TCDD
		Complement C4	↑, current TCDD
		IgM Complement C3 Lymphocytes, natural killer cells, B-cells, T-cells, T-helper cells, T-suppressor cells, CD4/CD8 ratio	↔

Table 2-16. Immunological Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Tonn et al. 1996 Cross-sectional study of 11 workers at a 2,4,5-trichlorophenol production facility in Germany and 10 matched controls	Mean serum 2,3,7,8-TCDD levels: 329.5 pg/g lipid in workers	Lymphocyte subsets	↔
		Lymphocyte proliferation in response to phytohemagglutinin and pokeweed	↔
		Response to human lymphocyte antigen-allogeneic lymphocytes and interleukin-2 boosted proliferation	↓
Zober et al. 1994 Cohort morbidity study of 175 2,4,5-T production workers accidently exposed to 2,3,7,8-TCDD; referents were workers with no known 2,3,7,8-TCDD exposure	Geometric mean 2,3,7,8-TCDD levels back calculated to the time of the accident: 148 ppt in workers without chloracne and 1,118 ppt in workers with severe chloracne	Infectious and parasitic disease	↑, severe chloracne subgroup ↑, TCDD levels >1,000 ppt
Seveso, Italy			
Baccarelli et al. 2004 Retrospective cohort study of 62 adults from zones A and B and 59 controls	Not reported	IgG	↓
		IgM, IgA, complement C3, complement #4	↔
Vietnam War veterans and Operation Ranch Hand veterans			
Kim et al. 2003 Cross-sectional study of Korean Vietnam War veterans; 24 veterans with service in Agent Orange sprayed areas with chronic illness, 27 veterans with service in Agent Orange sprayed areas without chronic illness, and 36 age-matched controls with no Vietnam War military service	Not measured	Total and differential leukocyte counts	↔
		IgE	↑, both veteran groups
		IgG1	↓, veterans with illness
		Interferon-γ	↓, veterans with illness
		IL-4	↑, both veteran groups
		Tumor necrosis factor-α, IL-10	↔

Table 2-16. Immunological Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Michalek et al. 1999b Cross-sectional study 914 Operation Ranch Hand veterans (n=393 background exposure, n=261 low exposure, and n=260 high exposure) and 1,186 veterans not involved in spraying herbicides	Median current serum 2,3,7,8-TCDD levels: background exposure group 5.7 ppt; low-exposure group 52.8 ppt; high-exposure group 194.7 ppt; comparison group 4.0 ppt	$CD16^+CD56^+CD3^+$	↓, high-exposure group
		CD3, CD5, $CD4^+CD3+$, $CD8^+CD3^+$, CD20, $CD16^+CD56^+CD3^-$, CD25, $CD25^+CD3^+$	↔
		IgA, IgG, IgM	↔
USAF 1991 Cross-sectional study of 866 Operation Ranch Hand personnel and a comparison group of 1,198	Not reported	IgA	↑
		IgG, IgM	↔
Communities living in areas with contaminated soil			
Evans et al. 1988 Cross-sectional study; follow-up to the Hoffman et al. (1986) study examining subjects who had anergy or relative anergy on skin testing, 28/50 exposed and 15/27 unexposed subjects were re-evaluated	Not measured	Delayed hypersensitivity response	↔
		Total lymphocyte count, T-cell subset population	↔
		Lymphocyte proliferation response to phytohemagglutinin, concanavalin A, pokeweed mitogen, tetanus toxoid	↔
		IgG	↔
Hoffman et al. 1986 Cross-sectional study of 154 people living in Quail Run Mobile Home Park and exposed to 2,3,7,8-TCDD in soil and 155 control subjects	Years of residence in the park used as surrogate for exposure	Lymphocyte proliferation response to phytohemagglutinin, concanavalin A, pokeweed mitogen, tetanus toxoid	↔
		IgG	↔
		Delayed-type hypersensitivity skin test	↑
		Lymphocyte subsets: CD3, CD4, CD8, CD11	↔

Table 2-16. Immunological Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Webb et al. 1989 Cross-sectional study of 41 individuals in Missouri exposed TCDD-contaminated soil by living in an area with contaminated soil, riding or caring for horses in contaminated stable arenas, or working in a hexachlorophene production facility or truck terminals where the grounds were sprayed with TCDD-contaminated waste oil	Adipose tissue 2,3,7,8-TCDD levels: 16 subjects had levels <20 ppt, 13 had levels 20–60 ppt, and 12 had levels >60 ppt	Delayed-type hypersensitivity skin test	↔
		IgG	↑
		IgA, IgM	↔
		Lymphocyte subsets: CD3, CD8	↑
		Lymphocyte subsets: CD4, CD14, CD18	↔
		Lymphocyte proliferation response to phytohemagglutinin, concanavalin A, pokeweed mitogen, tetanus toxoid	↔
General population			
Nakamoto et al. 2013 Cross-sectional study of 1,063 men and 1,201 women in Japan	Median serum total CDDs/CDFs: 9.8 pg TEQ/g lipid	Atopic dermatitis	↔, 4th quartile ↓, trend
		Allergic rhinitis	↔, 4th quartile ↔, trend

↑ = association; ↓ = inverse association; ↔ = no association; 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid; CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; Ig = immunoglobin; IL = interleukin; TEQ = toxic equivalency

Four studies found associations between CDD exposure and serum IgG levels, with two studies finding positive associations (Ott et al. 1994; Webb et al. 1989) and two studies finding inverse associations (Baccarelli et al. 2004; Kim et al. 2003). Other studies found no association (Evans et al. 1988; Hoffman et al. 1986; Jennings et al. 1988; Jung et al. 1998; Halperin et al. 1998; Hosnijeh et al. 2011; Michalek et al. 1999b; USAF 1991). Similarly, studies by Ott et al. (1994) and USAF (1991) found associations between CDD exposure and serum IgA levels in workers and Ranch Hand veterans, respectively, but most studies did not find an association (Baccarelli et al. 2004; Jennings et al. 1988; Jung et al. 1998; Hosnijeh et al. 2011; Michalek et al. 1999b; Webb et al. 1989). In general, most studies looking at possible associations with other immunoglobulins have not found associations (see Table 2-16). Some studies have found associations between CDD exposure and levels of specific cytokines or complement (Hosnijeh et al. 2012a, 2012b; Kim et al. 2003; Ott et al. 1994); however, interpretation is limited by the small number of studies and differences in the cytokines and complement examined. Similarly, several studies have examined possible associations with altered lymphocyte phenotypes (Evans et al. 1988; Jennings et al. 1988; Jung et al. 1998; Halperin et al. 1998; Hoffman et al. 1986; Hosnijeh et al. 2012a, 2012b; Michalek et al. 1999b; Neubert et al. 1993, 1995; Ott et al. 1994; Tonn et al. 1996; Webb et al. 1989), B and T cell levels (Evans et al. 1988; Hosnijeh et al. 2012a, 2012b; Kim et al. 2003; Ott et al. 1994), and NK cell levels (Jennings et al. 1988; Ott et al. 1994), but the findings are not consistent across studies or populations; see Table 2-16 for individual study results.

A number of epidemiological studies have evaluated the potential impairment of immune function. Halperin et al. (1998) reported an impaired response to the mitogens concanavalin and pokeweed in lymphocyte proliferation tests and a normal response to phytohemagglutinin among workers at two 2,4,5-T production facilities. Other studies found no response to phytohemagglutinin (Evans et al. 1988; Hoffman et al. 1986; Jennings et al. 1988; Jung et al. 1998; Neubert et al. 1993, 1995; Tonn et al. 1996; Webb et al. 1989), pokeweed (Evans et al. 1988; Hoffman et al. 1986; Jung et al. 1998; Neubert et al. 1993, 1995; Tonn et al. 1996; Webb et al. 1989), concanavalin A (Evans et al. 1988; Hoffman et al. 1986; Neubert et al. 1993, 1995; Webb et al. 1989), or tetanus toxoid (Evans et al. 1988; Hoffman et al. 1986; Jung et al. 1998; Webb et al. 1989). Zober et al. (1994) reported an increased incidence of infectious and parasitic diseases among highly exposed workers, and Jung et al. (1998) reported no association between serum 2,3,7,8-TCDD levels and the frequency of infectious diseases in former workers. Delayed-type hypersensitivity was reported in one of the studies examining residents exposed to contaminated soil (Hoffman et al. 1986), but not in the other two studies (Evans et al. 1988; Webb et al. 1989). A general population study reported an inverse trend for atopic dermatitis and serum total CDD/CDF levels and no association for allergic rhinitis (Nakamoto et al. 2013).

2,3,7,8-TCDD—Animal Studies. A large number of studies have evaluated the immunotoxicity of 2,3,7,8-TCDD in laboratory animals. These studies reported alterations in immune tissue weights and histopathology and immunosuppressive outcomes.

Effects on primary and secondary immune organs. Decreased thymus weights have been observed in several animal species; the lowest LOAELs are 0.66 µg/kg in rats (Fletcher et al. 2001) and 1 µg/kg in mice (Silkworth et al. 1989b; Smialowicz et al. 1997) following acute-duration oral exposure and 0.014 µg/kg/day in rats (Van Birgelen et al. 1995) and 0.005 µg/kg/day in guinea pigs (Decaprio et al. 1986) following intermediate-duration oral exposure. Thymic atrophy is also commonly reported in laboratory animals; the lowest LOAELs are 70 µg/kg in monkeys (McConnell et al. 1978a), 25 µg/kg in rats (De Heer et al. 1994b), 280 µg/kg in mice (Hanberg et al. 1989), 48 µg/kg in hamsters (Hanberg et al. 1989), and 0.8 µg/kg in guinea pigs (Hanberg et al. 1989) following acute-duration oral exposure; 0.016 µg/kg in rats (NTP 2006) and 0.03 µg/kg in guinea pigs (DeCaprio et al. 1986) following intermediate-duration oral exposure; and 0.0071 µg/kg/day in rats (NTP 2006) following chronic-duration oral exposure. A species comparison of effective doses resulting in thymic atrophy, reported ED_{50} values of 26 µg/kg in Sprague-Dawley rats, 0.8 µg/kg in Hartley guinea pigs, 280 µg/kg in C57BL/6 mice, and 48 µg/kg in Syrian hamsters (Hanberg et al. 1989). Depletion of cortical lymphocytes in the thymus has been observed in rats exposed to a single dose of 30 µg/kg (Luebke et al. 1999) and in mice exposed to a single dose of ≥1 µg/kg (Ao et al. 2009; Inouye et al. 2005). Age-related differences in the sensitivity of the thymus to 2,3,7,8-TCDD-induced toxicity have been examined in two studies. In 3-week-old C57BL/6 mice, decreases in thymus weight and number of thymocytes were observed following a single-dose administration of ≥1 µg/kg; however, in 6-week-old C57BL/6 mice, exposure to 1 or 3 µg/kg resulted in decreased thymus weights, but did not alter the number of thymocytes (Inouye et al. 2005). Similarly, a single dose administration of 10 µg/kg to 12-week-old B6C3F1 mice resulted in decreased thymus weight and number of thymocytes; however, no significant alterations were observed in similarly exposed 76-week-old mice (Luebke et al. 1999). Huang and Koller (1998, 1999) compared the toxicity of 2,3,7,8-TCDD following a single-dose exposure to that of equivalent multiple doses. Exposure of female Long-Evans rats to a single dose of 25 µg/kg resulted in a pronounced thinning of the thymic cortex with most of the thymus consisting of medulla (Huang and Koller 1998, 1999). In contrast, administration of 5 µg/kg/day for 5 days resulted in a less dramatic thinning of the thymic cortex, but no effect on cellular density (Huang and Koller 1999).

Like the effects observed in the thymus, acute-duration exposure to 2,3,7,8-TCDD resulted in decreased number of lymphocytes in the spleen and decreased spleen weight in mice administered ≥1 µg/kg (Ao et al. 2009; Ito et al. 2002; Luebke et al. 1999; Smialowicz et al. 1997) and F344 rats administered 30 µg/kg (Luebke et al. 1999). In contrast, Inouye et al. (2005) did not find alterations in the number of splenocytes in C57BL/6 mice administered ≤3 µg/kg. Age-related differences in 2,3,7,8-TCDD-induced effects in the spleen were also observed in B6C3F1 mice; decreased numbers of splenocytes and relative spleen weight were observed in 12-week-old mice administered ≥10 µg/kg, but not in 76-week-old mice (Luebke et al. 1999). Lymph node atrophy was observed in monkeys exposed to 0.011 µg/kg/day for 9 months (Allen et al. 1977).

A decrease in serum total hemolytic complement activity (CH50) was observed in B6C3F1 mice administered ≥0.01 µg/kg/day 2,3,7,8-TCDD for 14 days (White et al. 1986); complement component C3 levels were decreased at ≥0.5 µg/kg/day. When animals exposed to 1 µg/kg/day for 14 days were allowed to recover, serum CH50 levels were significantly lower than controls after 14 days of recovery but were not significantly different at 28 days post-exposure (White et al. 1986). In contrast, C3 levels returned to control levels by post-exposure day 14. Serum C3 levels were also significantly decreased in mice following a single dose exposure to 20 µg/kg 2,3,7,8-TCDD (Lin and White 1993).

Effects on adaptive immune function. A summary of animal studies examining immunosuppression is presented in Table 2-17. Several studies have found decreased cytokine production by spleen cells in response to an antigen in 2,3,7,8-TCDD exposed mice. When mice were immunized with ovalbumin immediately before or after 2,3,7,8-TCDD exposure, significantly decreased production of IL-5 levels in the spleen was observed at ≥0.3 µg/kg in C57BL/6 mice (Ao et al. 2009; Inouye et al. 2005; Ito et al. 2002) and at 20 µg/kg in BALB/c mice (Chen et al. 2013). A time-course study by Ito et al. (2002) examined the response of several cytokines in the spleen after 20 µg/kg 2,37,8-TCDD exposure of C57BL/6N mice immunized with ovalbumin immediately after exposure. Unlike control mice, which had biphasic increases in IL-2, IL-4, IL-5, and IL-6 levels in response to antigen exposure, 2,3,7,8-TCDD-exposed mice had significant decreases in these cytokine levels in the spleen. The significant decrease in IL-4 and IL-6 levels were observed as early as 1-day postexposure and IL-2 and IL-5 were first observed 4-days postexposure (Ito et al. 2002). IL-5 appeared to be the most sensitive to 2,3,7,8-TCDD exposure with no ovalbumin-induced increases in IL-5 levels from days 4 through 14 post-immunization. Exposure to 2,3,7,8-TCDD also significantly decreased IL-5 and IL-6 production by Th2 cells. In Long-Evans rats administered 25 µg/kg 2,3,7,8-TCDD and 2 days later exposed to *Staphylococcal*

Table 2-17. Results of Studies Evaluating Immunosuppression in Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, duration	Dose (µg/kg/day)	Delayed-type hypersensitivity	Host resistance	Immune response to antigen	Comments	Reference
C57BL/6 mouse, once	1			↓ (OVA)	Decreased IL-5 production	Ao et al. 2009
C57BL/6 mouse, once	20			↓ (OVA)	Decreased IL-5 production	Ao et al. 2009
B6C3F1 mouse, once	0.01		↓ (influenza A)		Increased mortality	Burleson et al. 1996
BALB/c mouse, once	20			↓ (OVA)	Decreased interferon-γ, IL-2, IL-4, IL-5, and IL-10 levels Decreased OVA-specific IgG1 and IgM levels	Chen et al. 2013
Sprague-Dawley rat, once	10	↑				Fan et al. 1996
B6C3F1/N mouse, once	0.1			↓ (sRBC)	Decreased antibody plaque forming cell response	Frawley et al. 2014
B6C3F1 mouse, once	1			↓ (sRBC)	Decreased IgM anti-sRBC antibody forming cells	Holsapple et al. 1986
B6C3F1 mouse, 14 days	1			↓ (sRBC)	Decreased IgM antibody-forming cells	Holsapple et al. 1986
Long-Evans rat, once	25		↓ (*Staphylococcal enterotoxin* B)		Increased IL-2 levels and no change in IL-1 or IL-6 levels	Huang and Koller 1998
C57BL/6 mouse, once	20			↓ (OVA)	Decreased IgM and IgG levels; suppressed increase in B cells; formation of germinal center and high affinity antibody forming cell generation in spleen	Inouye et al. 2003
C57BL/6N mouse, once	0.3			↓ (OVA)	Decreased IL-5 levels	Inouye et al. 2005

Table 2-17. Results of Studies Evaluating Immunosuppression in Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, duration	Dose (µg/kg/day)	Delayed-type hypersensitivity	Host resistance	Immune response to antigen	Comments	Reference
C57BL/6 mouse, once	20			↓ (OVA)	Decreased IL-2, IL-4, IL-5, and IL-6 levels Decreased $CD3^+$ and $CD4^+$ T cells and CD45R/B220 B cells	Ito et al. 2002
C57BL/6N mouse, once	1			↓ (OVA)	Decreased IgG1 and IL-5 levels	Ito et al. 2002
C57BL/6 mouse, once	5		↓ (influenza A)		Decreased plasma IgM and IgG levels and increased IgA levels Re-infection with influenza resulted in IgM and IgG2 levels lower than controls	Lawrence and Vorderstrasse 2004
B6C3F1 mouse (12 weeks of age), once	1			↓ (*Trichinella spiralis* antigen)	Decreased lymphoproliferative response in spleen Decreased response to LPS antigen at 10 µg/kg	Luebke et al. 1999
B6C3F1 mouse (76 weeks of age), once	1			↓ (*T. spiralis* antigen)	Decreased lymphoproliferative response in spleen No alteration in response to LPS antigen at 10 µg/kg	Luebke et al. 1999
B6C3F1 mouse, once	4.2			↓ (sRBC)	Decreased IgM antibody-forming cells	Matulka et al. 1997
B6C3F1 mouse, 14 days	1			↓ (sRBC)	Decreased IgM antibody-forming cells	Matulka et al. 1997
C57BL/6 mouse, once	10		↓ (influenza A)		Decreased $CD8^+$ T cell response	Mitchell and Lawrence 2003
B6C3F1 mouse, once	0.5		↔ (influenza A)		No change in mortality	Nohara et al. 2002

Table 2-17. Results of Studies Evaluating Immunosuppression in Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, duration	Dose (µg/kg/day)	Delayed-type hypersensitivity	Host resistance	Immune response to antigen	Comments	Reference
B6C3F1 mouse, once	1			↓ (sRBC)	Decreased antibody plaque forming cell response	Smialowicz et al. 1997
C57BL/6 mouse, once	1		↓ (influenza A)		Decreased IgG2 levels and increased IgA levels at 1 µg/kg Decreased survival and decreased IgG1 levels at 2.5 µg/kg Decreased $CD4^+$ cells at 5 µg/kg	Vorderstrasse et al. 2003
C57BL/6 mouse, once	10		↓ (influenza A)		Decreased $CD4^+$ and $CD8^+$ T cells Decreased IL-2 and interferon-γ levels Decreased plasma IgM, IgG1, and IgG2 levels and increased plasma IgA levels	Warren et al. 2000
Fischer 344 rat, 14 days	0.72		↓ (influenza A)		Suppression in virus-augmented NK cell activity	Yang et al. 1994
Siberian Hamster, once	2			↔ (allogeneic antigen)		Yellon et al. 2000
B6C3F1 mouse, 13 weeks	0.0011			↓ (sRBC)	Decreased antibody plaque forming cell response	Smialowicz et al. 2008
C57Bl/6Jfh mouse, 4 weeks	0.14		↓ (*Salmonella*)		Increased deaths	Thigpen et al. 1975
C57BL/6 mouse, 5–8 weeks	0.07			↓ (sRBC)	Decreased antibody plaque forming cell response	Vecchi et al. 1983
CD rat, 6 weeks	0.71	↔ (tuberculin)				Vos et al. 1973

Table 2-17. Results of Studies Evaluating Immunosuppression in Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, duration	Dose (µg/kg/day)	Delayed-type hypersensitivity	Host resistance	Immune response to antigen	Comments	Reference
B6D2F1 mouse, 4 weeks	0.71		↓ (graph versus host)			Vos et al. 1973
Hartley Guinea pig, 8 weeks	0.006	↓ (tuberculin)			Decreased skin diameter and thickness	Vos et al. 1973
Rhesus monkey, 3.5–4 years	0.00012			↓ (PHA)	Increased tumor necrosis factor-α levels	Rier et al. 2001a

↓ = impaired response; ↔ = no alteration in response; Ig = immunoglobulin; IL = interleukin; LPS = lipopolysaccharide; NK = natural killer; OVA = ovalbumin; PHA = phytohemagglutinin; sRBC = sheep red blood cell

enterotoxin B (SEB), there was a significant increase in IL-2 levels 2 hours after SEB injection, as compared to controls exposed to SEB; no changes in IL-6 or IL-1 levels were observed (as compared to SEB controls) (Huang and Koller 1998). Additionally, exposure to 2,3,7,8-TCDD without SEB exposure did not significantly alter cytokine levels, as compared to naïve controls (Huang and Koller 1999). Thirteen years after termination of 3.5–4 years of 2,3,7,8-TCDD exposure, significant increases in peripheral blood monocyte production of tumor necrosis factor-α in response to phytohemagglutinin were observed in Rhesus monkeys exposed to 0.00012 or 0.00064 μg/kg/day 2,3,7,8-TCDD in the diet (Rier et al. 2001a). Similarly, a significant increase in interferon-γ production in response to stimulation with phytohemagglutinin was observed in NC/Nga mice exposed to 5 μg/kg 2,3,7,8-TCDD; however, there was no effect at 20 μg/kg (Ito et al. 2008).

Suppression of the normal proliferation of CD45R/B220+ B cells in response to antigen exposure was observed in C57BL/6N mice administered a single dose of 20 μg/kg 2,3,7,8-TCDD and ovalbumin (Inouye et al. 2003; Ito et al. 2002). Examining the effect of 2,3,7,8-TCDD on germinal center formation, Inouye et al. (2003) found significant decreases in the number of germinal center B cells in C57BL/6N mice 7, 10, and 14 days after administration of 20 μg/kg 2,3,7,8-TCDD and immunization with ovalbumin. An apparent reduction in the size of the germinal center was observed in the spleen. To assess the effect of 2,3,7,8-TCDD exposure on high-affinity antigen-forming cells, mice were immunized with alum-precipitated (4-hydroxy-3-nitrophenyl) acetyl linked to chicken γ-globulin (NP-CG) immediately after dosing with 20 μg/kg 2,3,7,8-TCDD. Significant decreases in the total number of NP-specific antigen-forming cells were observed in the spleen and bone marrow of 2,3,7,8-TCDD exposed mice. A 96% reduction in the number of high-affinity, NP-specific antigen-forming cells in the spleen was observed 10 days postimmunization and a 64% reduction was observed on day 14; no significant alterations were observed in the bone marrow. Additionally, there were significant decreases in the production of total anti-NP and high-affinity anti-NP IgG1. Inouye et al. (2003) concluded that the inhibited generation of high-affinity antigen-forming cells and antibody production were likely caused by suppression of antigen-responding B cell proliferation induced by 2,3,7,8-TCDD during germinal center formation.

Numerous studies have examined the effects of 2,3,7,8-TCDD exposure on adaptive immune function by examining T cell subpopulations with or without exposure to an antigen. Suppression of the normal increase in $CD4^+$ T cells and/or $CD8^+$ T cells was observed in C57BL/6N or C57BL/10 mice administered a single dose of ≥5 μg/kg and exposed to ovalbumin (Ito et al. 2002) or influenza virus (Mitchell and Lawrence 2003; Vorderstrasse et al. 2003; Warren et al. 2000). Suppression of the normal increase in CD8+ T

cells is likely indicative of suppressed development of cytotoxic T lymphocyte response (Mitchell and Lawrence 2003). In the absence of an antigen, no alterations in splenic $CD4^+$ or $CD8^+$ T cell populations were observed in Long-Evans rats 2 days after administration of a single dose of 25 µg/kg 2,3,7,8-TCDD (Huang and Koller 1999). However, a decrease in the percentage of CD4+ cells in the spleen was observed when the rats were administered 5 µg/kg/day for 5 days (rats examined 2 days after the last dose); no change in $CD8^+$ T cells subpopulations were observed. Nohara et al. (2000) reported no alterations in the percentage of $CD4^+$ $CD8^+$, $CD4^-$ $CD8^-$, or $CD4^+$ T cell subpopulations in the thymus of Sprague-Dawley rats administered a single dose of 1 or 2 µg/kg 2,3,7,8-TCDD. However, there was a decrease in the ratio of $CD4^+$ T cells to $CD8^+$ T cells in the thymus and mesenteric lymph nodes at 1 µg/kg and an increase in the percentage of $CD8^+$ T cells in the thymus at 2 µg/kg. Similarly, Chen et al. (2013) and Oughton et al. (1995) found no alterations in splenic $CD3^+$, $CD4^+$, and/or $CD8^+$ cells in BALB/c mice administered 20 µg/kg or C57BL/6N mice administered 0.03 µg/kg/day for 14–15 months. However, in the chronic-duration study, alterations in splenic $CD4^+$ subsets (increases in naïve T helper cells and decreases in memory T cells) were observed (Oughton et al. 1995).

Acute-duration exposure to 2,3,7,8-TCDD also suppressed the production of antigen-specific IgM and IgG1 in C57BL/6N mice administered ≥2.5 µg/kg and immunized with ovalbumin (Inouye et al. 2003; Ito et al. 2002) or influenza A (Lawrence and Vorderstrasse 2004; Vorderstrasse et al. 2003; Warren et al. 2000) and in BALB/c mice administered 20 µg/kg 2,3,7,8-TCDD and immunized with ovalbumin (Chen et al. 2013). Increases in IgA levels have also been reported in C57BL/6 mice inoculated with influenza A and exposed to ≥1 µg/kg 2,3,7,8-TCDD (Lawrence and Vorderstrasse 2004; Vorderstrasse et al. 2003; Warren et al. 2000).

A number of studies have found that 2,3,7,8-TCDD exposure suppressed the primary antibody response to sheep red blood cells. Following an acute-duration exposure to 2,3,7,8-TCDD and sensitization with sheep red blood cells, suppression of the response (as measured by splenic plaque-forming cells or antibody-forming cells) was observed in B6C3F1 mice administered a single dose ≥0.1 µg/kg (Frawley et al. 2014; Holsapple et al. 1986; Matulka et al. 1997; Smialowicz et al. 1997), a 5-day exposure to 6 µg/kg/day (Kaplan et al. 2011), or a 14-day exposure to 1 µg/kg (Holsapple et al. 1986). Evaluating the effect of the time of administration of a single 14 µg/kg dose of 2,3,7,8-TCDD relative to sensitization with sheep red blood cells, Matulka et al. (1997) found immunosuppression (measured as total IgM antibody forming cells) when the 2,3,7,8-TCDD was administered 1, 2, or 3 days prior to sensitization, on the day of sensitization, and 1 or 2 days after sensitization; there was no significant effect when the 2,3,7,8-TCDD was administered 3 days after sensitization. Comparing total IgM antibody-forming cell

response in B6C3F1 and DBA/2 mice following a single exposure and repeated exposure, Matulka et al. (1997) found significant decreases at ≥14 µg/kg for a single exposure and ≥1 µg/kg/day for a 14-day exposure in the B6C3F1 mice, although the magnitude of the suppression was greater following repeated exposures than single exposure. In the DBA/2 mice, significant decreases were observed at 42 µg/kg and 14 µg/kg/day; at a given cumulative dose, the magnitude of the decrease was similar when the dose was administered once or over a 14-day period. Intermediate-duration exposure resulted in a lower adverse effect level; a significant decrease in the response to sheep red blood cells was observed in B6C3F1 mice administered 0.0011 µg/kg 5 days/week for 13 weeks (mice immunized with sheep red blood cells 3 days after the last exposure) (Smialowicz et al. 2008) and in C57BL/6 mice administered 0.5 µg/kg/day 1 day/week for 5–8 weeks (Vecchi et al. 1983).

Luebke et al. (1999) examined age-related differences in 2,3,7,8-TCDD-induced suppression of adaptive immune function in B6C3F1 mice administered 2,3,7,8-TCDD and infected with *Trichinella spiralis* larvae 7 days later. Exposure to ≥10 µg/kg resulted in a significant decrease in parasite elimination in 12-week-old mice, but not in 76-week-old mice. Similarly, there were no effects on the proliferative response to concanavalin A or lipopolysaccharide (LPS) in the spleen of aged mice, but a decreased response to LPS was observed in the spleen of young mice exposed to 10 µg/kg. However, a decrease in response to parasite antigens were observed in the spleen of young and aged mice exposed to ≥1 µg/kg. An increase in the splenic proliferative response to *Salmonella typhimurium* mitogen was also observed in aged rats administered 30 µg/kg and infected with *T. spiralis*; there were no alterations in the response to parasite antigens or concanavalin A (Luebke et al. 1999); the investigators noted that these results were in contrast to the enhanced response to concanavalin A and parasite antigens observed in young rats in other studies.

A significant decrease in lymphocyte proliferation, when measured during the light cycle, was observed in Siberian hamsters administered a single dose of 2 µg/kg 2,3,7,8-TCDD; however, no alterations were observed during the dark cycle (Yellon et al. 2000). Additionally, no alterations in lymphocyte proliferation in response to alloantigen were observed 2 or 20 weeks after 2,3,7,8-TCDD administration.

Burleson et al. (1996) reported a significant increase in mortality in B6C3F1 mice administered a single dose of ≥0.01 µg/kg 2,3,7,8-TCDD and infected with influenza A virus (A/Hong Kong/8/68 strain) 7 days later. Using the same protocol, Nohara et al. (2002) attempted to replicate these results. Groups of B6C3F1, BALB/c, C57BL/6N, and DBA/2 mice were administered a single dose of 2,3,7,8-TCDD and infected with influenza A virus (A/PR/34/8) 7 days later. No significant alterations in survival rate were

observed and the highest dose tested, 0.50 µg/kg, was considered a NOAEL in all four mouse strains. Vorderstrasse et al. (2003) reported increases in mortality in C57BL/6 mice administered ≥2.5 µg/kg and infected with influenza A virus (A/HKx31 strain); no deaths were observed in controls or mice administered 1 µg/kg. Although these results support the findings of Nohara et al. (2002), Vorderstrasse et al. (2003) cautioned that it is not appropriate to compare the results of their study with those of Burleson et al. (1996) and Nohara et al. (2002) because they utilized a virus strain that is not lethal to immunocompetent mice.

Increased mortality that was indicative of altered immunity was also observed in C57BL/6Jfh mice challenged with *Salmonella bern* following exposure to 0.14 µg/kg/day of 2,3,7,8-TCDD by gavage for 4 weeks (Thigpen et al. 1975); no significant effects were observed at 0.07 µg/kg/day. In the same study, using the same experimental design, doses of up to 2.8 µg/kg/day of 2,3,7,8-TCDD had no significant effect on mortality in mice infected with *Herpesvirus suis* (Thigpen et al. 1975).

Delayed-type hypersensitivity response to tuberculin was observed in guinea pigs exposed to 0.006 µg/kg/day 2,3,7,8-TCDD for 8 weeks (Vos et al. 1973), but not in CD rats similarly exposed to 0.71 µg/kg/day (Vos et al. 1973). Another study reported a delayed-type hypersensitivity response in Sprague-Dawley rats sensitized with keyhole limpet hemocyanin following a single dose of 10 µg/kg 2,3,7,8-TCDD (Fan et al. 1996). Vos et al. (1973) also reported a suppressed response in the graft versus host test in B6D2F1 mice exposed to 0.71 µg/kg/day for 4 weeks.

In addition to the increased mortality, Vorderstrasse et al. (2003) reported a number of other alterations in immunological endpoints. At ≥1 µg/kg, there was a significant decrease in IgG2a levels and increase in IgA levels; at ≥2.5 µg/kg, there were decreases in IgG1 and IgG2b levels and decreases in the number of lymphocytes and macrophages in bronchoalveolar lavage fluid; and at 7.5 µg/kg, there was suppression of $CD8^+$ T cells in the mediastinal lymph node. The decreased IgG levels, increased IgA levels, and lack of alterations in IgM levels suggested that 2,3,7,8-TCDD affected antibody class switching. In addition to these alterations in adaptive immune function, there was also evidence of a dysregulation of the innate immune response to the influenza virus infection. A significant increase in the number of neutrophils (≥5 µg/kg) and a decrease in interferon-γ levels (10 µg/kg) were observed in bronchoalveolar lavage fluid. Similarly, Warren et al. (2000) reported decreases in $CD4^+$ and $CD8^+$ T cells, IL-2, and interferon-γ levels and cytotoxic T lymphocyte activity in the mediastinal lymph nodes; decreases in plasma IgM, IgG1, IgG2a, and IgG2b levels; increases in plasma IgA levels; and decreases in IL-2 and increases in interferon-γ levels in bronchoalveolar lavage fluid in mice administered 10 µg/kg 2,3,7,8-TCDD and

infected with influenza A virus (A/HKx31 strain). Increases in mortality were also observed; however, the data were not presented in a way that would facilitate identifying an adverse effect level.

Lawrence and Vorderstrasse (2004) examined the effect of 2,3,7,8-TCDD on immunological memory in C57BL/6 mice administered a single dose of 5 or 10 µg/kg and infected with influenza A virus (HKx31 strain). The primary infection resulted in significant suppression of IgM, IgG2a, and IgG2b levels in the plasma and bronchoalveolar lavage fluid 10 and 40 days after infection; a significant increase in plasma IgA levels was also observed at both examination periods. Upon re-infection, plasma levels of IgM, IgG2a, and IgG2b were still significantly lower than the vehicle controls for at least 7 days after reinfection. In contrast, there were no significant alterations in the number of IgG or IgA producing cells in the mediastinal lymph nodes after the primary infection or after re-infection. After the primary infection, a 70% decrease in $CD8^+$ cells was found in the mediastinal lymph nodes of mice exposed to 10 µg/kg. Examination of virus-specific memory $CD8^+$ T cells measured 60 days after the primary infection showed a 50% decrease in mice exposed to 2,3,7,8-TCDD. Upon re-infection, there was a delay in the expansion of virus-specific memory $CD8^+$ cells; 3 days after re-infection, there was a 70% difference between the number of virus-specific memory $CD8^+$ cells in the 2,3,7,8-TCDD group compared to the vehicle controls. However, 5-days after re-infection, the recall response was equivalent to that of the control group. To evaluate host resistance, survival and pulmonary virus titers were monitored for 7 or 21 days after the primary infection or re-infection, respectively, in two sets of animals. In the 10 µg/kg group, 37% of the mice died after the primary infection, compared to 3% mortality in the vehicle controls. In contrast, no deaths were observed in either group after re-infection. Additionally, no detectable virus was found in the lungs of exposed or control mice 3–14 days after the re-infection. The investigators noted that although exposure to 2,3,7,8-TCDD did not adversely affect the recall response to homotypic infection, it is likely that the decreased number of memory cytotoxic T lymphocytes would have a negative impact on host resistance to a heterosubtypic infection because the excess levels of IgA that are host-protective for homotypic infection would not be effective in a heterosubtypic infection.

Two studies demonstrated that oral exposure to ≥1 µg/kg 2,3,7,8-TCDD and oral immunization with ovalbumin resulted in impaired oral tolerance (Chmill et al. 2010; Kinoshita et al. 2006). Oral tolerance is defined as the antigen-specific inhibition of systemic IgG production by oral pre-administration of protein antigens. Both studies also found decreased fecal IgA levels that were indicative of impaired gut mucosal immunity.

Although not as well studied as other immunological endpoints, Yang et al. (1994) reported suppression of pulmonary NK cell activity in Fischer-344 rats infected with influenza A virus and exposed to 0.72 µg/kg/day 2,3,7,8-TCDD for 14 days. However, in the absence of infection, there was no alteration in pulmonary NK cell activity, and splenic NK cell activity was not altered by 2,3,7,8-TCDD exposure or by the virus.

Other CDD Congeners—Animal Studies. Other CDD congeners also appear to affect the immune system. Decreases in relative spleen and thymus weight were observed in C57BL/6 mice administered a single dose of ≥10 µg/kg 1,2,3,7,8-PeCDD (Ao et al. 2009) and decreases in the number of thymocytes were observed at ≥3 µg/kg. Significant dose-related decreases in absolute and relative thymus weight were observed in male Sprague-Dawley rats administered doses equivalent to 4–110 µg/kg/day 1,2,3,4,6,7,8-HpCDD for 13 weeks by gavage (Viluksela et al. 1994). A dose level of 0.3 µg/kg/day was without significant effect. Treatment with 1,2,3,4,6,7,8-HpCDD had no significant effect on spleen weight. Splenic hyperplasia was observed in Osborne-Mendel rats after exposure to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD at 1 µg/kg/day for 13 weeks (NCI/NTP 1980).

Suppressed antibody response was reported in B6C3F1 mice after 2 weeks of exposure to 0.1 µg/kg/day of 2,7-DCDD, but not after exposure to 10 µg/kg/day of OCDD (Holsapple et al. 1986). Immunization with ovalbumin resulted in significant decreases in IL-5 levels in the spleen of mice exposed to ≥1 µg/kg 1,2,3,7,8-PeCDD (Ao et al. 2009). Depressed antibody response was found in C57BL/6 mice exposed to a single dose of 33 µg/kg/day 1,2,3,4,6,7,8-HpCDD (Kerkvliet and Brauner 1987). Suppressed serum complement activity was found in B6C3F1 mice following 2 weeks of exposure to 1 µg/kg/day 1,2,3,6,7,8-HxCDD (White et al. 1986).

Immunological mechanisms. Many of the health effects of CDDs share a common initiating event in AhR binding. Section 2.21, Mechanisms of Toxicity, provides a detailed discussion of the evidence for this initiating event and its physiological sequelae. In this subsection, an overview of the mechanisms involved in immunotoxic effects is provided. Detailed mechanistic explanations are beyond the scope of this profile.

2,3,7,8-TCDD has been shown to induce a variety of effects on the immune system of experimental animals, including thymic involution, neutrophilia, and immune suppression manifested as decreased antibody production, reduced development of cytotoxic T-lymphocytes, and increased susceptibility to infections. Several detailed reviews of the mechanisms of immunotoxicity related to 2,3,7,8-TCDD have

been published (Corsini et al. 2011; Kerkvliet 2009, 2012; Marshall and Kerkvliet 2010; Prasad Singh et al. 2020) and provide the experimental evidence for the current understanding of the mechanisms. Key conclusions of these reviews are: (1) AhR is expressed in most immune system cells; (2) AhR is necessary for 2,3,7,8-TCDD immune suppression; (3) AhR responsive element (AhRE) sequences are found in many genes related to immune system function; (4) the primary pathway by which 2,3,7,8-TCDD suppresses immune function is via increasing the proportion of anti-inflammatory Treg cells; and (5) 2,3,7,8-TCDD effects on immune signaling depends on the physiological context (cell type and activation status, tissue, species, etc.).

Thymic involution is characteristic of exposure to 2,3,7,8-TCDD and structurally related chemicals in all species examined. The mechanism for 2,3,7,8-TCDD-induced thymic atrophy is not completely understood, but available data indicate that AhR activation is important. A recent study (Beamer et al. 2019) showed that AhR activation in dendritic cells is key to this effect because targeted deletion of the AhR in these cells prevented thymic atrophy in mice exposed to 2,3,7,8-TCDD. Thymic atrophy induced by 2,3,7,8-TCDD may, in part, result from apoptosis of thymocytes (Camacho et al. 2004), albeit not via Fas/Fas ligand signaling (Beamer et al. 2019; Nagai et al. 2006). Other studies have demonstrated that 2,3,7,8-TCDD can also decrease the proliferation of precursor thymocytes (Lai et al. 1998) and increase the migration of thymocytes out of the thymus (Poland et al. 1994; Temchura et al. 2005).

The innate immune response is largely mediated by myeloid cells including granulocytes, macrophages, dendritic cells, and NK cells. Microbial pathogens activate these cells via toll-like receptors (TLRs) that recognize structural components of common microbes. The TLRs initiate signaling to upregulate pro-inflammatory cytokines and complement activation. Many TLR and complement genes have been shown to contain AhRE sequences, suggesting potential susceptibility to modulation by 2,3,7,8-TCDD-liganded AhR (Kerkvliet 2009), although data to show the influence of 2,3,7,8-TCDD on these genes are lacking.

Exposure to 2,3,7,8-TCDD has been shown to induce dose-dependent increases in neutrophils (the most abundant type of granulocyte) in the blood, peritoneal cavity, spleen, and lungs of mice (Kerkvliet 2009). In addition, 2,3,7,8-TCDD alters the oxidative burst and cytolytic activity of neutrophils in a context-dependent fashion; under different circumstances, experiments have demonstrated suppression, enhancement, and absence of an effect of 2,3,7,8-TCDD on this function (Kerkvliet 2009). Similarly, the cytolytic activity of NK cells after 2,3,7,8-TCDD exposure varies from no response to either suppression or enhancement. The mechanisms by which 2,3,7,8-TCDD affects neutrophils and NK cells are not

known; however, several genes for neutrophil cytosolic factors and NK receptor subunits have AhRE sequences and may play a role (Kerkvliet 2009).

In mice exposed to 2,3,7,8-TCDD, a decrease in dendritic cell counts in the spleen was shown to occur 1 week after exposure, and *in vitro* studies showed that 2,3,7,8-TCDD enhanced both maturation and apoptosis of dendritic cells (Kerkvliet 2009). The mechanisms for these effects may include altered expression of apoptotic genes or upstream signaling pathways. For example, *in vitro* data show that 2,3,7,8-TCDD increased the expression of *Fadd*, a gene that mediates apoptosis, and also suppressed NFkB signaling (Kerkvliet 2009).

The adaptive immune response begins with activation of dendritic cells upon recognition of a pathogen. With prolonged interaction with activated dendritic cells, $CD4^+$ T cells are stimulated to differentiate, by one of several pathways, into T helper cells (TH1, TH2, TH17, Tregs). TH1, TH2, and TH17 cells facilitate the immune response to pathogens and are also involved in allergic and autoimmune responses. Tregs, in contrast, produce cytokines (e.g., IL-10, TGFβ) that suppress the immune response by modulating the activation and/or survival of T helper/effector cells and dendritic cells. A growing body of experimental data has shown that exposure to 2,3,7,8-TCDD enhances differentiation of T cells into Tregs and suppresses TH17 cells, tipping the balance toward suppression of all forms of adaptive immune responses, including not only pathogen responses but also allergic and autoimmune responses. There appear to be several pathways by which 2,3,7,8-TCDD influences T cell differentiation. For example, TCDD exposure has been shown to modulate expression of microRNAs, deoxyribonucleic acid (DNA) methylation, and histone modifications in the promoter region of the FoxP3 and IL-17 transcription factors, which play critical roles in the differentiation of Treg and TH17 cells (respectively). In addition, many genes involved in T helper cell differentiation have one or more AhRE sequences, as shown in Table 2-18.

Table 2-18. Numbers of Aryl Hydrocarbon Receptor Responsive Elements (AhREs) in Genes Regulating T Helper Cell Differentiation

Gene	Number of AhREs	Gene	Number of AhREs	Gene	Number of AhREs
Tgfb1	10	Il17b	3	Stat2	5
Tgfb2	15	Il17d	8	Stat3	5
Tgfb3	5	Il21	4	Stat4	4
Il2	3	Il32a	5	Stat5a	9
Il4	2	Gata3	10	Stat5b	7

Table 2-18. Numbers of Aryl Hydrocarbon Receptor Responsive Elements (AhREs) in Genes Regulating T Helper Cell Differentiation

Gene	Number of AhREs	Gene	Number of AhREs	Gene	Number of AhREs
Il6	6	Foxp3	5	Stat6	12
Il10	3	Jak1	5	Socs1	18
Il12a	3	Jak2	9	Socs2	8
Il12b	3	Jak3	20	Socs3	11
Il17	3	Stat1	9		

Source: Kerkvliet 2009

In summary, the mechanisms and pathways by which 2,3,7,8-TCDD modulates immune responses are complex and depend upon the physiological milieu in which the exposure occurs. Most of the data on immune mechanisms are from studies in mice, and there are well-known differences in the responses of various species to TCDD exposure, suggesting the need for studies in other species to better evaluate species differences in immune effects.

2.15 NEUROLOGICAL

Overview. A small number of epidemiological studies have evaluated the neurotoxicity of CDDs. The most studied neurological endpoint is peripheral neuropathy, which has been examined in workers, Vietnam War veterans, and the Seveso cohort. The results are inconsistent across studies and populations.

The potential neurotoxicity of 2,3,7,8-TCDD has not been well studied in laboratory animals. Two studies examined motor activity and found decreased activity. The scope of the remaining studies was limited to histopathological examination of nervous tissues in which no alterations were found.

Epidemiological Studies. The potential neurotoxicity of CDDs has been examined in a number of epidemiological studies with mixed results (Table 2-19). Apart from peripheral neuropathy, most neurological outcomes have only been investigated by a couple of studies. A number of studies have investigated the potential association between CDD exposure and peripheral neurotoxicity; studies have examined the incidence of peripheral neuropathy, clinical signs of neuropathy, and motor conduction velocity. The results have been inconsistent across studies. An increased occurrence of peripheral neuropathy has been reported in workers (Pazderova-Vejlupková et al. 1981) and Vietnam War veterans

Table 2-19. Neurological Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Occupational			
Mannetje et al. 2018 Cross-sectional study in former employees (n=245) of a phenoxy herbicide production facility in New Zealand	Work history and 2007–2008 serum 2,3,7,8-TCDD levels ≥10 pg/g lipid	Frequent mood changes	↔
		Trouble sleeping	↔
		Abnormal reflexes	↑, serum level ≥25 pg/g lipid
Moses et al. 1984 Cross-sectional study of current and former workers at a 2,4,5-T production facility in West Virginia (n=226 workers; 117 with current or history of chloracne)	Chloracne used as a surrogate for heavy exposure to 2,3,7,8-TCDD	Pin prick sensation	↓, workers with chloracne
Singer et al. 1982 Cross-sectional study of current and former workers at a phenoxy herbicide production facility in Arkansas (n=45 workers and 25 controls)	Not evaluated	Nerve conduction velocity	
		Median motor nerve	↓
		Median sensory nerve	↔
		Sural sensory nerve	↓
Sweeney et al. 1993 Cross-sectional study of former workers at two 2,4,5-T, 2,4,5-trichlorophenate, and 2,4-D production facilities in New Jersey and Missouri (n=281 workers and 260 referents)	Mean serum 2,3,7,8-TCDD level: 220 pg/g lipid (workers) and 7 pg/g lipid (referents)	Peripheral neuropathy	↔
Pazderova-Vejlupková et al. 1981 Case series of 55 male workers at an herbicide production facility in the former Czechoslovakia (no comparison group was used)	Not reported	Polyneuropathy	↑, 31% of subjects

Table 2-19. Neurological Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Thömke et al. 1999 Cross-sectional study of 121 workers at a pesticide production facility in Germany	Comparisons made between workers with chloracne (n=35) and without chloracne (n=86)	Nerve conduction velocity Sural nerve Peroneal nerve Ulnar nerve	 ↔ ↔ ↔
		Neurophysiological abnormalities	↑
		Diminished vibration sense	↑
Thömke et al. 2002 Cross-sectional study of 121 workers at a pesticide production facility in Germany	Comparisons made between workers with chloracne (n=35) and without chloracne (n=86) Median blood CDD/CDF TEQ: 871 pg/g lipid in chloracne group and 330 pg/g pg/g lipid in non-chloracne group	Visual evoked potential	↔
		Brainstem auditory evoked potential	↔
		Blink reflex	↔
Urban et al. 2007 Cross-sectional study of 15 workers exposed to CDDs at an herbicide production facility in the former Czechoslovakia (no comparison group was used); follow-up to the Pazderova-Vejlupková et al. (1981) study	Mean plasma 2,3,7,8-TCDD level: 128 pg/g lipid	Symptoms of polyneuropathy	↑, 60% of subjects
		Nerve conduction velocity Median, ulnar, tibial, and sural motor and sensory nerve fibers	↔
		Visual evoked potential abnormalities	↑, 33% of subjects
		Neuropsychological tests	↑, correlations with plasma 2,3,7,8-TCDD levels
		Color confusion index	↔
Seveso, Italy			
Ames et al. 2018 Retrospective cohort study of women (n=159 for physical function subgroup and 459 for working memory subgroup) participating in the Seveso Women's Health Study; physical function subgroup was evaluated in 1996 and working memory subgroup was evaluated in 2008	Median serum 2,3,7,8-TCDD levels (measured at time of accident): 45.2 ppt for physical function subgroup and 60.1 ppt for working memory subgroup	Walking speed	↔
		Manual dexterity	↔
		Lower body flexibility	↔
		Grip strength	↑, lower serum levels ↓, higher serum levels
		Verbal or spatial working memory	↔

Table 2-19. Neurological Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Assennato et al. 1989 Retrospective cohort study of 133 subjects who developed chloracne after the accident and 191 referents	Not measured	Nerve conduction velocity Median motor nerve Peroneal motor nerve Sural sensory nerve	 ↔ ↔ ↔
Filippini et al. 1981 Retrospective cohort study of 197 subjects living in Seveso at the time of the accident; 305 referents were used to establish reference values	Not measured	Peripheral neuropathy (as assessed via motor nerve conduction velocity)	↑, among subjects with indicators of exposure (chloracne or increased serum enzymes [γ-glutamyl transferase, ALT, AST])
Vietnam War veterans and Operation Ranch Hand veterans			
Beard et al. 2016 Case-control study of U.S. veterans with amyotrophic lateral sclerosis (n=621 cases and 958 controls)	Military service during Vietnam War, self-reported exposure to Agent Orange in the field	Amyotrophic lateral sclerosis	↑
Beard et al. 2017 Cross-sectional study of 616 U.S. veterans with amyotrophic lateral sclerosis	Military service during Vietnam War, self-reported exposure to Agent Orange in the field	Amyotrophic lateral sclerosis survival	↓
Lee et al. 2022 Retrospective study of 348 Korean Vietnam veterans with exposure to defoliants and 670 veterans without defoliant exposure	Military service during Vietnam War and reported exposure to defoliants	Brain atrophy progression	↑

Table 2-19. Neurological Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Levy 1988 Cross-sectional study of 6 U.S. Vietnam veterans with chloracne and 25 Vietnam veterans without chloracne	Chloracne used as a surrogate for Agent Orange exposure	Posttraumatic stress disorder	↑
Martinez et al. 2021 Cross-sectional study of U.S. Vietnam War veterans (n=316,351; 12.1% had presumed Agent Orange exposure)	Presumed Agent Orange exposure based on self-reported exposure and clinician indicated that a health care encounter was associated with Agent Orange	Dementia	↑
USAF 1991 Cross-sectional report of 866 Operation Ranch Hand personnel and a comparison group of 1,198	Not measured	Peripheral neuropathy	↔
		Coordination abnormalities	↑, high group
		CNS index (based on coordination, tremor, gait)	↑, high group
Wolfe et al. 1995 Retrospective study of the offspring of 454 male veterans involved in Operation Ranch Hand and 570 comparison fathers	Background serum dioxin level: <10 ppt Low exposure serum dioxin level: ≤110 ppt High exposure serum dioxin level: >110 ppt	Nerve conduction velocity	↔
		Scores on functional and performance psychological tests	↔
Yi et al. 2013 Cross-sectional study of a group of 114,562 Korean veterans of the Vietnam War exposed to Agent Orange	Exposure based on military record	Central nerve disorders	↔
		Peripheral neuropathy	↔
		Multiple nerve palsy	↑
		Multiple sclerosis	↑
		Amyotrophic lateral sclerosis	↔

Table 2-19. Neurological Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Yi et al. 2014 Cross-sectional study of a group of 111,726 Korean veterans of the Vietnam War exposed to Agent Orange	Self-reported exposure; veterans divided in low- and high-exposure groups	Spinal muscular atrophy	↔
		Parkinson's disease	↔
		Alzheimer's disease	↑
		Multiple sclerosis	↔
		Epilepsy	↑
		Polyneuropathies of peripheral nervous system	↑
		Paralytic syndromes	↔

↑ = association; ↓ = inverse association; ↔ = no association; 2,4-D = 2,4-dichlorophenoxyacetic acid; 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; CNS = central nervous system; TCDD = tetrachlorodibenzo-*p*-dioxin; TEQ = toxic equivalency

(Yi et al. 2014); other studies of workers (Sweeney et al. 1993) and Vietnam War veterans (USAF 1991; Yi et al. 2013) have not found increases. Pazderova-Vajlupková et al. (1981) reported a high incidence of fatigue and weakness in the lower extremities in workers. In studies of workers with chloracne (used as a biomarker of exposure to high levels of 2,3,7,8-TCDD), a decrease in pin prick sensation (Moses et al. 1984) and an increase in the incidence of simultaneous occurrence of sensory and deep tendon reflex abnormalities (Thömke et al. 1999) were observed. However, the Thömke et al. (1999) study did not find increases in the incidence of symptoms (such as paresthesia, numbness, or cramps) suggestive of peripheral neuropathy or differences in deep tendon reflexes or sensation to touch or pain in comparisons between workers with or without chloracne. In a follow-up of 15 surviving workers examined in the Pazderova-Vajlupková et al. (1981) study, no associations between symptoms of polyneuropathy and serum 2,3,7,8-TCDD levels were found (Urban et al. 2007); however, diminished sensation to touch and pain, diminished vibration sense, and bilateral or lost ankle and/or knee jerks were observed in 9 of the 15 workers. Another study reported an association between serum 2,3,7,8-TCDD levels and abnormal reflexes (Mannetje et al. 2018). Decreased nerve conduction velocities were observed in the median motor nerve and sural sensory nerve in workers (Singer et al. 1982) and among Seveso residents with chloracne or increased serum enzymes (γ-glutamyl transferase, ALT, AST) (Filippini et al. 1981). No alterations in nerve conduction velocity were observed in other studies of workers (Suskind and Hertzberg 1984; Sweeney et al. 1993; Urban et al. 2007), Seveso residents (Assennato et al. 1989), or Operation Ranch Hand veterans (Wolfe et al. 1985); Thömke et al. (1999) did not find alterations in sural, peroneal, or ulnar nerve conduction velocities in workers with chloracne, but did find an increase in the number of individuals with one or two, or with two and more, neurophysiologic abnormalities in the workers with chloracne.

Three studies evaluated possible associations between CDD exposure and amyotrophic lateral sclerosis (ALS) in Vietnam War veterans. An increased incidence of ALS (Beard et al. 2016) and decreased survival (Beard et al. 2017) was found among U.S. veterans with self-reported exposure to Agent Orange; a study of Korean veterans found no association between self-reported exposure to Agent Orange and ALS (Yi et al. 2013). A study in workers did not find evidence of altered cranial nerve function as evidenced by no difference in auditory brainstem evoked potential, visual evoked potential, or blink reflex in comparisons between workers with and without chloracne (Thömke et al. 2002). Abnormal neurological symptoms were observed in a group of 41 Missouri residents with measured 2,3,7,8-TCDD serum lipid levels (Webb et al. 1989). The symptoms included abnormal pain sensation in lower extremities, abnormal vibratory sensation, and abnormal reflexes. However, the distribution of these effects among residents with serum lipid 2,3,7,8-TCDD levels of <20, 2–60, or >60 ppt was not dose-

related. Another study found visual evoked potential abnormalities in 33% of workers (Urban et al. 2007). Several neurological effects have been reported in single studies including altered grip strength (Ames et al. 2018), posttraumatic stress disorder (Levy 1988), dementia (Martinez et al. 2021), coordination abnormalities (USAF 1991), multiple sclerosis (Yi et al. 2013), multiple nerve palsy (Yi et al. 2013), Alzheimer's disease (Yi et al. 2014), epilepsy (Yi et al. 2014), and brain atrophy (Lee et al. 2022). Additional research is needed to assess the possible relationship between CDD exposure and these neurological effects.

2,3,7,8-TCDD—Animal Studies. Limited information was obtained regarding neurological effects in animals. Decreased motor activity was observed in Sprague-Dawley rats after a single dose of 15 µg/kg 2,3,7,8-TCDD that was not associated with mortality (Seefeld et al. 1984a) and after 14 daily doses of 2 µg/kg/day to pregnant females that were sacrificed on pregnancy day 21 (Giavini et al. 1983). The NOAEL value was 0.01 µg/kg/day. Administration of 2,3,7,8-TCDD by gavage to male and female Osborne-Mendel rats and male B6C3F1 mice at doses of up to 0.071 µg/kg/day and female B6C3F1 mice dosed with up to 0.3 µg/kg/day for 104 weeks did not result in significant histological alterations in the brain, spinal cord, or sciatic nerve (NTP 1982b); no histological alterations were observed in the brain of female Sprague-Dawley rats administered up to 0.071 µg/kg/day 2,3,7,8-TCDD for 2 years (NTP 2006).

2.16 REPRODUCTIVE

Overview. Epidemiological studies have evaluated a number of reproductive outcomes in men and women. Overall, epidemiological studies examining reproductive hormone levels have not found associations in several populations including male workers, males living in areas with contaminated soil, Seveso residents, and the general population. No associations between 2,3,7,8-TCDD levels and menstrual cycle or ovarian function were observed in Seveso women. Mixed results were found in studies examining the possible association between CDDs and risk of endometriosis. A study of Seveso men exposed as young boys found alterations in sperm parameters that were not found in men who were young adults at the time of the accident. Increased time-to-pregnancy was observed in two studies of Seveso women.

Laboratory animal studies of 2,3,7,8-TCDD provide strong evidence that the reproductive system is a sensitive target of toxicity. The observed effects include decreases in sperm production, count, viability, and motility; decreased ovulation; decreased female fertility; and altered nursing behavior. Alterations in sperm parameters have been observed at ≥0.1 and ≥0.001 µg/kg/day following acute or intermediate

durations, respectively. In females, reproductive effects have been observed at doses of 1 µg/kg/day (altered nursing behavior), 0.05 µg/kg/day (decreased implantation sites), and 0.00012 µg/kg/day (endometriosis) following acute-, intermediate-, or chronic-duration exposures, respectively. The potential for reproductive toxicity has not been evaluated for other CDD congeners.

Epidemiological Studies. Epidemiological studies have evaluated possible associations between CDD exposure and reproductive hormone levels in several populations. As presented in Table 2-20, most of these studies have not found associations in male workers (Egeland et al. 1994), male Operation Ranch Hand veterans (Henriksen et al. 1996; USAF 1991), male residents in Agent Orange contaminated areas in Vietnam (Sun et al. 2017, Van Luong et al. 2018), male Seveso residents (Mocarelli et al. 2008), female Seveso residents (Warner et al. 2007), or the post-menopausal general population (Lambertino et al. 2021). Some studies did find associations (Egeland et al. 1994; Gupta et al. 2006; Lambertino et al. 2021; Mocarelli et al. 2008; Van Luong et al. 2018) but the findings were not consistent across studies.

Several studies investigated the impact of TCDD exposure on women's menstrual cycles >20 years following the Seveso incident. The individual TCDD serum levels were not related to the age at menarche in a group of women who were premenarcheal at the time of initial exposure in 1976 (Warner et al. 2004). Eskenazi et al. (2002b) reported an increased menstrual cycle length in female adults who were premenarcheal at the time of the initial exposure; however, the confidence intervals included unity. The cycle length increased 0.93 days for each 10-fold increase in TCDD levels. There was also a dose-related association between the TCDD levels and an increased risk of early menopause in the Seveso women (Eskenazi et al. 2005). However, the relationship was not demonstrated at the highest exposures (>100 ppt). When indicators of ovarian function (ovarian cysts, ovarian follicles, ovulation rate) were evaluated in Seveso women, no clear evidence of TCDD-induced effects was observed (Warner et al. 2007).

The relationship between CDD exposure and endometriosis has been evaluated in several studies. In Seveso residents, no significant increase in the risk of endometriosis was found in a cohort of women from zones A and B (Eskenazi et al. 2002a). The risk of uterine leiomyoma (fibroids) associated with exposure to 2,3,7,8-TCDD for women who resided near Seveso in 1976 was investigated (Eskenazi et al. 2007). In total, about 26% of the women had confirmed fibroids. However, higher levels of serum 2,3,7,8-TCDD were found to be associated with lower risk for the fibroid development. Apart from the Seveso studies, there were several case-control and cross-sectional studies in the general population. Increased risks of deep endometriotic (adenomyotic) nodules and peritoneal endometriosis were associated with CDD/CDF TEQ serum levels in a study of Belgian women (Heilier et al. 2005). The

Table 2-20. Reproductive Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Occupational			
Egeland et al. 1994 Cross-sectional study of 248 male workers employed at two 2,4,5-T production facilities and 231 referents	Past serum dioxin levels were estimated from current levels. Workers divided into four quartiles (pg/g): • Q1: <20 • Q2: 20–75 • Q3: 76–240 • Q4: 241–3,400	LH	↑, for trend
		FSH	↔, for trend
		Testosterone	↔, for trend
Vietnam veterans and Operation Ranch Hand veterans			
Gupta et al. 2006 Prospective cohort study of 971 veterans involved in Operation Ranch Hand and 1,266 Air Force veterans not involved in spraying	Mean serum 2,3,7,8-TCDD level: 26.93 ppt in Ranch Hand veterans and 4.57 ppt in referent veterans Ranch Hand mean serum levels (ppt) • Q1: 4.14 • Q2: 8.95 • Q3: 18.40 • Q4: 76.16	Benign prostatic hyperplasia	↑, Ranch Hand veterans ↓, comparison veterans
		Serum testosterone	↓, Q2

Table 2-20. Reproductive Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Henriksen et al. 1996 Retrospective study of participants in the Air Force Health Study; 848–918 Operation Ranch Hand veterans and 1,011–1,154 non-exposed Air Force veterans, subjects were examined in 1982, 1985, 1987, and 1992	Serum "dioxin" levels at the end of veteran's tour of duty were estimated using current serum levels. Median serum "dioxin" levels in Ranch Hand veterans: ≤10 ppt (background group), >10 ppt (low-exposure group) and 130 ppt (high-exposure group) 98th percentile of serum dioxin levels in comparison group was 10 ppt	Serum testosterone <400 ng/mL in 1982 or <260 ng/mL in 1987 or 1992	↑, low-exposure group only in 1987 ↔, all other groups and time periods
		Serum FSH >25 IU in 1982 or >17.2 IU in 1987, or >15 IU in 1992	↔, all groups and time periods
		Serum LH >30 IU/mL in 1982, >25.1 IU/mL in 1987, or >9.8 IU/mL in 1992	↔, all groups and time periods
		Testicular abnormality (atrophic or missing)	↔, all groups and time periods
		Sperm counts ≤60 million/mL	↔, all groups and time periods
USAF 1991 Cross-sectional report of 866 Operation Ranch Hand personnel and a comparison group of 1,198 unexposed Air Force veterans	Not reported	Serum testosterone <260 ng/dL	↔ ↓ when body fat was not considered
Wolfe et al. 1985 Retrospective study of 1,278 Operation Ranch Hand personnel	Not measured	Sperm count	↔
Seveso, Italy			
Eskenazi et al. 2002a Retrospective cohort study of women participating in the Seveso Women's Health Study (n=637, 97 from zone A and 540 from zone B)	Median serum 2,3,7,8-TCDD levels: 257 ppt for zone A and 47.0 for zone B	Endometriosis	↔

Table 2-20. Reproductive Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Eskenazi et al. 2002b Retrospective cohort study of women participating in the Seveso Women's Health Study (n=301)	Median serum 2,3,7,8-TCDD level: 67.5 ppt	Menstrual cycle length	↔
		Days of menstrual flow	↔
		Risk of irregular cycle	↓
Eskenazi et al. 2003 Retrospective cohort study of women participating in the Seveso Women's Health Study (n=510, 888 total pregnancies)	Median 2,3,7,8-TCDD serum level at the time of the incident: 46.6 ppt	Spontaneous abortion	↔
Eskenazi et al. 2005 Retrospective cohort study of women participating in the Seveso Women's Health Study (n=616)	Median serum 2,3,7,8-TCDD level: 43.7 ppt	Early menopause	↔
Eskenazi et al. 2007 Retrospective cohort study of women participating in the Seveso Women's Health Study (n=956)	Serum 2,3,7,8-TCDD tertiles (ppt): • T1: ≤20 • T2: 20.1–75.0 • T3: >75	Uterine fibroids	↓, T2
Eskenazi et al. 2010 Retrospective cohort study of women participating in the Seveso Women's Health Study (n=278)	Median serum 2,3,7,8-TCDD level: 49.7 ppt at time of accident Extrapolated median serum 2,3,7,8-TCDD level at time of pregnancy: 13.4 ppt	Time to pregnancy	↑
		Infertility	↑
Eskenazi et al. 2021 Retrospective cohort study of women participating in the Seveso Women's Health Study (n=446)	Median serum 2,3,7,8-TCDD level at the time of accident: 61.4 ppt Estimated median serum 2,3,7,8-TCDD level at pregnancy: 12.8 ppt	Time to pregnancy	↑, initial level ↑, at pregnancy
		Infertility	↑, initial level ↔, at pregnancy

Table 2-20. Reproductive Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Mocarelli et al. 2000 Retrospective cohort study of 296 mothers and 239 fathers living in zones A, B, or R at the time of the accident	Median serum 2,3,7,8-TCDD levels: 96.5 ppt in fathers and 62.75 ppt in mothers	Sex ratio (male:female)	↓, fathers with 2,3,7,8-TCDD levels >15 ppt ↔, mothers with 2,3,7,8-TCDD levels >80 ppt
Mocarelli et al. 2008 Retrospective cohort study of 135 males (age at the time of the accident: 71 aged 1–9 years, 44 aged 10–17 years, and 20 aged 18–26 years) living in zones A, B, or R at the time of the accident and 372 referents	Median serum 2,3,7,8-TCDD level: 175 ppt for whole group, 201 ppt for ages 1–9 years, 164 ppt for ages 10–17 years, and 123 ppt for ages 18–26 years	Sperm concentration	↓, exposure at 1–9 years ↔, exposure at 10–17 years ↔, exposure at 18–26 years
		Progressive sperm motility	↓, exposure at 1–9 years ↔, exposure at 10–17 years ↔, exposure at 18–26 years
		Motile sperm	↓, exposure at 1–9 years ↓, exposure at 10–17 years ↔, exposure at 18–26 years
		Serum 17β-estradiol	↓, exposure 1–9 years ↓, exposure 10–17 years ↔, exposure at 18–26 years
		Serum FSH	↑, exposure 1–9 years ↑, exposure 10–17 years ↔, exposure at 18–26 years
		Serum LH	↔, all age groups
		Serum testosterone	↔, all age groups
		Serum inhibin B	↔, all age groups
Warner et al. 2004 Retrospective cohort study of women participating in the Seveso Women's Health Study (n=446)	Median serum 2,3,7,8-TCDD level in 1976: 140.3 ppt	Age at onset of menarche	↔

Table 2-20. Reproductive Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Warner et al. 2007 Retrospective cohort study of women participating in the Seveso Women's Health Study (n=282 premenarcheal at exposure)	Median serum 2,3,7,8-TCDD level: 77.3 ppt	Ovarian follicles >10 mm	↔
		Ovulation	↔
		Serum progesterone	↔
		Serum estradiol	↔
Populations living in contaminated areas of Vietnam			
Van Luong et al. 2018 Cross-sectional study of 42 men living in areas of Vietnam with Agent Orange contamination	Geometric mean serum levels (pg/g lipid) • 2,3,7,8-TCDD: 7.3 • 1,2,3,7,8-PeCDD: 10.0 • 1,2,3,4,7,8-HxCDD: 7.5 • 1,2,3,6,7,8-HxCDD: 14.5 • 1,2,3,7,8,9-HxCDD: 9.2 • 1,2,3,4,6,7,8-HpCDD: 28.1 • OCDD: 648.6	FSH	↔, all congeners
		LH	↔, all congeners
		Progesterone	↔, all congeners
		Prolactin • 2,3,7,8-TCDD • 1,2,3,7,8-PeCDD • 1,2,3,4,7,8-HxCDD • 1,2,3,6,7,8-HxCDD • 1,2,3,7,8,9-HxCDD • 1,2,3,4,6,7,8-HpCDD • OCDD	 ↑ ↑ ↔ ↑ ↔ ↑ ↔
		Estradiol • 2,3,7,8-TCDD • 1,2,3,7,8-PeCDD • 1,2,3,4,7,8-HxCDD • 1,2,3,6,7,8-HxCDD • 1,2,3,7,8,9-HxCDD • 1,2,3,4,6,7,8-HpCDD • OCDD	 ↔ ↔ ↔ ↔ ↔ ↓ ↔

Table 2-20. Reproductive Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Testosterone • 2,3,7,8-TCDD • 1,2,3,7,8-PeCDD • 1,2,3,4,7,8-HxCDD • 1,2,3,6,7,8-HxCDD • 1,2,3,7,8,9-HxCDD • 1,2,3,4,6,7,8-HpCDD • OCDD	 ↔ ↓ ↔ ↔ ↓ ↔ ↔
Sun et al. 2016 Cross-sectional study of men living in areas of Vietnam with Agent Orange contamination (n=50) or in non-sprayed areas (n=48)	Geometric mean serum levels in hotspot (pg TEQ/g lipid) • 2,3,7,8-TCDD: 2.63 • 1,2,3,7,8-PeCDD: 8.32 • 1,2,3,4,7,8-HxCDD: 0.50 • 1,2,3,6,7,8-HxCDD: 1.91 • 1,2,3,7,8,9-HxCDD: 0.65 • 1,2,3,4,6,7,8-HpCDD: 0.28 • OCDD: 0.10 Geometric mean serum levels in non-sprayed area (pg TEQ/g lipid) • 2,3,7,8-TCDD: 145 • 1,2,3,7,8-PeCDD: 2.40 • 1,2,3,4,7,8-HxCDD: 0.27 • 1,2,3,6,7,8-HxCDD: 0.45 • 1,2,3,7,8,9-HxCDD: 0.07 • 1,2,3,4,6,7,8-HpCDD: 0.28 • OCDD: 0.02	Prostate specific antigen	↔, all congeners
Sun et al. 2017 Cross-sectional study of men living in areas of Vietnam with Agent Orange contamination (n=50) or in non-sprayed areas (n=48)	Geometric mean serum 1,2,3,7,8-PeCDD levels in hotspot and non-sprayed area: 9.5 and 2.2 pg/g lipid	Reproductive hormones • Testosterone • DHT • DHEA • Estradiol • 3β-HSD	↔

Table 2-20. Reproductive Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Geometric mean serum 1,2,3,6,7,8-HxCDD levels in hotspot and non-sprayed area: 21.6 and 3.8 pg/g lipid	Reproductive hormones • Testosterone • DHT • DHEA • Estradiol • 3β-HSD	↔
	Geometric mean serum 1,2,3,4,6,7,8-HpCDD levels in hotspot and non-sprayed area: 33.2 and 6.2 pg/g lipid	Reproductive Hormones • Testosterone • DHT • DHEA • Estradiol • 3β-HSD	↔
General population			
Cai et al. 2011 Cross-sectional study of infertile women in Japan with (n=10) or without (n=7) endometriosis	Mean CDD/CDF levels in peritoneal fluid in endometriosis and control groups: 12.2 and 10.8 pg TEQ/g lipid	Endometriosis	↑
De Felip et al. 2004 Case-control study in 22 Italian and 18 Belgian women with and without endometriosis	Total TEQs in women without endometriosis: 18 pg/g lipid (Italian) and 45 pg/g lipid (Belgium)	Endometriosis	↔
Fierens et al. 2003 Volunteer-case study in Belgium; environmental exposure to CDDs, CDFs, PCBs+12 marker PCB (not TEQs)	Total TEQs (geometric mean): Cases (n=10) 34.6 pg TEQ/g lipid Controls (n=132) 34.5 pg TEQ/g lipid	Endometriosis	↔

Table 2-20. Reproductive Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Heilier et al. 2005 Case control study of 25 women with peritoneal endometriosis, 25 women with deep endometriotic nodules, and 21 controls in Belgium	Geometric mean CDD/CDF serum levels (pg TEQ/g lipid): 20.9 in women with peritoneal endometriosis, 26.0 in women with deep endometriotic nodules, and 15.5 in controls	Peritoneal endometriosis	↑
		Deep endometriotic nodules	↑
Lambertino et al. 2021 Cross-sectional study using the NHANES (1999–2000 and 2001–2002) database of 89 post-menopausal women	Mean serum CDD/CDF/PCB levels: 0.11 pg TEQ/g	LH	↓
		FSH	↔
Martínez -Zamora et al. 2015 Case-control study of 32 women with deep infiltrating endometriosis and 34 controls (Spain)	Median adipose levels (pg/g lipid) in cases • 2,3,7,8-TCDD: 0.70 • 1,2,3,7,8-PeCDD: 2.41 • 1,2,3,4,7,8-HxCDD: 1.45 • 1,2,3,6,7,8-HxCDD: 9.20 • 1,2,3,7,8,9-HxCDD: 1.21 • 1,2,34,6,7,8-HpCDD: 7.80 • OCDD: 68.10 Median adipose levels (pg/g lipid) in controls • 2,3,7,8-TCDD: 0.40 • 1,2,3,7,8-PeCDD: 1.67 • 1,2,3,4,7,8-HxCDD: 1.23 • 1,2,3,6,7,8-HxCDD: 8.40 • 1,2,3,7,8,9-HxCDD: 1.10 • 1,2,34,6,7,8-HpCDD: 10.22 • OCDD: 61.20	Deep infiltrating endometriosis • 2,3,7,8-TCDD • 1,2,3,7,8-PeCDD • 1,2,3,4,7,8-HxCDD • 1,2,3,6,7,8-HxCDD • 1,2,3,7,8,9-HxCDD • 1,2,34,6,7,8-HpCDD • OCDD	 ↑ ↑ ↔ ↔ ↔ ↔ ↔

Table 2-20. Reproductive Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Pauwels et al. 2001 Cases of infertile women with endometriosis and 27 infertile controls in the Netherlands	Median serum CDD/CDF/PCB levels (pg TEQ/g lipid): 29 in cases and 27 in controls	Endometriosis	↔

↑ = association; ↓ = inverse association; ↔ = no association; 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid; 3β-HSD= 3β-hydroxysteroid dehydrogenase; CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; DHEA = dehydroepiandrosterone; DHT = dihydrotestosterone; FSH = follicle-stimulating hormone; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; LH = luteinizing hormone; NHANES = National Health and Nutrition Examination Survey; OCDD = octachlorodibenzo-*p*-dioxin; PCB = polychlorinated biphenyl; PeCDD = pentachlorodibenzo-*p*-dioxin; Q = quartile; T = tertile; TCDD = tetrachlorodibenzo-*p*-dioxin; TEQ = toxic equivalency

cases presented themselves at a gynecology ward of a university hospital. In contrast to previous studies in the literature, the control group was not recruited from the infertility clinic. A second case-control study found associations between the risk of deep infiltrating endometriosis and adipose 2,3,7,8-TCDD levels and 1,2,3,7,8-PeCDD levels but not with 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, or OCDD levels (Martínez-Zamora et al. 2015). An increased risk of endometriosis was also associated with CDD/CDF peritoneal fluid levels in a cross-sectional study of Japanese women (Cai et al. 2011). In contrast, other population-based, case-control studies reported no association between total TEQs of dioxins and endometriosis (De Felip et al. 2004; Fierens et al. 2003; Pauwels et al. 2001).

A small number of studies have examined reproductive endpoints in males. An increased risk of benign prostatic hyperplasia was observed among Operation Ranch Hand veterans (Gupta et al. 2006). No associations between prostate specific antigen levels and serum levels of 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD, or OCDD were observed in men living in areas of Vietnam contaminated with Agent Orange (Sun et al. 2016). Among Seveso residents, inverse associations between serum 2,3,7,8-TCDD levels and sperm concentration, progressive sperm motility, and total number of motile sperm were observed among males who were 1–9 years of age at the time of the accident (Mocarelli et al. 2008). An inverse association was also observed for total number of motile sperm in men aged 10–17 years at the time of the accident. No associations between serum 2,3,7,8-TCDD levels and sperm parameters were observed in men aged 18–26 years at the time of the accident. No alterations in sperm count were observed in two studies of Operation Ranch Hand veterans (Henriksen et al. 1996; Wolfe et al. 1985).

Fertility has been evaluated in a small number of epidemiological studies. Two studies of female Seveso residents reported associations between serum 2,3,7,8-TCDD levels and increased time to pregnancy and infertility (Eskenazi et al. 2010, 2021). In another study of Seveso residents, a decrease in male:female sex ratio was observed among fathers with 2,3,7,8-TCDD levels >15 ppt; no association was found among females with serum 2,3,7,8-TCDD levels >80 ppt (Mocarelli et al. 2000).

2,3,7,8-TCDD—Animal Studies. A number of animal studies have evaluated the effect of oral exposure to 2,3,7,8-TCDD on reproductive hormone levels; the results of these studies are summarized in Table 2-21. In male rats and mice, 2,3,7,8-TCDD exposure resulted in decreased levels of serum testosterone (Dhanabalan et al. 2010, 2011; Ma et al. 2010; Moore et al. 1985; Yin et al. 2012) and

Table 2-21. Effects on Reproductive Hormone Levels in Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, exposure duration	Dose (µg/kg/day)	Testosterone	Estradiol	Progesterone	Luteinizing hormone	Follicle-stimulating hormone	Reference
Sprague-Dawley rat, once	10				↑ (F)	↑ (F)	Li et al. 1995a
Sprague-Dawley rat, once	12.5	↓ (M)					Moore et al. 1985
Sprague-Dawley rat, once	10		↔ (F)	↔ (F)			Petroff et al. 2000
Sprague-Dawley rat, once	32				↑ (F)	↑ (F)	Petroff et al. 2002
Line C rat, once	30	↓ (M)					Simanainen et al. 2004a
Sprague-Dawley rat, once	20		↔ (F)	↔ (F)	↔ (F)		Son et al. 1999
Sprague-Dawley rat, once	32		↑ (F)	↔ (F)			Ushinohama et al. 2001
Sprague-Dawley rat, 29 weeks	0.02		↓ (F)				Chen et al. 2009
Wistar/NIN rats, 15 day	0.1	↓ (M)					Dhanabalan et al. 2010
Wistar/NIN rat, 15 days	0.1	↓ (M)					Dhanabalan et al. 2011
Sprague-Dawley rat, 29 weeks	0.05	↓ (M)					Ma et al. 2010
Sprague-Dawley rat, 29 weeks	0.125				↓ (M testicular)	↓ (M testicular)	Ma et al. 2010
NIH mouse, GDs 1–3, 1–8, or 4–8	0.002			↓ (F)			Li et al. 2006

Table 2-21. Effects on Reproductive Hormone Levels in Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, exposure duration	Dose (µg/kg/day)	Testosterone	Estradiol	Progesterone	Luteinizing hormone	Follicle-stimulating hormone	Reference
NIH mouse, GDs 1–3, 1–8, or 4–8	0.01		↔ (F)				Li et al. 2006
BALB/c mouse, 28 days	0.09	↑ (F)	↔ (F)				Maranghi et al. 2013
BALB/c mouse, 28 days	0.0009	↔ (F)	↔ (F)				Rasinger et al. 2018
Mouse (strain NS), 7 weeks	0.1	↓ (M)			↓ (M testicular)	↓ (M testicular)	Yin et al. 2012
Cynomolgus monkey, once	4		↔ (F)	↓ (F)			Morán et al. 2001

↑ = association; ↓ = inverse association; ↔ = no association; F = females; GD = gestation day; M = males

decreased testicular levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) (Ma et al. 2010; Yin et al. 2012). In female rats, exposure to 2,3,7,8-TCDD resulted in increased serum testosterone levels (Maranghi et al. 2013). Although there is some inconsistency, most studies of rats and mice have not found alterations in serum estradiol levels in females (Li et al. 2006; Maranghi et al. 2013; Morán et al. 2001; Petroff et al. 2000; Rasinger et al. 2018; Son et al. 1999). Decreased progesterone levels have been observed in female monkeys (Morán et al. 2001) and mice (Li et al. 2006) acutely exposed but have not been found in rats following acute-duration exposure (Son et al. 1999; Petroff et al. 2000; Ushinohama et al. 2001). Increased serum LH and FSH levels have been observed in rats acutely exposed (Li et al. 1995a; Petroff et al. 2002), although a third study did not find an alteration in LH levels at a similar dose level (Son et al. 1999). In a study of pregnant mice, decreased progesterone and estradiol levels were observed on GD 17; no alterations in prolactin levels were observed (Vorderstrasse et al. 2004).

A variety of reproductive effects have been observed in male and female animals orally exposed to 2,3,7,8-TCDD; the results of these studies are summarized in Table 2-22. Several studies in rats have reported decreased epididymal sperm counts, daily sperm production, sperm viability, and sperm motility (Dhanabalan et al. 2010, 2011; El-Tawil and Elsaieed 2005; Latchoumycandane et al. 2002; Ma et al. 2010; Simanainen et al. 2004a). The lowest LOAEL was 0.001 µg/kg/day observed in Wistar rats administered 2,3,7,8-TCDD for 45 days (Latchoumycandane et al. 2002). A dose-related decrease in epididymal sperm counts was observed; the magnitudes of the changes were approximately 9, 23, and 36% at 0.001, 0.01, and 0.1 µg/kg/day, respectively. Decreased sperm motility, decreased sperm viability, and increased sperm head and tail abnormalities were observed at ≥0.05 µg/kg/day (Dhanabalan et al. 2010, 2011; El-Tawil and Elsaieed 2005). In the only study examining sperm parameters in mice, decreased testicular spermatozoa and necrosis of spermatocytes and spermatogonia were observed in mice (strain not specified) administered 0.1 µg/kg/day for 7 weeks (Yin et al. 2012).

Table 2-22. Reproductive Effects in Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)

Species, duration of exposure	Dose (µg/kg/day)	Effect	Reference
Males			
Line C rat, once	10	↓ daily sperm production and caudal sperm reserve	Simanainen et al. 2004a
Wistar/NIN rat, 15 days	0.1	↓ epididymal count, ↓ sperm viability, ↓ sperm motility	Dhanabalan et al. 2010

Table 2-22. Reproductive Effects in Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)

Species, duration of exposure	Dose (µg/kg/day)	Effect	Reference
Wistar/NIN rat, 15 days	0.1	↓ epididymal count, ↓ sperm viability, ↓ sperm motility ↓ testicular daily sperm production	Dhanabalan et al. 2011
Sprague-Dawley rat, 60 days	0.05	↓ sperm counts, motility ↑ sperm mortality and abnormalities	El-Tawil and Elsaieed 2005
ICR mouse, 5 weeks	0.1	↓ male/female ratio	Ishihara et al. 2007
ICR mouse, 5 weeks	0.1	↓ male/female ratio	Ishihara et al. 2010
Wistar rat, 45 days	0.001	↓ epididymal sperm count	Latchoumycandane et al. 2002
Sprague-Dawley rat, 29 weeks	0.05	↓ sperm counts	Ma et al. 2010
Mouse (strain NS), 7 weeks	0.1	↓ testicular spermatozoa; necrosis of spermatocytes and spermatogonia	Yin et al. 2012
Females			
CRCD rat, 2 weeks	2	↓ corpora lutea, ↑ pre-implantation loss	Giavini et al. 1983
Sprague-Dawley rat, once	32	Inhibition of ovulation	Jung et al. 2010
Sprague-Dawley rat, once	10	↓ ovulation (number of animals ovulating and number of ova recovered)	Li et al. 1995a
Sprague-Dawley rat, once	10	↓ ovulation; irregular estrous cycle	Li et al. 1995b
Sprague-Dawley rat, once	10	↓ ovarian weight, ↓ ovulation	Petroff et al. 2000
Sprague-Dawley rat, once	32	inhibition of ovulation	Petroff et al. 2002
Cynomolgus monkey, once	4	↑ uterine antral follicle size, anovulation, lack of menstrual cycle	Morán et al. 2001
Cynomolgus monkey, once	1	Squamous metaplasia in endocervix	Scott et al. 2001
Sprague-Dawley rat, once	20	↓ ovulation	Son et al. 1999
Wistar rat, once (GD 15)	1	↓ maternal nursing behavior and milk ejection volume	Takeda et al. 2020
Sprague-Dawley rat, once	32	Delayed ovulation	Ushinohama et al. 2001
Siberian hamster, once	2	↑ time to pregnancy	Yellon et al. 2000
C57BL/6J mouse, GD 0, 7, 14	1	Suppression of mammary gland differentiation	Vorderstrasse et al. 2004
Wistar rat, 15 weeks	0.046	↔ mating, fertility, or fecundity indices	Bell et al. 2007b

Table 2-22. Reproductive Effects in Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)

Species, duration of exposure	Dose (µg/kg/day)	Effect	Reference
Sprague-Dawley rat, 2–6 doses in 3–15 weeks	10	↑ endometriotic growth	Cummings et al. 1996
B6C3F1 mouse, 2–6 doses in 3–15 weeks	3	↑ endometriotic growth	Cummings et al. 1996
Wistar rat, 16 weeks	0.14	Decreased number of ovarian follicles at the post-primordial phase and corpus luteum	Gül et al. 2018
Holtzman rat, 9 weeks	0.02	↔ sex ratio	Ikeda et al. 2005b
B6C3F1 mouse, 5 doses in 12 weeks	0.6	↑ endometriotic growth	Johnson et al. 1997
NIH mouse, GDs 1–3, 1–8, or 4–8	0.05	↓ implantation sites	Li et al. 2006
Sprague-Dawley rat, 90 days prior to mating and throughout gestation	0.1	↓ fertility	Murray et al. 1979
Sprague-Dawley rat, 15 or 31 weeks	0.071	↔ histopathology	NTP 2006
Sprague-Dawley rat, 105 weeks	0.016	Dilation of clitoral gland ducts	NTP 2006
Rhesus monkey, 3.5–4 years	0.00012	↑ endometriosis	Rier et al. 1993
Rhesus monkey, 3.5–4 years	0.00064	↓ reproductive success	Bowman et al. 1989a, 1989b; Hong et al. 1989; Schantz and Bowman 1989; Schantz et al. 1986, 1992

↑ = increase; ↓ = decrease; ↔ = no change; GD = gestation day; NS = not specified

Reproductive effects have also been observed in female animals, including effects on ovarian function, menstrual cycle, endometriosis, and fertility (summarized in Table 2-22). Effects on ovarian function include decreased number of ovarian follicles in the post-primordial phase and corpus luteum in rats administered 0.14 µg/kg/day for 16 weeks (Gül et al. 2018) and decreased ovulation, inhibition of ovulation, or delayed ovulation in rats receiving a single dose of ≥10 µg/kg/day (Jung et al. 2010; Li et al. 1995a, 1995b; Petroff et al. 2000, 2002; Son et al. 1999; Ushinohama et al. 2001). Anovulation and an increase in antral follicle size were observed in monkeys administered a single dose of 4 µg/kg and examined 443–625 days post-exposure (Morán et al. 2001). Alterations in menstrual cycle have also been

observed. Morán et al. (2001) reported a lack of menstrual cycle in monkeys administered a single dose of 4 µg/kg 2,3,7,8-TCDD; prolonged periods of diestrus with a loss of proestrus and estrus phases was observed in rats following administration of a single dose of 10 µg/kg.

Rier et al. (1993) reported a dose-related increase in the incidence and severity of endometriosis in monkeys chronically exposed to 0.00012 or 0.00064 µg/kg/day for 3.5–4 years of 2,3,7,8-TCDD in the diet and maintained for 10 years. In a follow-up study of these monkeys, blood levels of 2,3,7,8-TCDD and other related compounds were measured in blood samples taken 13 years post-exposure termination (Rier et al. 2001b). An increased level of the PCB congener, 3,3′,4,4′-tetrachlorobiphenyl, was observed in both groups of 2,3,7,8-TCDD exposed animals in a 2,3,7,8-TCDD dose-related manner. 2,3,7,8-TCDD levels did not significantly differ in animals with or without endometriosis. However, serum 3,3′,4,4′-tetrachlorobiphenyl levels were associated with endometriosis; elevated 3,3′,4,4′-tetrachlorobiphenyl levels were only observed in animals with endometriosis and exposed to 2,3,7,8-TCDD and the severity of the endometriosis was correlated with 3,3′,4,4′-tetrachlorobiphenyl levels. These data suggest that 3,3′,4 4′-tetrachlorobiphenyl may have been the causative agent rather than 2,3,7,8-TCDD. Surgical-induced endometriosis was enhanced by 2,3,7,8-TCDD exposure in rats and mice. In a surgically induced endometriosis model, significant increases in the diameter of the endometriotic site and an acceleration of growth were observed in rats (Cummings et al. 1996) and mice (Cummings et al. 1996; Johnson et al. 1997), respectively. In this model, the animals received a gavage dose of 2,3,7,8-TCDD every 3 weeks (first dose was administered 3 weeks prior to surgical induction of endometriosis) for a total of five doses. Mice appear to be more sensitive than rats in terms of the magnitude of the effect on endometrial site diameter and adverse effect levels (endometriosis promotion was observed at 1, 3, and 10 µg/kg in mice (Cummings et al. 1996; Johnson et al. 1997) and at 10 µg/kg in rats (Cummings et al. 1996; no effects were observed in rats at 3 µg/kg). In contrast to these results, Foster et al. (1997) found that 2,3,7,8-TCDD exposure (route of exposure not reported) suppressed endometrial growth in mice. In their model, the mice were not pre-exposed to 2,3,7,8-TCDD prior to the induction of endometriosis. Foster et al. (1997) noted that pre-exposure to 2,3,7,8-TCDD results in endometriosis development due to immune suppression rather than an estrogen responsive disease. A study in Rhesus monkeys found that exposure to 0.0035 µg/kg/day 2,3,7,8-TCDD exposure for 12 months resulted in increased survival of an endometrial implant (Yang et al. 2000).

In a 3-generation study in rats, decreased fertility indices were observed in the F0 rats exposed to 0.1 µg/kg/day for 90 days prior to mating and during gestation (Murray et al. 1979). Following a 12-month exposure, a decreased fertility index was observed when the exposed females were mated with

unexposed younger males; no effect was observed when males were mated with unexposed younger females (Murray et al. 1979). A decrease in reproductive success (evaluated using an ordinal scale of offspring survival time) was observed in monkeys exposed to 0.0064 µg/kg/day for 7 or 27 months (Bowman et al. 1989a, 1989b; Hong et al. 1989; Schantz and Bowman 1989; Schantz et al. 1986, 1992). No effects on fertility or fecundity were observed in rats exposed to 0.046 µg/kg/day for 15 weeks (Bell et al. 2007b).

A study in Wistar rats examined maternal behaviors following exposure to 1 µg/kg 2,3,7,8-TCDD on GD 15 (Takeda et al. 2020). Maternal licking behavior was significantly reduced on postnatal days (PNDs) 2, 4, 7, and 10; there were no alterations in time spent crouching, nesting, or retrieving. A decrease in milk ejection volume was also observed. The study also found decreased levels of circulating prolactin in the dams on PNDs 2, 4, 7, and 10, which corresponded to the decreased maternal licking behavior. A group of 2,3,7,8-TCDD-exposed dams were administered prolactin intracerebroventricularly, which resulted in a significant increase in maternal licking behavior; licking time was no longer significantly different from controls.

Two studies reported histological alterations in female reproductive tissue. Squamous metaplasia was observed in the endocervix of monkeys administered a single dose of 1 µg/kg 2,3,7,8-TCDD and examined 1.2–2.7 years post exposure (Scott et al. 2001). Dilation of clitoral gland ducts were observed in rats exposed to 0.016 µg/kg/day for 2 years (NTP 2006); histological alterations were observed from exposure to 0.071 µg/kg/day for 15 or 31 weeks (NTP 2006). Other reproductive effects observed in females orally exposed to 2,3,7,8-TCDD include decreased pre-implantation sites in NIH mice exposed to 0.05 µg/kg/day 2,3,7,8-TCDD on GDs 1–3, 4–8, or 1–8 (Li et al. 2006), increased pre-implantation loss in CRCD rats exposed to 2 µg/kg/day (Giavini et al. 1983), decreased sex ratio in the offspring of female Holtzman rats exposed to 0.02 µg/kg/day for 9 weeks prior to mating (Ikeda et al. 2005b) and of the offspring of male ICR mice exposed to 0.1 µg/kg/day for 5 weeks (Ishihara et al. 2007, 2010), increased time to pregnancy in Siberian hamsters exposed to a single dose of 2 µg/kg (Yellon et al. 2000), and suppression of mammary gland differentiation in mice exposed to 1 µg/kg/day on GDs 0, 7, and 14 (Vorderstrasse et al. 2004). No effects on mating, fertility, or fecundity indices were observed in female Wistar rats exposed to 0.046 µg/kg/day for 15 weeks (Bell et al. 2007b).

2.17 DEVELOPMENTAL

Overview. The potential developmental toxicity of CDDs in humans has been extensively investigated in highly exposed populations and the general population examining birth outcome, birth defects, endocrine and other systemic effects, immunological development, neurological development, and reproductive development.

- In general, studies involving paternal exposure to high levels of CDDs did not find associations between CDD levels and birth outcomes or birth defects; inconsistent results have been reported in highly exposed populations (male and female exposures) and birth outcome.
- One study of the Seveso cohort found an association between maternal blood 2,3,7,8-TCDD levels and neonatal TSH levels and the risk of elevated TSH levels; no associations were found in adult children. General population studies have not found consistent associations between maternal CDD levels and thyroid hormone levels in children.
- General population studies have not found consistent results for associations between maternal CDD levels and infections. The small number of general population studies evaluating associations between maternal CDD exposure and the child's risk of other immune responses such as asthma, wheezing, allergies, sensitization, or vaccine antibodies have not found consistent effects.
- Associations between exposure to CDDs and neurodevelopment have been evaluated in several prospective cohort studies of highly exposed populations and the general population. Results of these studies are mixed, with some studies finding associations between increasing exposure concentrations and decreasing performance on tests of cognition and behavior, but most studies found no associations.
- Epidemiological studies evaluating development of the reproductive system have found associations between CDD exposure and impaired development (decreases in sperm concentrations and delayed puberty) in boys in highly exposed populations.

The developmental toxicity of 2,3,7,8-TCDD has been extensively investigated, particularly following acute-duration oral exposure in rats and mice. The observed effects include increased offspring mortality, structural malformations and anomalies, impaired growth, impaired development of respiratory, cardiovascular, skeletal, and gastrointestinal systems, impaired thyroid function, and impaired development and function of the immune, nervous, and reproductive systems.

- Increased fetal/newborn mortality have been observed at ≥0.7 μg/kg/day in acute-duration studies, often at doses associated with no or minimal maternal toxicity. Intermediate-duration exposure to ≥0.01 μg/kg/day resulted in decreased neonatal survival.
- The most reported structural anomalies are cleft palate at doses ≥1 μg/kg/day and hydronephrosis at doses ≥0.5 μg/kg/day.

- Decreases in birth weight and growth were observed at doses ≥0.7 μg/kg/day.
- Impaired development of the lungs, heart abnormalities and decreased heart rate, decreased bone mineral density, impaired mandible and tooth development, and gastrointestinal hemorrhages have been reported.
- Decreased thymus weight and thymic atrophy and functional alterations in the response to bacteria, viruses, or mitogens at doses ≥0.011 μg/kg/day.
- Neurodevelopmental effects including morphological alterations, delays in neurodevelopmental milestones, hyperactivity, alterations in motor activity, alterations in social behaviors, and impaired learning have been reported in rats, mice, and/or monkeys. The lowest LOAELs for neurodevelopmental effects are ≥0.1, ≥0.046, and ≥0.00012 μg/kg/day following acute-, intermediate-, and chronic-duration exposure, respectively.

Developmental effects have also been observed in animals exposed to other CDD congeners.

- Cardiac myofibril edema in rat offspring exposed to 2,7-DCDD.
- Decreased thymus weight in rat offspring exposed to 1,2,3,7,8-PeCDD.
- Decreased fetal growth and skeletal and soft tissue anomalies in rat offspring exposed to mixed HxCDD congeners.
- No developmental effects were observed following oral exposure to 2-MCDD, 2,3-DCDD, 1,2,3,4-TCDD, or OCDD.

Epidemiological Studies. The potential for 2,3,7,8-TCDD to induce developmental effects has been examined in several populations: residents exposed to 2,3,7,8-TCDD during aerial spraying of 2,4,5-T or from accidental releases of 2,3,7,8-TCDD or 2,3,7,8-TCDD-contaminated chemicals, workers involved in manufacturing or application of phenoxy herbicides and/or chlorophenols, and Vietnam veterans and Vietnamese residents living in contaminated areas. In most of the human studies, exposure was poorly characterized; however, most studies used serum and/or human milk levels of CDDs as a biomarker of exposure. A summary of the epidemiological studies is presented in Table 2-23.

Birth outcomes. Among potentially highly exposed populations, no associations between dioxin or 2,3,7,8-TCDD exposure and an increased risk of spontaneous abortions were found (Aschengrau and Monson 1990; Schnorr et al. 2001; Townsend et al. 1982; Wesselink et al. 2014; Wolfe et al. 1995). Apart from the Wesselink et al. (2014), which used maternal biomarkers to examine the possible association, the other studies evaluating spontaneous abortions involved paternal exposure to CDDs. It

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Occupational			
Dimich-Ward et al. 1996 Nested case control study of 9,512 male sawmill production and maintenance workers at 10 sawmills in Canada using chlorophenate	Cumulative hours of exposure estimated based on work history. Workers divided into three cumulative exposure groups and a group of workers with the maximum exposure	Prematurity	↔
		Small for gestational age	↔
		Low birth weight	↔
		Stillborn	↔
		Neonatal deaths	↔
		Spina bifida or anencephaly	↑, maximum exposure
		Cataracts	↑, two highest cumulative exposure groups and maximum exposure group
		Undescended testicles	↑, highest cumulative exposure group
Lawson et al. 2004 Cross-sectional study of 176 male workers at two sodium trichlorophenol (or one of its derivatives) or 2,4,5-T production facilities in the United States and 217 neighborhood referents	Serum 2,3,7,8-TCDD levels estimated at the time of conception using current TCDD levels; median level of 254 pg/g lipid in workers and 6 pg/g lipid in referents.	Birth weight	↑, pregnancy occurred during employment
		Preterm birth	↔
Mannetje et al. 2017 Cross-sectional study of 355 children of 127 male workers and 21 female workers at a phenoxy herbicide production facility in New Zealand	Mean serum 2,3,7,8-TCDD level: 9 pg/g lipid High exposure: ≥4 pg/g lipid	Probability of male children of male workers	↓
		Probability of male children of female workers	↔

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Schnorr et al. 2001 Cross-sectional study of 259 male workers (300 pregnancies before exposure and 332 pregnancies after exposure) at two sodium trichlorophenol or one of its derivatives production facilities in the United States and 243 neighborhood referents (707 pregnancies)	Median paternal 2,3,7,8-TCDD serum level at pregnancy: 254 ppt in workers with pregnancies during exposure and 6 ppt in workers with pregnancies before exposure and in referents 4th quartile serum 2,3,7,8-TCDD level: ≥1,120 ppt	Spontaneous abortion	↔, 4th quartile
		Sex ratio	↔, 4th quartile
Smith et al. 1982 Cross-sectional study of 548 male workers spraying 2,4,5-T in New Zealand and 441 referents working as agricultural contractors	Not measured	Congenital defect	↔
		Miscarriage	↔
Townsend et al. 1982 Cross-sectional study of children of 370 male workers involved in chlorophenol processing and 345 male workers at the same facility but not exposed to dioxins	Exposure to 2,3,7,8-TCDD only Exposure to any dioxin Exposure levels were not reported	Spontaneous abortion	
		2,3,7,8-TCDD exposure	↔
		Dioxin exposure	↔
		Stillbirths	
		2,3,7,8-TCDD exposure	↔
		Dioxin exposure	↔
		Infant deaths	
		2,3,7,8-TCDD exposure	↔
		Dioxin exposure	↔
		Health defects	
		2,3,7,8-TCDD exposure	↔
		Dioxin exposure	↔
		Congenital malformations	
		2,3,7,8-TCDD exposure	↔
		Dioxin exposure	↔

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Vietnam veterans and Operation Ranch Hand veterans			
Aschengrau and Monson 1989 Case-control study of 201 women having spontaneous abortions through gestation week 27 and 1,119 controls (United States)	CDD levels were not measured; paternal military service in Vietnam was used as a surrogate for exposure to CDDs	Spontaneous abortion	↔
Aschengrau and Monson 1990 Case control study of 1,314 women delivering infants with one or more congenital anomalies, 121 women delivering stillborn infants without anomalies, 76 women with infants without anomalies dying shortly after birth, and 1,490 controls delivering infants without anomalies (United States)	CDD levels were not measured; paternal military service in Vietnam was used as a surrogate for exposure to CDDs	Congenital anomalies	↔
		Stillbirth	↔
		Newborn death	↔
Erickson et al. 1984 Case control study of 1,659 cases of major congenital abnormalities and 1,047 control infants living in Atlanta, Georgia	An Exposure Opportunity Index (EOI) was calculated to estimate the likelihood of exposure to Agent Orange among paternal Vietnam veterans	Multiple defects	↔
		Spina bifida	↑, highest EOI score
		Cleft palate	↔
		Cleft lip without cleft palate	↑, highest EOI score
		Other neoplasms	↑, highest EOI score
Grufferman et al. 2014 Case-control study of children with rhabdomyosarcoma (n=319 cases and 319 controls) in United States	Not measured	Rhabdomyosarcoma association with parental military service, particularly Vietnam War veterans	↔
Michalek et al. 1998 Retrospective study of 2,082 children (859 children of fathers involved in Operation Ranch Hand and 1,223 children in the comparison group)	Background group dioxin level: <10 ppt Low-exposure group dioxin level: ≤79 ppt High-exposure group dioxin level: >79 ppt	Preterm births	↔
		Intrauterine growth retardation	↔
		Infant deaths	↑, background, high

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Ngo et al. 2010 Meta-analysis of 7 studies examining 330 cases of spina bifida and 134,884 non-cases associated with paternal Agent Orange exposure	Not reported	Spina bifida	↑
Wolfe et al. 1995 Retrospective study of the offspring of 454 male veterans involved in Operation Ranch Hand and 570 comparison fathers	Background dioxin level: <10 ppt Low-exposure dioxin level: ≤110 ppt High-exposure dioxin level: >110 ppt	Spontaneous abortion	↑, low exposure ↔, high exposure
		Stillbirth	↔, low and high exposure
		Congenital defects	↑, low exposure ↔, high exposure
Populations living in contaminated areas in Vietnam			
Anh et al. 2017 Prospective study of 52 mother-infant pairs living in Bien Hoa, Vietnam; the control group of 52 mother-infant pairs lived in a noncontaminated area in northern Vietnam	Geometric mean CDDs/CDFs human milk levels: 9.19 and 3.48 pg TEQ/g lipid in Bien Hoa residents and controls, respectively	Salivary DHEA in 1-year-old children	↑, as compared to controls
		Salivary cortisol in 1-year-old children	↔, as compared to controls
Boda et al. 2018 Prospective study of 162 mother-newborn pairs living near the Bien Hoa airbase	Geometric mean levels in human milk: 2,3,7,8-TCDD: 2.2 pg/g lipid 1,2,3,6,7,8-HxCDD: 4.5 pg/g lipid	Estradiol cord blood levels	
		2,3,7,8-TCDD	↔, boys and girls
		1,2,3,6,7,8-HxCDD	↔, boys and girls
		Testosterone cord blood levels	
		2,3,7,8-TCDD	↔, boys and girls
		1,2,3,6,7,8-HxCDD	↔, boys and ↓ girls

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Dao et al. 2016 Cross-sectional study of 58 mother-infant pairs living near the Phu Cat airbase and 62 mother infant pairs living in a similar rural area in North Vietnam that was not sprayed with Agent Orange	Mean human milk levels of total CDDs 7.432 and 2.064 pg TEQs/g lipid in exposed and control populations Estimated dietary intake of CDDs and CDFs in infants: 54.2 and 18.0 pg TEQ/kg/day in exposed and control 8–9-week-old infants and 42.7 and 12.3 pg TEQ/kg/day in 12–14-week-old infants	Height	↔, compared to controls
		Weight	↔, compared to controls
		Head circumference	↔, compared to controls
		Chest circumference	↔, compared to controls
Nguyen et al. 2018 Prospective study of 185 mother-child (3 years of age) pairs living in Da Nang, Vietnam	Median human milk levels in mothers of boys and girls, respectively: 2,3,7,8-TCDD: 1.5 and 1.7 pg/g lipid 1,2,3,7,8-PeCDD: 4.2 and 4.5 pg/g lipid 1,2,3,4,7,8-HxCDD: 2.2 and 2.4 pg/g lipid 1,2,3,7,8,9-HxCDD: 8.3 and 8.4 pg/g lipid 1,2,3,4,6,7,8-HpCDD:2.5 and 2.7 pg/g lipid OCDD: 63.9 and 68.1 pg/g lipid	Food approach score (food responsiveness, enjoyment of food, desire to drink, and emotional overeating)	↔ for all CDD congeners
		Food avoidance score (satiety responsiveness, slowness in eating, fussiness, and emotional undereating)	↔ for all CDD congeners
Nishijo et al. 2012 Prospective study of 210 mother-infant pairs living in Da Nang, Vietnam	4th quartile CDD/CDF human milk level: 25.09 pg TEQ/g lipid	Weight	↔, boys at birth, 1 month, and 4 months ↓, boys 0–4 months ↔, girls at birth, 1 month, and 4 months ↓, girls 0–4 months
		Length	↔, boys at birth, 1 month, and 4 months ↔, boys 0–4 months ↔, girls at birth, 1 month, and 4 months ↔, girls 0–4 months

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Head circumference	↔, boys at birth, 1 month, and 4 months ↔, boys 0–4 months ↑, girls at birth, 1 month, and 4 months ↑, girls at 0–4 months
		Abdominal circumference	↔, boys at birth, 1 month, and 4 months ↔, girls at birth, 1 month, and 4 months
		BMI	↔, boys at birth, 1 month, and 4 months ↓, boys at 0–4 months ↔, girls at birth, 1 month, and 4 months ↓, girls at 0–4 months
Nishijo et al. 2014 Prospective study of 153 3-year-old children living in Da Nang, Vietnam follow-up to the Tai et al. (2013) study	Human milk 2,3,7,8-TCDD levels of <3.5 pg/g fat or ≥3.5 pg/g lipid Human milk CDDs/CDFs levels of <17.6 pg TEQ/g fat or ≥17.6 pg TEQ/g lipid	Bayley neurodevelopmental test	TCDD
		Cognitive total score	↔, boys and girls
		Language total score	↔, boys and girls
		Motor total score	↔, boys and girls
		Adaptive behavior total score	↔, boys and girls
		Autism Spectrum Rating Scale	TCDD
		Total score	↑, boys and girls
		DSM-IV-TR Scale	↑, boys and girls
		Social communication	↑, boys; ↔, girls
		Unusual behavior	↔, boys and girls

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Bayley neurodevelopmental test	CDDs/CDFs TEQ
		Cognitive total score	↓, boys; ↔, girls
		Language total score	↓, boys; ↔, girls
		Motor total score	↓, boys; ↔, girls
		Adaptive behavior total score	↓, boys; ↔, girls
		Autism Spectrum Rating Scale	CDDs/CDFs TEQ
		Total score	↔, boys and girls
		DSM-IV-TR Scale	↔, boys and girls
		Social communication	↔, boys and girls
		Unusual behavior	↔, boys and girls
Nishijo et al. 2021 Prospective study of 181 8-year-old children (follow-on study to Nishijo et al. 2014)	Mean human milk 2,3,7,8-TCDD levels of 1.1–1.7 pg/g lipid Mean human milk CDDs/CDFs levels of 11.6–13.7 pg TEQ/g fat	C-SHARP Aggression scores	CDDs/CDFs TEQ
		Verbal	↔
		Bullying	↔
		Covert	↔
		Hostility	↔
		Physical	↔
		C-SHARP Aggression scores	TCDD
		Verbal	↔
		Bullying	↔
		Covert	↑
		Hostility	↔
		Physical	↔
Pham et al. 2015 Prospective study of 214 mother-infant (1 year of age) pairs living in Da Nang, Vietnam; follow-up to the Tai et al. (2013) study	4th quartile human milk 2,3,7,8-TCDD levels of >3.5 pg/g lipid 4th quartile human milk CDDs/CDFs levels of ≥17.6 pg TEQ/g fat 4th quartile estimated dietary dioxin intake (DDI) of infants ≥118.2 pg TEQ/kg/day	Neurodevelopmental scores	↔, CDDs/CDFs TEQ
		Cognitive	↔, TCDD
			↔, DDI
		Neurodevelopmental scores	↔, CDDs/CDFs TEQ
		Motor	↔, TCDD
			↔, DDI
		Social emotional score	↓, CDDs/CDFs TEQ
			↓, TCDD
			↔, DDI
		Adaptive behavioral score	↔, CDDs/CDFs TEQ
			↔, TCDD
			↔, DDI

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Pham et al. 2019 Prospective study of 226 mother-child pairs living in Bien Hoa, Vietnam and 75 mother-child pairs living in a non-exposed area of Vietnam; children were tested at 2 years of age	Human milk level 2,3,7,8-TCDD 2nd tertile: 1.8–5.5 pg/g lipid 3rd tertile: ≥5.5 pg/g lipid 1,2,3,7,8-PeCDD 2nd tertile: 3.1–4.9 pg/g lipid 3rd tertile: ≥4.9 pg/g lipid 1,2,3,4,7,8-HxCDD 2nd tertile: 1.4–2.7 pg/g lipid 3rd tertile: ≥2.7 pg/g lipid 1,2,3,6,7,8-HxCDD 2nd tertile:2.9–9.2 pg/g lipid 3rd tertile: ≥9.2 pg/g lipid 1,2,3,7,8,9-HxCDD 2nd tertile: 1.7–3.6 pg/g lipid 3rd tertile: ≥3.6 pg/g lipid 1,2,3,4,6,7,8-HpCDD 2nd tertile: ≥4.5–22.0 pg/g lipid 3rd tertile: ≥22.0 pg/g lipid OCDD 2nd tertile: 54.0–162 pg/g lipid 3rd tertile: ≥162 pg/g lipid CDDs TEQ 2nd tertile: 5.3–11.9 pg TEQ/g lipid 3rd tertile: ≥11.9 pg TEQ/g lipid	Bayley scale test scores Cognitive Composite language Composite motor	TCDD ↔, boys, girls ↔, boys, girls ↓, boys 2nd tertile, ↔, girls
		Bayley scale composite score	1,2,3,7,8-PeCDD ↓, boys 2nd tertile ↔, girls
		Bayley scale composite score	1,2,3,4,7,8-HxCDD ↓, boys 2nd tertile ↔, girls
		Bayley scale composite score	1,2,3,6,7,8-HxCDD ↓, boys 2nd tertile ↔, girls
		Bayley scale composite score	1,2,3,7,8,9-HxCDD ↓, boys 2nd tertile ↔, girls
		Bayley scale composite score	1,2,3,4,6,7,8-HpCDD ↔, boys ↓, girls 2nd tertile
		Bayley scale composite score	OCDD ↓, boys 2nd tertile ↔, girls
		Bayley scale composite score	CDDs TEQ ↓, boys 2nd tertile ↓, girls 3rd tertile

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Pham et al. 2020b Prospective study of 815 mother-child (8 years of age) pairs living in Da Nang, Vietnam; follow-up to the Tai et al. (2013, 2016), Pham et al. (2015), Nishijo et al. (2012, 2014), and Tran et al. (2016) studies	Human milk CDD levels 2,3,7,8-TCDD 2nd tertile: 1.8–3.5 pg/g lipid 3rd tertile: ≥3.5 pg/g lipid CDD/CDF TEQ 2nd tertile: 11.5–17.6 pg TEQ/g lipid 3rd tertile: ≥17.6 pg TEQ/g lipid	Feminine index of gaze behavior in response to biological stimuli (human line drawing)	2,3,7,8-TCDD ↔, boys ↑, girls, 3rd tertile
		Feminine index of gaze behavior in response to biological stimuli (human line drawing)	CDD/CDF TEQ ↑, boys, 3rd tertile ↔, girls
		Feminine index of gaze behavior in response to non-biological stimuli (toy photos)	2,3,7,8-TCDD ↔, boys ↑, girls
		Feminine index of gaze behavior in response to non-biological stimuli (toy photos)	CDD/CDF TEQ ↔, boys ↔, girls
Pham et al. 2021 Prospective cohort study of 51 mother-newborn pairs living in Bien Hoa, Vietnam	Human milk CDD levels, geometric mean 2,3,7,8-TCDD: 2.2 pg/g lipid CDD/CDF TEQ: 7.9 pg TEQ/g lipid	Alterations in EEG power values in the quiet sleep stage	↑, 2,3,7,8-TCDD
Phuong et al. 1989 Retrospective cohort study of 1,249 families living in area that was heavily sprayed with Agent Orange and 1,224 families living in a non-sprayed area	Not measured	Hydatidiform mole	↑

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Sun et al. 2020	Human milk levels median	Salivary DHEA	
	2,3,7,8-TCDD	1-year-old children	
Prospective cohort study; follow-on study to Anh et al. (2017); examined 26 exposed and 26 unexposed children examined at 1, 3, and 5 years of age	Exposed: 1.8 pg/g lipid	2,3,7,8-TCDD	↔
	Unexposed: 0.5 pg/g lipid	1,2,3,7,8-PeCDD	↔
	1,2,3,7,8-PeCDD	1,2,3,4,7,8-HxCDD	↔
	Exposed: 2.6 pg/g lipid	1,2,3,6,7,8-HxCDD	↔
	Unexposed: 1.0 pg/g lipid	1,2,3,7,8,9-HxCDD	↔
	1,2,3,4,7,8-HxCDD	1,2,3,4,6,7,8-HpCDD	↑
	Exposed: 1.4 pg/g lipid	OCDD	↑
	Unexposed: 0.7 pg/g lipid	3-year-old children	
	1,2,3,6,7,8-HxCDD	2,3,7,8-TCDD	↔
	Exposed: 4.5 pg/g lipid	1,2,3,7,8-PeCDD	↔
	Unexposed: 1.3 pg/g lipid	1,2,3,4,7,8-HxCDD	↔
	1,2,3,7,8,9-HxCDD	1,2,3,6,7,8-HxCDD	↔
	Exposed: 1.5 pg/g lipid	1,2,3,7,8,9-HxCDD	↔
	Unexposed: 0.5 pg/g lipid	1,2,3,4,6,7,8-HpCDD	↔
	1,2,3,4,6,7,8-HpCDD	OCDD	↔
	Exposed: 8.0 pg/g lipid	5-year-old children	
	Unexposed: 2.6 pg/g lipid	2,3,7,8-TCDD	↓
	OCDD	1,2,3,7,8-PeCDD	↓
	Exposed: 56.3 pg/g lipid	1,2,3,4,7,8-HxCDD	↔
	Unexposed: 13.5 pg/g lipid	1,2,3,6,7,8-HxCDD	↓
		1,2,3,7,8,9-HxCDD	↓
		1,2,3,4,6,7,8-HpCDD	↓
		OCDD	↓

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Salivary testosterone	
		3-year-old children	
		2,3,7,8-TCDD	↓
		1,2,3,7,8-PeCDD	↔
		1,2,3,4,7,8-HxCDD	↔
		1,2,3,6,7,8-HxCDD	↓
		1,2,3,7,8,9-HxCDD	↔
		1,2,3,4,6,7,8-HpCDD	↔
		OCDD	↔
		5-year-old children	
		2,3,7,8-TCDD	↔
		1,2,3,7,8-PeCDD	↓
		1,2,3,4,7,8-HxCDD	↔
		1,2,3,6,7,8-HxCDD	↔
		1,2,3,7,8,9-HxCDD	↔
		1,2,3,4,6,7,8-HpCDD	↓
		OCDD	↓
Tai et al. 2013 Prospective study of 216 mother-infant (4 months of age) pairs living in Da Nang, Vietnam	Human milk levels 2,3,7,8-TCDD Moderate group: 1.8–3.5 pg/g lipid CDDs High group: ≥12.3 pg TEQ/g lipid	Bayley Scales of Infant and Toddler Development Cognitive score Language composite score Motor composite score	 ↓, moderate TCDD ↔, high CDDs ↓, moderate TCDD ↔, high CDDs ↓, moderate TCDD ↔, high CDDs
Tai et al. 2016 Prospective study of 217 mother-child (3 years of age) pairs living in Da Nang, Vietnam; follow-up to the Tai et al. (2013) and Pham et al. (2015) studies	Mean human milk levels of 2,3,7,8-TCDD 1.4 pg/g lipid and CDD/CDF 12.5 pg TEQ/g lipid	Bayley Scales of Infant and Toddler Development Cognitive score Language composite score Motor composite score	 ↔, TCDD ↔, CDD/CDF ↔, TCDD ↔, CDD/CDF ↓, TCDD (boys only) ↔, CDD/CDF

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Weight	TCDD ↓, boys ↔, girls CDDs ↓, boys ↔, girls
		Height	TCDD ↓, boys ↔, girls CDDs ↔, boys ↔, girls
		Head circumference	TCDD ↓, boys ↔, girls CDDs ↓, boys ↔, girls
		Abdominal circumference	TCDD ↓, boys ↔, girls CDDs ↓, boys ↑, girls
		BMI	TCDD ↔, boys ↔, girls CDDs ↓, boys ↔, girls

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Tai et al. 2020 Prospective study of 185 mother-child (8 years of age) pairs living in Da Nang, Vietnam; follow-up to the Tai et al. (2013, 2016), Tran et al. (2016), and Pham et al. (2015) studies	Geometric mean human milk levels Boys 2,3,7,8-TCDD: 1.34 pg/g fat 1,2,3,7,8-PeCDD: 4.21 pg/g fat 1,2,3,4,7,8-HxCDD: 2.21 pg/g fat 1,2,3,6,7,8-HxCDD: 8.11 pg/g fat 1,2,3,7,8,9-HxCDD: 2.59 pg/g fat 1,2,3,4,6,7,8-HpCDD: 11.94 pg/g fat OCDD: 68.23 pg/g fat Girls 2,3,7,8-TCDD: 1.46 pg/g fat 1,2,3,7,8-PeCDD: 4.17 pg/g fat 1,2,3,4,7,8-HxCDD: 2.39 pg/g fat 1,2,3,6,7,8-HxCDD: 8.24 pg/g fat 1,2,3,7,8,9-HxCDD: 2.68 pg/g fat 1,2,3,4,6,7,8-HpCDD: 12.22 pg/g fat OCDD: 68.71 pg/g fat	Colorado Learning Difficulties Questionnaire-math score CDD TEQs 2,3,7,8-TCDD 1,2,3,7,8-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,6,7,8-HxCDD 1,2,3,7,8,9-HxCDD 1,2,3,4,6,7,8-HpCDD OCDD	 ↔, boys, girls ↔, boys, girls ↔, boys, girls ↔, boys, girls ↔, boys, girls ↔, boys, girls ↔, boys, girls ↔, boys, girls
		Colorado Learning Difficulties Questionnaire-reading score CDD TEQs 2,3,7,8-TCDD 1,2,3,7,8-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,6,7,8-HxCDD 1,2,3,7,8,9-HxCDD 1,2,3,4,6,7,8-HpCDD OCDD	 ↔, boys, girls ↔, boys, ↓, girls ↔, boys, ↔, girls ↔, boys, ↔, girls ↔, boys, ↔, girls ↔, boys, ↔, girls ↔, boys, ↔, girls ↔, boys, ↔, girls
		Math achievement tests CDD TEQs 2,3,7,8-TCDD 1,2,3,7,8-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,6,7,8-HxCDD 1,2,3,7,8,9-HxCDD 1,2,3,4,6,7,8-HpCDD OCDD	 ↔, boys, girls ↓, boys, ↔, girls ↔, boys, ↔, girls ↓, boys, ↔, girls ↔, boys, ↔, girls ↓, boys, ↔, girls ↓, boys, ↔, girls ↔, boys, ↔, girls

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Language achievement tests	
		CDD TEQs	↔, boys, girls
		2,3,7,8-TCDD	↔, boys, girls
		1,2,3,7,8-PeCDD	↔, boys, girls
		1,2,3,4,7,8-HxCDD	↔, boys, girls
		1,2,3,6,7,8-HxCDD	↔, boys, girls
		1,2,3,7,8,9-HxCDD	↔, boys, girls
		1,2,3,4,6,7,8-HpCDD	↔, boys, girls
		OCDD	↔, boys, girls
		Oral reading tests, reading speed	
		CDD TEQs	↔, boys, girls
		2,3,7,8-TCDD	↔, boys, girls
		1,2,3,7,8-PeCDD	↔, boys, girls
		1,2,3,4,7,8-HxCDD	↔, boys, girls
		1,2,3,6,7,8-HxCDD	↔, boys, girls
		1,2,3,7,8,9-HxCDD	↔, boys, girls
		1,2,3,4,6,7,8-HpCDD	↔, boys, girls
		OCDD	↔, boys, girls
		Oral reading tests, reading errors	
		CDD TEQs	↑, boys, ↔, girls
		2,3,7,8-TCDD	↔, boys, ↔, girls
		1,2,3,7,8-PeCDD	↑, boys, ↔, girls
		1,2,3,4,7,8-HxCDD	↑, boys, ↔, girls
		1,2,3,6,7,8-HxCDD	↑, boys, ↔, girls
		1,2,3,7,8,9-HxCDD	↑, boys, ↔, girls
		1,2,3,4,6,7,8-HpCDD	↑, boys, ↔, girls
		OCDD	↔, boys, ↔, girls

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Tran et al. 2016 Prospective study of 181 mother-infant pairs living in Da Nang, Vietnam; children were evaluated at 5 years of age; follow-up to the Tai et al. (2013, 2016) and Pham et al. (2015) studies	Mean human milk levels in the low-, middle-, and high-exposure groups for CDDs/CDFs: 8.3, 13.9, 21.1 pg TEQ/g lipid for boys and 7.2, 14.4, and 22.6 pg TEQ/g lipid for girls Mean human milk levels in the low-, middle-, and high-exposure groups for 2,3,7,8-TCDD: 0.86, 1.6, 2.3 pg/g lipid for boys and 0.62, 1.6, 3.3 pg/g lipid for girls	Movement tests (manual dexterity, aiming and catching, and balance)	CDDs/CDFs TEQ ↓, high-exposure boys ↔, high-exposure girls
		Cognitive function tests (nonverbal index, short term memory, visual processing)	TCDD ↓, high-exposure boys ↔, high-exposure girls
Seveso, Italy			
Ames et al. 2019 Prospective study of 161 (82 males and 79 females) 7–17 years old, born after the Seveso accident	Maternal serum TCDD levels in 1976: 74.6 ppt Estimated serum TCDD levels during pregnancy: 4.5 ppt	Performance on neuropsychological tests per 10-fold increase in maternal serum TCDD	↔, 1976 serum levels ↔, pregnancy levels
Baccarelli et al. 2008 Retrospective cohort study on 1,014 children born to the 1,772 women of reproductive age in the most contaminated zones; 1,772 age-matched women controls	Geometric mean plasma 2,3,7,8-TCDD: 6.1, 17.6, and 60.5 ppt for control, zone B and zone A, respectively.	Neonatal blood TSH	↑, zones B and A
		Risk of blood TSH >5 μU/mL	↑, zone A
Eskenazi et al. 2003 Retrospective cohort study of women participating in the Seveso Women's Health Study (n=510, 888 total pregnancies)	Median maternal TCDD serum level at the time of the incident: 46.6 ppt	Low birth weight	↔
		Small for gestational age	↔
		Preterm delivery	↔
Mastroiacovo et al. 1988 Retrospective cohort study of 15,291 infants born to mothers living in zone A (n=26), zone B (n=435), zone R (n=2,439), and non-exposed areas (n=12,391)	Not reported	Total birth defects	↔

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Mocarelli et al. 2011 Retrospective cohort study of 39 sons (mean age 22.5 years) of mothers living in the highest TCDD exposure area and 58 controls whose mothers did not live in the TCDD exposed area	Estimated serum TCDD levels at the time of conception using 1976 blood levels: 19.0 ppt in breastfed sons and 27.9 ppt in formula-fed sons	Semen volume (comparison between exposed and controls)	↔, all ↔, breastfed ↔, formula fed
		Sperm concentration (comparison between exposed and controls)	↓, all ↓, breastfed ↔, formula fed
		Sperm count (comparison between exposed and controls)	↓, all ↓, breastfed ↔, formula fed
		Sperm progressive motility (comparison between exposed and controls)	↔, all ↓, breastfed ↔, formula fed
		Progressive motile sperm count (comparison between exposed and controls)	↓, all ↓, breastfed ↔, formula fed
		FSH (comparison between exposed and controls)	↔, all ↑, breastfed ↔, formula fed
		Inhibin B (comparison between exposed and controls)	↔, all ↓, breastfed ↔, formula fed
Warner et al. 2020a Retrospective cohort study of 426 children (≥18 years of age) born to 383 mothers exposed to TCDD	Maternal initial 1976 serum 2,3,7,8-TCDD levels: Q2: 28.0–60.9 ppt Q3: 61.0–149.0 ppt Q4: 150.0–914.0 ppt	Total T4	↔
		Free T4	↓, Q2
		Free T3	↓, Q2
		TSH	↔
Warner et al. 2020b Retrospective cohort study of 570 adult children born to 303 mothers exposed to TCDD	Maternal initial 1976 serum 2,3,7,8-TCDD levels and 2,3,7,8-TCDD levels estimated at pregnancy were not reported	Insulin Initial 1976 serum levels Estimated pregnancy levels	 ↔, men; ↔, women ↔, men; ↓, women
		Blood glucose Initial 1976 serum levels Estimated pregnancy levels	 ↔, men; ↔, women ↔, men; ↔, women

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		HOMA2-IR	
		Initial 1976 serum levels	↔, men; ↔, women
		Estimated pregnancy levels	↔, men; ↔, women
		HOMA2-β	
		Initial 1976 serum levels	↔, men; ↔, women
		Estimated pregnancy levels	↔, men; ↓, women
Wesselink et al. 2014 Retrospective study of 617 women participating in the Seveso Women's Health Study	Median 1976 serum 2,3,7,8-TCDD level: 55.0 ppt Median estimated 2,3,7,8-TCDD level at pregnancy: 9.9 ppt	Spontaneous abortion	↔
		Birth weight	↔
		Small for gestational age	↔
		Gestational age	↔
Ye et al. 2018 Retrospective study of 676 children (2–38 years of age) of 438 mothers participating in the Seveso Second Generation Health Study	Maternal 1976 serum 2,3,7,8-TCDD level: 64.7 ppt	Eczema (doctor diagnosed)	↓
		Asthma	↔
		Hay fever	↔
Communities with contaminated soil			
Burns et al. 2016 Prospective study of 315 boys aged 17–18 years living in Chapaevsk, Russia	Median serum CDD/CDF/PCB TEQ: 21.1 pg TEQ/g lipid • 2nd Q: 14.6–21.0 pg TEQ/g lipid • 3rd Q: 21.1–33.2 pg TEQ/g lipid • 4th Q: 33.3–174.7 pg TEQ/g lipid	Pubertal onset	
		• Testicular volume >3 mL	↓, 3rd Q
		• Genitalia stage ≥2	↓ 2nd Q
		• Pubarche stage ≥2	↔, 4th Q
		Sexual maturity	
		• Testicular volume >3 mL	↓, 2nd Q
		• Genitalia stage ≥2	↓, 3rd Q
		• Pubarche stage ≥2	↔, 4th Q
Hanify et al. 1981 Cross-sectional study of a community in Northland, New Zealand with contaminated soil from 2,4,5-T spraying	Not reported	Birth malformations	↑
		Anencephaly	↔
		Spina bifida	↔
		Cleft lip	↑
		Isolated cleft palate	↔
		Heart malformations	↑

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Hypospadias, epispadias	↑
		Talipes	↑
Korrick et al. 2011 Prospective study of 473 boys aged 8–9 years living in Chapaevsk, Russia	4th quartile blood CDD, CDF, and dioxin-like PCBs: 30–175 pg TEQ/g lipid 4th quartile 2,3,7,8-TCDD: 4.0–45 pg TEQ/g lipid 3rd quartile CDDs: 8–12.9 pg TEQsg lipid	Puberty onset, as assessed by a testicular volume of >3 mL	↔, total TEQs ↓, 2,3,7,8-TCDD ↓, CDD TEQs
		Puberty onset, as assessed by genitalia at ≥stage 2	↔, total TEQs ↔, 2,3,7,8-TCDD ↔, CDDs
Nelson et al. 1979 Retrospective study of a residents living in counties in Arkansas in which 2,4,5-T was sprayed on rice crops (1,201 cases of cleft lip and/or cleft palate)	Cases divided into high-, medium-, or low-exposure groups based on rice acreage in the county	Cleft lip and/or cleft palate	↑, high and low groups
Stockbauer et al. 1988 Retrospective study of a community in eastern Missouri; 402 births to exposed mothers and 804 births to unexposed mothers in 1972–1982 and 235 and 470 births to exposed and unexposed mothers, respectively, in 1978–1982	Not reported	Fetal deaths, infant deaths, perinatal deaths	↔, 1972–1982
		Very low birth weight	↔, 1972–1982
		Intrauterine growth retardation	↔, 1972–1982
		Low birth weight	↔, 1972–1982 ↔, 1978–1982
		Birth defects	↔, 1972–1982
Communities in China near electronic waste recycling facilities			
Wang et al. 2019 Longitudinal study of 27 mother infant pairs living in Taizhou, China (an electronic waste recycling area) and Jiaxing (an area with almost no residents involved in electronic waste recycling)	Mean human milk 2,3,7,8-TCDD level: 2.7 and 0.5 pg/g lipid in exposed and control groups Mean human milk CDDs: 6.3 and 2.2 pg TEQ/g lipid	Height 6 months TCDD CDDs 3 years TCDD CDDs	 ↔, boys, girls ↔,boys, girls ↔, boys, ↑, girls ↓, boys, ↑, girls

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Weight	
		6 months	
		TCDD	↔, boys, girls
		CDDs	↔, boys, girls
		3 years	
		TCDD	↔, boys, girls
		CDDs	↔, boys, ↑, girls
		BMI	
		6 months	
		TCDD	↔, boys, girls
		CDDs	↔, boys, girls
		3 years	
		TCDD	↔, boys, girls
		CDDs	↔, boys, girls
		Head circumference	
		6 months	
		TCDD	↔, boys, girls
		CDDs	↔, boys, girls
		3 years	
		TCDD	↔, boys, girls
		CDDs	↔, boys, girls
		Chest circumference	
		6 months	
		TCDD	↔, boys, girls
		CDDs	↔, boys, girls
		3 years	
		TCDD	↔, boys, girls
		CDDs	↔, boys, girls

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Communities living near municipal incinerators			
Lin et al. 2006 Cross-sectional study of 3,025 infants of mothers living near a municipal incinerator in Taiwan; comparison group was 3,421 infants born prior to the operation of the incinerator	Mean emission concentration of CDD/CDF levels in exhaust air: 6.47 ng TEQ/m^3	Birth weight	↔
		Gestation length	↔
		Preterm birth	↔
General population			
Alaluusua et al. 1996 Prospective cohort study of 6–7-year-old children (n=102) in Finland	High-exposure group: >16.0 pg TEQ/g milk fat Medium-exposure group: 8.0–16.0 pg TEQ/g low-exposure group: <8.0 pg TEQ/g	Hypomineralization of teeth in 6–7-year-old children	↑, frequency and severity
Cao et al. 2008 Cross-sectional study of 104 mother-infant pairs in Duisburg, Germany	Maternal blood fat CDDs/CDFs: 15.3 pg TEQ/g Milk fat CDDs/CDFs in milk fat: 13.1 pg TEQ/g	Cord serum testosterone	↓, females
		Cord serum estradiol	↓, males
Caspersen et al. 2016a Longitudinal prospective study of 1,024 children (mean age 3.5 years) participating in the Norwegian Mother and Child Cohort Study	Median maternal dietary exposure to 17 2,3,7,8-substiuted CDDs/CDFs and 13 dioxin-like PCBs: 0.6 pg TEQ/kg/day	Performance on tests for ADHD	↔
Caspersen et al. 2016b Longitudinal prospective study of 44,092 3-year-old children participating in the Norwegian Mother and Child Cohort Study	Median maternal dietary exposure to 17 2,3,7,8-substiuted CDDs/CDFs and 13 dioxin-like PCBs: 0.6 pg TEQ/kg/day Low exposure:≤14 ng TEQ/kg/day High exposure:>14 ng TEQ/kg/day	Incomplete grammar	↑
		Moderate language delay	↔
		Severe language delay	↑
		Speech problem	↔
		Low score for communication skills	↔, boys and girls ↔, boys ↑, girls

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Darnerud et al. 2010 Prospective study of 180 mother-infant pairs living in Sweden	Median CDD/CDF human milk level: 9 pg TEQ/g lipid	Infant TSH	↑, 3 weeks ↔, 3 months
		Infant total T3	↔, 3 weeks ↔, 3 months
		Infant free T4	↔, 3 weeks ↔, 3 months
Hui et al. 2016, 2019 Prospective study of 161 11-year-old children born in Hong Kong	4th quartile mean human milk: 22.5 pg CALUX-TEQ/g lipid[a]	Wechsler Intelligence Scale Children IV (Hong Kong)	↔
		Hong Kong List Learning test	↔
		Test for Everyday Attention in Children	↔
		Grooved Peg Board Test	↔
Huisman et al. 1995a Prospective study of 418 mother-infant (newborns) pairs living in the Netherlands	Human milk levels (median concentration): 2,3,7,8-TCDD: 3.61 pg/g lipid 1,2,3,7,8-PeCDD:10.25 pg/g lipid, 1,2,3,4,7,8-HxCDD: 8.71 pg/g lipid, 1,2,3,6,7,8-HxCDD: 45.98 pg/g lipid, 1,2,3,7,8,9-HxCDD: 6.72 pg/g lipid, 1,2,3,4,6,7,8-HpCDD: 57.38 pg/g lipid OCDD: 660.64 pg/g fat	Neurological optimality score 2,3,7,8-TCDD 1,2,3,7,8-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,6,7,8-HxCDD 1,2,3,7,8,9-HxCDD 1,2,3,4,6,7,8-HpCDD OCDD	 ↔ ↑ ↑ ↑ ↑ ↑ ↔
Huisman et al. 1995b Prospective study of 418 mother-child (age 18 months) pairs living in the Netherlands	Same children as Huisman et al. (1995a)	Neurological optimality score for motor function	↔, dioxins
Ikeno et al. 2018 Prospective study of 141 mother-child (age 42 months) pairs living in Japan	Maternal blood levels (median concentration) 1,2,3,7,8-PeCDD:: 4.1 pg/g lipid 1,2,3,6,7,8-HxCDD: 13.9 pg/g lipid 1,2,3,7,8,9-HxCDD: 2.2 pg/g lipid 1,2,3,4,6,7,8-HpCDD 24.3 pg/g lipid OCDD: 437.7 pg/g lipid Total CDD: 488.5 pg/g lipid	Cognitive development—achievement scale	↑, 1,2,3,7,8-PeCDD and 1,2,3,6,7,8-HxCDD in females ↔, other congeners and total CDDs
		Cognitive development—mental processing scale	↔, all congeners and total CDDs

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Ilsen et al. 1996 Prospective study of 38 mother-infant pairs living in the Netherlands	Mean human milk CDD/CDF levels: 18.5 pg TEQ/g lipid for the low-exposure group and 37.3 pg TEQ/g lipid for the high-exposure group	Bayley Scales of Infant Development at age 2 years	↔
		Neurological suboptimality score at age 2.7 years	↔
		Reflex score-suboptimality at age 2.7 years	↓, high-exposure group compared to low-exposure group
Iszatt et al. 2016 Prospective study using data from three European birth cohort studies (Belgium, Norway, Slovenia)	Mean prenatal exposure (estimated using human milk or cord blood samples): 31.2, 7.9, and 15.5 pg DR-CALUX/g lipid[a] in the Flemish, Norwegian, and Slovak cohorts, respectively	Infant growth	↔
		BMI at age 7 years	↔, boys and girls ↔, boys ↑, girls
		Risk of overweight BMI	↔, boys and girls ↔, boys ↑, girls
Kono et al. 2015 Prospective study of 175 mother-infant pairs in Japan	Median human milk levels of CDDs, CDFs, and dioxin-like PCBs from a human milk survey: 8.3 and 8.6 in boys and girls, respectively Median estimated dioxin exposure based on human milk survey levels and breastfeeding ratio during first year: 14.0 and 18.8 ng TEQ (CDDs, CDFs, PCBs)/kg/day boys and girls, respectively	Psychosocial behavioral development in 6–10- or 11–13-year-old children	↔, human milk levels ↔, estimated dioxin exposure levels
Koppe et al. 1991 Cross-sectional study of 14 mothers in the Netherlands	Human milk level of 2,3,7,8-TCDD: 5.35–17.0 pg/g milk fat (mean of 9.79)	Abnormal bleeding	↑
Koopman-Esseboom et al. 1994	12.44–76.43 (mean of 32.06 pg TEQ/g milk fat) High-exposure group: >30.75 pg TEQ/g milk fat	Total T3	↔, high exposure versus low exposure
		Total T4	↓, high exposure versus low exposure

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Prospective study of 78 mother-infant (2 weeks of age) pairs living in the Netherlands	Low-exposure group: ≤30.75 pg/TEQ/g milk fat	Free T4	↔, high exposure versus low exposure
		TSH	↑, high exposure versus low exposure
Miyashita et al. 2018a Prospective study of 183 mother-infant pairs in Japan	Median maternal blood levels of CDDs: 7.05 pg TEQ/g lipid for all subjects and 7.24 and 6.95 for boys and girls, respectively	Cord blood estradiol	↔
		Cord blood testosterone	↔
		Cord blood testosterone/estradiol ratio	↔, all ↔, boys ↔, girls
		Cord blood androstenedione	↔
		Cord blood DHEA	↔, all ↑, boys ↔, girls
		Cord blood cortisol	↔, all ↔, boys ↔, girls
		Cord blood cortisone	↔, all ↔, boys ↔, girls
		Cord blood adrenal androgen/ glucocorticoid ratio	↔, all ↔, boys ↔, girls
		Cord blood sex hormone binding globulin	↔, all ↔, boys ↔, girls
		Cord blood prolactin	↔
		Cord blood LH	↔, boys
		Cord blood FSH	↔, boys
		Cord blood inhibin B	↓, boys
		Cord blood insulin-like factor	↔, boys

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Miyashita et al. 2018b Prospective study of newborns and children in Japan. Three groups of children examined at birth (n=239), age 3.5 years (n=327), and 7 years of age (n=264)	Maternal median CDDs, CDFs, and dioxin-like PCBs: 14.0, 14.2, and 15.0 pg TEQ/g lipid in the birth, 3.5 years, and 7 years groups, respectively	Cord blood IgE	↔, all ↓, boys ↔, girls
		Allergy	Age 3.5 years ↔, all ↔, boys ↔, girls Age 7 years ↔, all ↔, boys ↔, girls
		Food allergy	Age 3.5 years ↔, all ↔, boys ↔, girls Age 7 years ↔, all ↔, boys ↔, girls
		Eczema	Age 3.5 years ↔, all ↔, boys ↔, girls Age 7 years ↔, all ↔, boys ↔, girls

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Wheezing	Age 3.5 years ↔, all ↑, boys ↔, girls Age 7 years ↔, all ↔, boys ↔, girls
		Infections	Age 3.5 years ↔, all ↔, boys ↔, girls Age 7 years ↔, all ↔, boys ↔, girls
		Otitis media infections	Age 3.5 years ↔, all ↔, boys ↔, girls Age 7 years ↔, all ↔, boys ↔, girls

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Respiratory infections	Age 3.5 years ↔, all ↔, boys ↔, girls Age 7 years ↔, all ↔, boys ↔, girls
Neugebauer et al. 2015 Prospective study of 117 school age children participating in the Duisburg Birth Cohort Study	Median maternal blood CDD/CDF level: 12.99 pg TEQ/g lipid Median human milk CDD/CDF level: 59.81 TEQ ng	Attentional performance test of distractibility	↔, maternal blood ↑, human milk
		Attentional performance test of divided attention	↑, maternal blood ↔, human milk
		ADHD-associated behavior assessed via parent questionnaire	↔, maternal blood ↔, human milk
Nowack et al. 2015 Prospective study of 116 9–10-year-old children participating in the Duisburg Birth Cohort Study	Median maternal blood CDDs/CDFs: 12.91 pg TEQ/g lipid for boys and girls, 12.79 pg TEQ/g lipid for boys, and 13.74 pg TEQ/g lipid for girls	Social responsiveness total score which measures autistic traits	↓ boys and girls ↔, boys ↓, girls
		Empathy-Systemizing Quotient, which measures sex-specific behaviors	↔, boys and girls, boys only, and girls only
Papadopoulou et al. 2013 Prospective study of 50,651 mother-infant pairs participating in the Norwegian Mother Child Cohort Study	Estimated maternal dietary intake of CDDs/CDFs/dioxin-like PCBs: 0.55 pg TEQ/kg body weight/day 2nd quartile estimated intake: 0.39–0.55 pg TEQ/kg body weight/day	Birth weight	↓, 2nd quartile
		Birth length	↓, 2nd quartile
		Birth head circumference	↓, 2nd quartile
Papadopoulou et al. 2014 Multicountry (Greece, Spain, Norway, Denmark, United Kingdom) cross-sectional study of 537 mother-infant pairs	Maternal dioxin-diet score	Birth weight	↓, 3rd tertile
		Gestational age	↔

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Pluim et al. 1993b Prospective study of 38 mother-infant pairs living in the Netherlands	Human milk CDD/CDF mean levels: 18.6 and 37.5 pg TEQ/g fat in the low- and high-exposure groups, respectively	Total T3	High exposure versus low exposure ↔, cord blood ↔, 11 weeks
		Total T4	High exposure versus low exposure ↔, cord blood ↑, 1 week ↑, 11 weeks
		Free T4	High exposure versus low exposure ↔, cord blood
		TSH	High exposure versus low exposure ↔, cord blood ↔, 1 week ↑, 11 weeks
		TBG	High exposure versus low exposure ↔, cord blood ↔, 1 week ↔, 11 weeks
Pluim et al. 1994a Prospective study of 35 mother-infant pairs living in the Netherlands	Human milk CDD/CDF levels: 8.7–62.7 pg TEQ/g fat (mean of 28.1 pg TEQ/g fat) Cumulative intake at 11 weeks: 5.7–123.7 ng TEQ (mean of 44.7 ng TEQ)	GGT	↔, cord blood ↔, 1 week ↔, 11 weeks ↔, cumulative intake
		AST	↔, cord blood ↔, 1 week ↔, 11 weeks ↑, cumulative intake
		ALT	↔, cord blood ↔, 1 week ↔, 11 weeks ↑, cumulative intake

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Plasma cholesterol	↔, cord blood ↔, 1 week ↔, 11 weeks ↔, cumulative intake
		Total and conjugated bilirubin	↔, cord blood ↔, 1 week ↔, 11 weeks ↔, cumulative intake
		Leukocytes	↔, cord blood ↔, 1 week ↔, 11 weeks ↔, cumulative intake
		Platelets	↔, cord blood ↔, 1 week ↔, 11 weeks ↓, cumulative intake
Pluim et al. 1994b Prospective study of 32 mother-infant pairs living in the Netherlands	Human milk CDD/CDF levels: 13.7–62.6 pg TEQ/g fat (mean of 29.4 pg TEQ/g fat)	Vitamin K	↔,cord blood ↔, 11 weeks
		PIVKA-II	↔,cord blood ↔, 11 weeks
Pluim et al. 1996 Prospective study of 32 mother-infant pairs living in the Netherlands	Mean human milk CDD/CDF levels: 18.1 and 37.4 pg TEQ/g fat in the low- and high-exposure groups, respectively	Gestation age	High exposure versus low exposure ↔
		Birth weight	High exposure versus low exposure ↔
		Body weight	High exposure versus low exposure ↔, 10 weeks of age ↔, 20 weeks of age

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Head circumference	High exposure versus low exposure ↔, 10 weeks of age ↔, 20 weeks of age
		Neurological optimality score	High exposure versus low exposure ↔
Rennert et al. 2012 Prospective study of 111 6–7- and 8–9-year-old children participating in the Duisburg Birth Cohort Study	Geometric mean CDD/CDF levels in maternal blood: 13.50 pg TEQ/g fat Geometric mean CDD/CDF levels in human milk: 10.94 pg TEQ/g fat	DHEA-S levels	↔, maternal blood ↑, human milk
Stølevik et al. 2011 Prospective study of 195 mother-infant (1 year old) participating in a subcohort study of the Norwegian Mother and Child Cohort Study	Median estimated maternal dietary intake of CDD/CDF/dioxin-like PCB 0.56 pg TEQ/kg body weight/day	Eczema	↓
		Wheeze	↑
		Otitis media	↔
		Gastric flu	↔
		Chicken pox	↔
		Exanthema subitem	↑
		Upper respiratory infections	↑
Stølevik et al. 2013 Prospective study of 162 mother-infant (1–3 years old) participating in a subcohort study of the Norwegian Mother and Child Cohort Study	Median estimated maternal dietary intake of CDD/CDF/dioxin-like PCB 0.59 pg TEQ/kg body weight/day	Eczema 0–3 years of age 2–3 years of age	 ↔ ↔
		Atopic eczema 0–3 years of age 2–3 years of age	 ↑ ↔
		Allergy 0–3 years of age 2–3 years of age	 ↔ ↔
		Asthma 0–3 years of age	 ↔

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Asthma medication	
		0–3 years of age	↔
		2–3 years of age	↔
		Wheeze	
		0–3 years of age	↔
		2–3 years of age	↔
		Otitis media	
		0–3 years of age	↔
		2–3 years of age	↔
		Chicken pox	
		0–3 years of age	↔
		Exanthema subitem	
		0–3 years of age	↔
		Gastroenteritis	
		0–3 years of age	↑
		2–3 years of age	↔
		Upper respiratory tract infection	
		0–3 years of age	↑
		2–3 years of age	↑
		Sensitization	↔
		Measles vaccine antibodies	↓
		Rubella vaccine antibodies	↔
		Tetanus vaccine antibodies	↔
		Hib vaccine antibodies	↔
Su et al. 2010 Prospective study of 92 mother-child pairs living in Taiwan; children examined at 2 and 5 years of age; follow-up to the Wang et al. (2005) study	Placental CDD/CDF levels Low exposure: <15 pg TEQ/g lipid High exposure: ≥15 pg TEQ/g lipid	Serum T3 at 2 years	↓
		Serum TSH at 2 years	↑
		Serum free T4 x TSH at 2 years	↑
		Serum TTR at 2 years	↔

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Su et al. 2012 Follow-up study to the Su et al. (2010) study of 56 children aged 8 years	Low CDD/CDF/PCB group: <14.83 pg TEQ/g lipid High CDD/CDF/PCB group: ≥14.83 pg TEQ/g lipid	Estradiol	↓
		FSH	↔
		LH	↔
		Testosterone	↔
		Sex characteristics	↔, boys ↔, girls
Su et al. 2015 Follow-up study to the Su et al. (2010) study of 56 children aged 8 years	Low CDD/CDF/PCB group: <14.83 pg TEQ/g lipid High CDD/CDF/PCB group: ≥14.83 pg TEQ/g lipid	Growth hormone	↔
		Total T3	↔
		Total T4	↔
		Free T4	↔
		TSH	↔
		TBG	↑, boys ↔, girls
		Aldosterone	↔, boys ↓, girls
ten Tusscher et al. 2014 Prospective cohort study of children living in Netherlands examined at ages 7–12 years (n=41) and 14–18 years (n=33); same group of children examined in the Ilsen et al. (1996) study	Estimated dioxin intake (calculated using human milk levels) for the pre-adolescents and Serum CDD/CDF levels in adolescents 2.2 pg TEQ/g lipid	Social problems	↑, pre-adolescents
		Aggressive behavior	↑, pre-adolescents
		Thought problems	↑, pre-adolescents
		Anxious/depressed feelings	↑, pre-adolescents
		External behavioral problems	↑, adolescents
		Wechsler Intelligence Scale	↔, pre-adolescents
Vafeiadi et al. 2013 Prospective study of 237 newborns and 462 young children (16 months of age) living in Greece or Spain	Mean maternal blood DR CALUX levels for newborns: 52.3 pg TEQ/g lipid Mean maternal blood DR CALUX levels for children: 49.7 pg TEQ/g lipid	Anogenital distance in newborns	↓, boys ↔, girls
		Anogenital distance in children	↔, boys ↔, girls

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Vafeiadi et al. 2014 Cross-sectional study of 967 mother-infant pairs living in Denmark, Greece, Norway, Spain, or England	3rd tertile maternal serum DR CALUX: 47.9–129.1 pg TEQ/g lipid 3rd tertile cord blood DR CALUX: 43.3–156 pg TEQ/g lipid	Birth weight Maternal serum Cord blood	 ↔ ↔
		Head circumference Maternal serum Cord blood	 ↔ ↔
		Gestational age Maternal serum Cord blood	 ↔ ↓
Vartiainen et al. 1998 Prospective study of 84 mother-infant pairs living in Finland	Human milk CDD/CDF levels: 10.8–96.3 pg TEQ/g fat	Birth weight	↔
Virtanen et al. 2012 Case-control study of 280 infants (95 cases and 185 controls) in Denmark and Finland	Median placental CDD/CDF levels: 8.47 and 9.78 pg TEQ/g lipid for Finnish controls and cases 10.88 and 11.75 for Danish controls and cases	Cryptorchidism	↔
		FSH	↔
		LH	↔
		Sex hormone binding globulin	↔
Wang et al. 2005 Prospective study in the general population of female (n=62) and male (n=57) newborns in the Taiwanese cohort	Placental levels of CDD/CDF/PCBs Low-exposure group: <15.1 1 pg TEQ/g lipid Higher-exposure group: >15.1 pg TEQ/g lipid dioxin/PCB	Cord TSH levels	↑, CDDs/CDFs
		Cord T4 levels	↑, CDDs/CDFs

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Weisglas-Kuperus et al. 1995 Prospective study of 207 mother-infant pairs in the Netherlands	Not reported; human milk CDD/CDF/PCB TEQ levels	Rhinitis, bronchitis, tonsillitis, otitis	↔
		Antibodies to mumps, measles, and rubella at 18 months of age	↔
		White blood cell counts Monocytes Granulocytes Lymphocytes	 ↓, 3 months ↓, 3 months ↔
		T cell markers	↔
		B cell markers	↓, 3 months
		NK cell markers	↔
Wilhelm et al. 2008 Prospective study of the Duisburg, Germany birth cohort of 189 mother-infant pairs	Blood levels (n=182) of CDDs/CDFs/PCBs ranged 3.8–58.4 pg TEQ/g lipid Human milk levels (n=149) of CDDs/CDFs/PCBs ranged 2.6–52.4 pg TEQ/g lipid	Thyroid hormones (cord blood) TSH T3 Free T3 T4 Free T4	Blood and human milk ↔ ↔ ↔ ↔ ↔
		Neurological optimality score Age 2 weeks Age 18 months	Blood and human milk ↔ ↔
		Bayley Scales of Infant Development Age 12 months Age 24 months	Blood and human milk ↔ ↔

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Winneke et al. 2014 Prospective study of 121 mother-child (mean age 6.6 years) pairs participating in the Duisburg birth cohort study in Germany	Mean CDD/CDF in maternal serum: 14.5 pg TEQ/g lipid Mean CDD/CDF in human milk: 11.6 pg TEQ/g lipid	Preschool Activities Inventory to assess sexually dimorphic behavior Maternal blood Masculine score Feminine score	 ↔, boys, girls ↔, boys, girls
		Preschool Activities Inventory Human milk Masculine score Feminine score	 ↔, boys; ↓, girls ↑, boys, ↔,girls
Wohlfahrt-Veje et al. 2014 Longitudinal study of 417 mother-child pairs participating in the Copenhagen Mother Child Cohort of Growth and Reproduction; children examined at 0, 3, 18, and 36 months of age	Median CDD/CDF/PCB human milk level: 20.2 pg TEQ/g lipid	Body weight 0 months 3 months 18 months 36 months	 ↔ ↔ ↔ ↔
		Body weight change 0–3 months 0–18 months 0–36 months	 ↔ ↑ ↔
		Skinfold fat 0 months 3 months 18 months 36 months	 ↓ ↔ ↔ ↔
		Length/height 0 months 3 months 18 months 36 months	 ↔ ↔ ↑ ↔

Table 2-23. Developmental Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Change in height	
		0–3 months	↑
		0–18 months	↑
		0–36 months	↑
		IGF1 at 3 months	↑

[a]Chemical activated luciferase (CALUX) is a cell-based assay used to measure dioxin levels.

↑ = association; ↓ = inverse association; ↔ = no association; 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid; ADHD = attention deficit hyperactivity disorder; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CALUX = chemical-activated luciferase gene expression; CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorodibenzofuran; C-SHARP = Children's Scale of Hostility and Aggression; DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone sulfate; DR CALUX = dioxin-responsive chemical-activated luciferase gene expression; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; EEG = electroencephalogram; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HiB = *Haemophilus influenzae* type b; HOMA2-β = homeostatic model assessment of pancreatic beta-cell function; HOMA2-IR = homeostatic model assessment of insulin resistance; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; Ig = immoglobulin; IGF1 = insulin-like growth factor 1; LH = luteinizing hormone; NK = natural killer; OCDD = octachlorodibenzo-*p*-dioxin; PCB = polychlorinated biphenyl; PeCDD = pentachlorodibenzo-*p*-dioxin; PIVKA-II = protein-induced by vitamin K absence-II; Q = quartile; T3 = triiodothyronine; T4 = thyroxine; TBG = thyroxine-binding globulin; TCDD = tetrachlorodibenzo-*p*-dioxin; TEQ = toxic equivalency; TSH = thyroid-stimulating hormone; TTR = transthyretin

should be noted that Wolfe et al. (1995) found an association between low dioxin levels and spontaneous abortion but did not find an association among highly exposed Operation Ranch Hand veterans.

Similarly, no alterations in miscarriages were observed in a study of male pesticide workers (Smith et al. 1982). No associations between paternal exposure to dioxins and increased risk of stillbirths were found in male workers (Dimich-Ward et al. 1996; Townsend et al. 1982) or Vietnam veterans (Aschengrau and Monson 1990; Wolfe et al. 1995).

No associations between neonatal or infant deaths and CDD exposure were found in the offspring of male workers at a chlorophenol manufacturing facility exposed to any dioxin or to 2,3,7,8-TCDD only (Dimich-Ward et al. 1996; Townsend et al. 1982), offspring of male Operation Ranch Hand veterans (Aschengrau and Monson 1990; Wolfe et al. 1985), or offspring of the Missouri cohort (Stockbauer et al. 1988). Michalek et al. (1998) reported an increased risk of infant deaths in the infants of fathers involved in Operation Ranch Hand, as compared to the referent group of veterans in Southeast Asia not exposed to Agent Orange. Disorders related to short gestation and low birth weight were the most common causes of infant deaths. Michalek et al. (1998) concluded that the increased infant mortality may not be due to paternal 2,3,7,8-TCDD exposure because the risk was increased in Operation Ranch Hand cohort members with essentially background current 2,3,7,8-TCDD levels (low-exposure group) and in the highest exposure group.

Several studies have evaluated prematurity or premature births and have not found associations with paternal (Dimich-Ward et al. 1996; Lawson et al. 2004; Michalek et al. 1998) or maternal (Eskenazi et al. 2003; Lin et al. 2006) exposure to CDDs. Gestational age was not associated with CDD levels in a study of women in Seveso (Wesselink et al. 2014) or in general population studies (Papadopoulou et al. 2014; Pluim et al. 1996). A general population study (Vafeiadi et al. 2014) did find an inverse association between cord blood dioxin levels and gestational age, but no association when maternal serum dioxin levels were used as a biomarker of exposure. No associations were found between paternal (Dimich-Ward et al. 1996) or maternal (Eskenazi et al. 2003; Wesselink et al. 2014) exposure to CDDs and the risk of small for gestational age.

Inconsistent results have been reported in studies examining birth weight and/or infant body weight. Several studies examining the children of residents living in contaminated areas of Vietnam have reported inverse associations between 2,3,7,8-TCDD or CDD biomarker levels and birth weight/infant weight (Dao et al. 2016; Nishijo et al. 2012; Tai et al. 2016). Two other high exposure studies (Wang et al. 2019;

Wesselink et al. 2014) did not find associations. Two general population studies conducted by Papadopoulou et al. (2013, 2014) found an inverse association between estimated maternal dietary intake of dioxins (CDD/CDF/dioxin-like PCBs) and birth weight. Other general population studies did not find associations with birth weight or body weight (Pluim et al. 1996; Vafeiadi et al. 2014; Vartiainen et al. 1998; Wohlfahrt-Veje et al. 2014). Similarly, no associations between CDDs and intrauterine growth (Michalek et al. 1998; Stockbauer et al. 1988) or low birth weight/very low birth weight (Dimich-Ward et al. 1996; Eskenazi et al. 2003; Stockbauer et al. 1988) were found among the children of highly exposed parents. Length/height in boys was inversely associated with 2,3,7,8-TCDD levels in studies of contaminated areas of Vietnam (Tai et al. 2016). A study of children living in a contaminated area of China (Wang et al. 2019) found no associations at 6 months of age and found an association between CDDs and 2,3,7,8-TCDD human milk levels and height in girls and an inverse association between CDDs levels in human milk and height in boys. Other studies in Vietnam (Dao et al. 2016; Nishijo et al. 2012) and in the general population (Papadopoulou et al. 2013; Pluim et al. 1996) did not find associations with length/height. Wohlfahrt-Veje et al. (2014) reported an association between human milk CDD/CDF/PCB levels and length/height, but only in children at 18 months of age; no associations were observed at birth, 3 months, or 36 months of age. Mixed results have also been reported in studies of head/chest circumference. In studies of children living in contaminated areas of Vietnam, an association between CDD/CDF human milk levels and head circumference was found in girls, but not in boys (Nishijo et al. 2012), whereas another study found an inverse association between human milk 2,3,7,8-TCDD and CDD levels and head circumference in boys, but not in girls. Other studies have not found associations in studies of Vietnamese children (Dao et al. 2016) or in children living in a contaminated area of China (Wang et al. 2019). In general population studies, one study reported in inverse association between maternal dietary intake of CDDs/CDFs/PCBs and birth head circumference (Papadopoulou et al. 2013) and two studies found no associations between maternal human milk (Pluim et al. 1996) or maternal serum levels of dioxins (Vafeiadi et al. 2014) and head circumference.

Birth defects. The potential for CDDs to induce birth defects or other congenital anomalies has been investigated in several populations including male workers, Vietnam veterans, Seveso residents, and communities living in contaminated areas. In the offspring of male workers at a chlorophenol manufacturing facility (Townsend et al. 1982) or males spraying 2,4,5-T (Smith et al. 1982), no significant increases in the incidence of congenital malformations were observed. An increased risk of spina bifida or anencephaly was observed in the offspring of male sawmill workers with the highest maximum exposure to chlorophenate (Dimich-Ward et al. 1996); an increased risk of cataracts was also observed in the offspring.

Two case-control studies (Aschengrau and Monson 1990; Erickson et al. 1984) have examined the risk of Vietnam veterans having a child with birth defects. The overall risk of having a child with birth defects was not increased in the Vietnam veterans in the Erickson et al. (1984) study. However, Vietnam veterans fathered a higher proportion of the children with some birth defects (spina bifida, cleft lips, and congenital tumors including dermoid cysts, teratomas, hepatoblastomas, central nervous system tumors, and Wilm's tumors) (Erickson et al. 1984). In the Aschengrau and Monson (1990) study, no increase in the risk of fathering a child with birth defects was observed for the Vietnam veterans. Among the children with birth defects, an increased risk of having one or more major systemic malformations was reported in infants fathered by Vietnam veterans. The largest increases were reported for malformations of the nervous system, cardiovascular system, genital organs, and urinary tract. No pattern of multiple malformations was found; the only pattern of multiple malformations observed in more than one infant was ventricular septal defect and talipes. The results of these two case-control studies (Aschengrau and Monson 1990; Erickson et al. 1984) should be interpreted cautiously because there is no documentation of 2,3,7,8-TCDD exposure. CDC (1988) found that in Vietnam veterans self-reporting exposure to Agent Orange, the levels of serum 2,3,7,8-TCDD were not significantly different than levels found in a control population. In a study of Vietnam veterans participating in Operation Ranch Hand (Wolfe et al. 1995), an increase in congenital malformations was observed in veterans in the low-exposure group, but not in the high-exposure group. The study also found an increase in nervous system defects with increasing paternal serum lipid 2,3,7,8-TCDD levels (statistical analysis was not performed due to the small number of defects: 3/981 in comparison group, 0/283 in Ranch Hand veterans in the background group, 2/241 in veterans in the low-exposure group, and 3/268 in veterans in the high-exposure group). However, the study authors cautioned that this relationship is based on a limited amount of data. No relationships between paternal 2,3,7,8-TCDD exposure (based on serum 2,3,7,8-TCDD levels) and the prevalence of other birth defects were observed. A meta-analysis of seven studies evaluating birth defects in the offspring of male Vietnam veterans (including Erickson et al. 1984 and Wolfe et al. 1995) found an increased risk of spina bifida (Ngo et al. 2010).

In residents of Seveso, a rise in the incidence of birth defects, as compared to pre-accident levels, was observed the year after the accident (Bisanti et al. 1980). A variety of birth defects were observed, but the incidence for any particular defect was not elevated. The study authors suggested that the rise in birth defects may not be related to 2,3,7,8-TCDD exposure. Prior to 1976, birth defects in Italy were usually under reported; the study authors noted that the reported incidences of birth defects after the accident (23 per 1,000 births) were similar to incidences reported in other western countries. Thus, the increased

incidence may be reflective of the increased reporting rather than an increased number of birth defects. In a study that assessed the risk of birth defects for the 6-year period after the Seveso accident, no increases were observed for the risk of total defects, major defects, or minor defects (Mastroiacovo et al. 1988). The small number of observed birth defects limits the statistical power of this study to detect increases in a specific defect.

In a study of residents of Northland, New Zealand exposed to 2,4,5-T during aerial spraying, an increase in the total number of birth defects was observed in children born between 1973 and 1976, as compared to the incidence in children born between 1959 and 1960 (before the aerial 2,4,5-T spraying began) (Hanify et al. 1981). Alterations in specific defects have also been observed; increases in cleft lip, heart malformations, talipes (club foot), and hypospadias or epispadias were found. There were no alterations in the occurrence of anencephaly, spina bifida, or isolated cleft palate. Stockbauer et al. (1988) studied the Missouri cohort and found no excess risk of birth defects among infants from exposed mothers compared to an unexposed referent group. The relationship between 2,4,5-T usage and the incidence of facial clefts was investigated in residents of Arkansas exposed during the spraying of rice acreage (Nelson et al. 1979). The population was divided into areas of high, medium, and low potential exposure based on herbicide application rates. Increasing trends over time in facial clefts for both the high- and low-exposure groups were observed. The study authors attributed this to better case-ascertainment rather than 2,4,5-T exposure. In Vietnamese families potentially exposed to 2,3,7,8-TCDD-contaminated herbicides during the Vietnam War, an increase in the incidence of unspecified congenital anomalies was observed as compared with a nonexposed population (Phuong et al. 1989). Serum lipid 2,3,7,8-TCDD levels were not measured, and the extent of exposure was based on subject recall of how many times they were exposed to herbicides during the Vietnam war.

Endocrine and other systemic effects. Several epidemiological studies have evaluated possible associations between exposure to CDDs and offspring thyroid hormone levels. An association between maternal blood 2,3,7,8-TCDD levels and neonatal TSH levels was found in the Seveso cohort (Baccarelli et al. 2008). The study also found an increased risk of serum TSH levels >5 μU/mL, which has been established by the WHO as an indicator of potential thyroid problems in neonates. No association was found between maternal 2,3,7,8-TCDD blood levels at the time of the Seveso accident and TSH levels in the adult children (Warner et al. 2020c). Mixed results have been observed in general population studies. Wang et al. (2005) reported an association between CDD/CDF/PCB TEQ levels and cord blood TSH levels; other studies have not found this association (Pluim et al. 1993b; Wilhelm et al. 2008). Associations were also found in children aged 3 weeks, 11 weeks, and 2 years (Darnerud et al. 2010;

Pluim et al. 1993b; Su et al. 2010), but not in children aged 1 week, 3 months, or 8 years (Darnerud et al. 2010; Pluim et al. 1993b; Su et al. 2015).

Warner et al. (2020a) found an inverse association between maternal 2,3,7,8-TCDD levels and free T3 levels in adult children. General population studies have not found associations between CDD/CDF/PCB levels and free or total T3 levels (Darnerud et al. 2010; Koopman-Esseboom et al. 1994; Pluim et al. 1993b; Su et al. 2010; Wilhelm et al. 2008). Similarly, mixed results have been observed in general population studies examining associations with free or total T4 levels. One study reported an association between maternal CDD/CDF levels and free T4 levels in 2-year-old children (Su et al. 2010). Other studies have not found an association (Darnerud et al. 2010; Koopman-Esseboom et al. 1994; Pluim et al. 1993b; Wilhelm et al. 2008). Two general population studies found associations between maternal dioxin levels and total T4 levels (Pluim et al. 1993b; Wang et al. 2005); one study found an inverse association (Koopman-Esseboom et al. 1994) and one study found no association (Wilhelm et al. 2008). The Warner et al. (2020a) study of adult children of mothers exposed to 2,3,7,8-TCDD in Seveso found an inverse association for free T4 levels and no association with total T4 levels.

Several studies have evaluated other systemic effects; however, only one study examined each endpoint and no conclusions can be drawn. Warner et al. (2020b) evaluated the possible relationship between maternal 2,3,7,8-TCDD exposure from the Seveso accident and glucose metabolism in adult children. Inverse associations between estimated 2,3,7,8-TCDD levels at pregnancy and insulin and pancreatic beta cell function (assessed using a homeostatic model assessment of beta-cell function, HOMA-β) were found in the female adult children; no associations were found for blood glucose levels or insulin resistance in the females or for any measure in males. An increase in the frequency and severity of hypomineralization of teeth was observed in a general population study of 6–7-year-old children (Alaluusua et al. 1996). An association between human milk 2,3,7,8-TCDD levels and abnormal bleeding was observed in infants (Koppe et al. 1991). Pluim et al. (1994b) did not find associations between human milk CDD/CDF levels and vitamin K or protein-induced vitamin K absence-II (PIVK-II) levels in cord blood or blood from 11-week-old infants. Another general population study by this group found no associations between human milk CDD/CDF levels and GGT, AST, ALT, plasma cholesterol, bilirubin, leukocyte, or platelet levels in cord blood or blood from 1- or 11-week-old infants (Pluim et al. 1994a). When cumulative intake at 11 weeks was used as the biomarker of exposure, associations with AST and ALT levels and an inverse association with platelet levels were found.

Immunological development. Several general population studies have examined associations between CDDs and infections in children; most studies did not find associations. No associations were found for infections (Miyashita et al. 2018b), respiratory tract infections (Miyashita et al. 2018b; Weisglas-Kuperus et al. 1995), otitis media infections (Miyashita et al. 2018b; Stølevik et al. 2011, 2013), gastrointestinal infections (Stølevik et al. 2011, 2013), or chicken pox (Stølevik et al. 2011, 2013). Some studies did find associations between maternal CDDs and infections; associations were found between maternal dietary CDD/CDF/PCB TEQs and upper respiratory infections (Stølevik et al. 2011, 2013), gastroenteritis in 0–3-years old children, but not in 2–3-year-old children (Stølevik et al. 2013), and exanthema subitem in 1-year-old children (Stølevik et al. 2011) but not in 0–3-year-old children (Stølevik et al. 2013). General population studies also evaluated other immune endpoints; as with infections, most studies did not find associations. In the three studies examining eczema incidence, two found inverse associations (Ye et al. 2018; Stølevik et al. 2011), one found no association (Stølevik et al. 2013) but did find an association with atopic eczema in 0–3-year-old children, but not in 2–3-year-old children. Two studies reported associations between wheezing in children and maternal CDD/CDF/PCB TEQs in the diet (Stølevik et al. 2013) or in blood (Miyashita et al. 2018b). The Miyashita et al. (2018b) study only found the associations in 3.5-year-old children; no associations were found in 7-year-old children. Another study of young children did not find an association between maternal dietary CDD/CDF/PCB TEQs and wheezing (Stølevik et al. 2013). No associations were found for asthma (Ye et al. 2018; Stølevik et al. 2013), hay fever (Ye et al. 2018), allergy (Miyashita et al. 2018b), food allergy (Miyashita et al. 2018b), or sensitization (Stølevik et al. 2013). Stølevik et al. (2013) measured vaccine antibodies in children, an inverse association between maternal dietary CDD/CDF/PCB TEQs and antibodies for the measles vaccine; no associations were found for the Rubella, tetanus, or *Haemophilus influenza* type B vaccines.

Neurological development. A number of studies have evaluated potential neurodevelopmental effects in children living in areas of Vietnam with contamination from Agent Orange, living in Seveso, or in the general population. Interpretation of the results of these studies is difficult due to differences in the biomarkers of exposure, tests used, and ages of the children.

A series of studies have followed the neurodevelopment of a group of children living in an area of Vietnam contaminated with Agent Orange. In infants, impaired performances on the Bayley Scales of Infant and Toddler development tests were observed in infants of mothers with human milk 2,3,7,8-TCDD levels in the second tertile, but not in the third tertile (Tai et al. 2013); when human milk CDD/CDF TEQ was used as the biomarker of exposure, no associations were found. At 1 year of age, no associations between human milk CDD/CDF TEQs or 2,3,7,8-TCDD levels and neurodevelopmental

scores for cognition, motor function, or adaptive behavior were observed (Pham et al. 2015); impaired performance on social emotional tests was observed. When the children were 3 years of age, no alterations in performance on Bayley Scales tests of cognition or language were found using 2,3,7,8-TCDD or CDD/CDF TEQ human milk levels as biomarkers of exposure; impaired performance on motor function was found in boys only when 2,3,7,8-TCDD human milk level was used as a biomarker (Tai et al. 2016). Another study of the 3-year-old children found impaired performance on cognitive, language, motor, and adaptive behavior scores in the high CDD/CDF TEQs group, as compared to the lower CDD/CDF group (Nishijo et al. 2014). At 5 years of age, impaired performance on tests of coordinated movement was observed in boys of mothers with high CDD/CDF human milk levels; no effect was observed in girls (Tran et al. 2016). Cognitive function was also impaired in boys of mothers with high levels of 2,3,7,8-TCDD in human milk. When the children were examined at 8 years of age, impaired reading (greater number of errors) in boys was associated with 1,2,3,7,8-Pe CDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, and 1,2,3,4,6,7,8-HpCDD levels, but not with 2,3,7,8-TCDD or OCDD levels (Tai et al. 2020). Impaired performance on math achievement tests were associated with 2,3,7,8-TCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, and 1,2,3,4,6,7,8-HpCDD levels. No alterations in performance on tests of math or reading learning difficulties or language achievement were associated with CDD TEQ levels or individual congener levels. However, comparisons between groups with low and high 2,3,7,8-TCDD human milk levels demonstrated an inverse effect on reading errors and language achievement and an association with reading learning difficulties in boys (Tai et al. 2020). Comparisons between high- and low-exposure groups also demonstrated impaired performance on reading tests for CDD TEQs, 1,2,3,4,7,8-HxCDD, and 1,2,3,4,6,7,8-HpCDD, math and language scores for 1,2,3,4,7,8-HxCDD, and math scores and reading learning disabilities for 1,2,3,4,6,7,8-HpCDD. This cohort of children has also been evaluated for other neurodevelopmental effects. An association between human milk 2,3,7,8-TCDD levels and impaired performance on tests of autism traits were found in 3-year-old boys, but not in girls (Nishijo et al. 2014); no associations were found when CDD/CDF TEQ levels were used as the biomarker of exposure. At 8 years of age, an association between scores of tests of covert aggression and 2,3,7,8-TCDD levels was observed (Nishijo et al. 2012). No associations were found between CDD congener levels in human milk and food approach or food avoidance scores in 3-year-old children (Nguyen et al. 2018).

One study evaluated potential neurodevelopmental effects in 7–17-year-olds whose mothers were exposed to 2,3,7,8-TCDD resulting from the Seveso accident (Ames et al. 2019). In general, performances on tests of executive functioning and reversal learning, non-verbal intelligence, attention

and hyperactivity, and memory were not affected by maternal serum 2,3,7,8-TCDD levels at the time of the accident or estimated 2,3,7,8-TCDD levels at the time of pregnancy.

A number of general population studies have evaluated neurodevelopmental endpoints in children of various ages. A study in newborns found an association between human milk CDD/CDF TEQs and neurological optimality score of motor function (Huisman et al. 1995a) but did not find associations for individual congeners. Another study found alterations in neurological optimality score in comparisons between newborns of mothers with high levels of CDD/CDF TEQs in human milk, as compared to those with low levels (Pluim et al. 1996). No associations were found when the children were 18 months of age (Huisman et al. 1995b) or in another study of 2.7-year-old children (Wilhelm et al. 2008). Other tests found enhanced neuromuscular maturation and higher reflexes in 2.7-year-old children (Ilsen et al. 1996). No alterations in tests of developmental delays (Bayley Scales of Infant and Toddler Development) were observed in infants 12 or 24 months of age (Ilsen et al. 1996; Wilhelm et al. 2008). Increased risks of severe language delays, low communication skills (girls only), and having incomplete grammar were found in 3-year-old children (Caspersen et al. 2016b). A study of 42-month-old children found an improvement in cognitive in cognitive development achievement score associated with 1,2,3,6,7,8-HxCDD (girls and boys and girls only) and 1,2,3,7,8-PeCDD (girls only) but not with other CDD congeners or total CDD congeners (Ikeno et al. 2018). In general, studies evaluating associations between CDD exposure and intelligence or learning have not found associations in general population studies. No alterations in performance on the Wechsler Intelligence Scale tests were found in 7–12-year-old children (ten Tusscher et al. 2014) or in 11-year-old children (Hui et al. 2016, 2019). No alterations were found in the Hong Kong List Learning test in 11-year-old children (Hui et al. 2016, 2019).

Several studies have examined behavior. No association between CDD/CDF/PCB human milk levels and psychosocial behavioral development was observed in 6–10- or 11–13-year-old children (Kono et al. 2015). In contrast, a study of 7–12-year-old children found associations between estimated dioxin intake and social problems, aggressive behavior, and external behavioral problems (ten Tusscher et al. 2014). Studies examining sex-specific behaviors have not found associations with maternal blood CDD/CDF TEQ levels in 6-year-old children (Winneke et al. 2014) or 9-year-old children (Nowack et al. 2015). Two studies evaluated possible associations between CDDs and attention deficit hyperactivity disorder (ADHD) in children; no associations were found between maternal dietary intake of CDDs/CDFs in 3.5-year-old children (Caspersen et al. 2016a).

A study of 10-year-old girls found an inverse association between maternal blood CDD/CDF TEQ levels and the score on a test measuring autistic traits; no association was found in males (Nowack et al. 2015). A second study examining autistic traits in 3-year-old children living in an area of Vietnam with Agent Orange contamination found associations between human milk 2,3,7,8-TCDD levels and performance on an autism spectrum rating scale (Nishijo et al. 2014); no associations were found between human milk CDD/CDF TEQs and performance on the autism tests or between maternal blood or human milk CDD/CDF TEQs in school-age children (Neugebauer et al. 2015). The Neugebauer et al. (2015) study did find associations between the attentional performance test of distractibility and human milk CDD/CDF TEQs and between attentional performance of divided attention and maternal blood CDD/CDF TEQs.

Reproductive development. A small number of epidemiological studies evaluated impaired development of the reproductive system. In a general population study, an inverse association between anogenital distance and maternal blood dioxin levels (as measured by dioxin-responsive chemical-activated luciferase gene expression [DR CALUX] bioassay) was observed in newborn boys, but not in young children (16 months of age) (Vafeiadi et al. 2013). Another general population study did not find an association between placental CDD/CDF levels and the occurrence of cryptorchidism (Virtanen et al. 2012). Decreased sperm concentration, count, and progressive motility were observed in the breastfed sons of women in the Seveso cohort (Mocarelli et al. 2011); however, no significant alterations were observed in formula-fed children. Higher blood 2,3,7,8-TCDD levels or CDDs TEQs levels were associated with later puberty onset in boys aged 8–9 years living in an area of Russia with contaminated soil (Korrick et al. 2011). When the boys were 17–18 years of age, CDD/CDF/PCB TEQs levels were also associated with delayed puberty and delayed sexual maturity (Burns et al. 2016). Su et al. (2012) found no associations between placental CDD/CDF/PCB TEQs and sex characteristics in boys and girls at 8 years of age.

A number of studies have evaluated the effects of developmental exposure on reproductive hormone levels. Interpretation of the results is complicated by the small number of studies examining a particular hormone and the different ages of the children. In studies of children living in areas of Vietnam contaminated by Agent Orange, an association between human milk CDD/CDF TEQs and salivary dehydroepiandrosterone (DHEA) was observed in 1-year-old children (Anh et al. 2017). When individual congeners were examined, associations were found for 1,2,3,4,6,7,8-HpCDD and OCDD, but not for 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, or HxCDD congeners (Sun et al. 2020). Sun et al. (2020) also examined salivary DHEA levels when the children were 3 and 5 years of age; no associations were

observed at 3 years of age. At 5 years of age, inverse associations were found for 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD. The study also evaluated salivary testosterone levels in 3- and 5-year-old children (Sun et al. 2020); the results were inconsistent at the two ages. At 3 years of age, inverse associations were found for 2,3,7,8-TCDD and 1,2,3,6,7,8-HxCDD; at 5 years of age, inverse associations were found for 1,2,3,7,8-PeCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD. In newborns, no associations were found for 2,3,7,8-TCDD and cord blood estradiol or testosterone levels; 1,2,3,6,7,8-HxCDD was inversely associated with cord blood testosterone levels in girls, but not in boys, and was not associated with estradiol levels (Boda et al. 2018). In the adult sons of mothers exposed during the Seveso accident, maternal serum 2,3,7,8-TCDD levels were associated with FSH levels and inversely associated with inhibin B levels among breastfed sons, but not in formula-fed sons (Mocarelli et al. 2011). Most general population studies have not found associations between CDD and testosterone (Miyashita et al. 2018a; Su et al. 2012), estradiol (Miyashita et al. 2018a), androstenedione (Miyashita et al. 2018a), sex hormone binding globulin (Miyashita et al. 2018a; Virtanen et al. 2012), FSH (Miyashita et al. 2018a; Su et al. 2012; Virtanen et al. 2012), LH (Miyashita et al. 2018a; Su et al. 2012; Virtanen et al. 2012), or inhibin B (Miyashita et al. 2018a). A couple of studies did find associations: an inverse association between maternal blood fat CDD/CDF TEQs and cord testosterone levels in females (Cao et al. 2008), inverse associations between estradiol levels and maternal blood fat CDD/CDF TEQs in infants (Cao et al. 2008) and CDD/CDF/PCB levels in 8-year-old children (Su et al. 2012), and an association between maternal CDD TEQs and cord DHEA levels in males (Miyashita et al. 2018a).

2,3,7,8-TCDD—Animal studies. The literature on developmental effects of 2,3,7,8-TCDD is extensive; over 150 studies have been published. The summary below includes representative examples with emphasis on low-dose studies that could help construct dose-response relationships and determine PODs for the various specific effects. The types of effects observed in the offspring of animals exposed to 2,3,7,8-TCDD include, but are not limited to, fetal/newborn mortality, altered growth, structural malformations, impaired development of the cardiovascular, respiratory, skeletal, and gastrointestinal systems, and impaired functional alterations of the immune, neurological, and reproductive systems.

Fetal/pup mortality. Several studies have reported increased mortality in the offspring of rodents and monkeys exposed to 2,3,7,8-TCDD during gestation. Fetal/newborn deaths have occurred at doses that were either nontoxic or minimally toxic to the mothers. Increased newborn mortality was observed in Han/Wistar rats exposed to 1 μg/kg on GD 15 (Bell et al. 2007a), Holtzman rats dosed with ≥0.7 μg/kg on GD 15 (Bjerke and Peterson 1994; Bjerke et al. 1994a; Ishimura et al. 2002) or GD 10 (Kransler et al.

2009), and Line C rats (defined as having no TCDD-resistant alleles) dosed with 1 µg/kg on GD 15 (Miettinen et al. 2006). Decreased litter sizes were observed in Dark-Agouti rats exposed to 0.7 µg/kg on GD 18 (Tomasini et al. 2012), Sprague-Dawley rats exposed to 0.8 µg/kg on GD 15 (Ikeda et al. 2002), and Wistar rats exposed to 1 µg/kg on GD 15 (Takeda et al. 2020). An increase in abortions was observed in monkeys after a single exposure to 1 µg/kg on GD 25, 30, 35, or 40 (McNulty 1984) and early fetal losses were observed after exposure on GD 12 (Guo et al. 2000). Exposure of pregnant C57BL/6 mice to 10 µg/kg 2,3,7,8-TCDD on GD 12 resulted in 90% lethality of the pups by PND 28 by a wasting-like syndrome (Mustafa et al. 2008); no deaths occurred at 0.2 µg/kg. Increased fetal mortality was also reported in Hartley guinea pigs following dosing of the dams with 1.5 µg/kg 2,3,7,8-TCDD on GD 14 (Kransler et al. 2007; Olson and McGarrigle 1992); no significant lethality was reported at 0.15 µg/kg.

Dietary exposure of female Han/Wistar rats to 0.046 µg/kg/day 2,3,7,8-TCDD for 12 weeks before mating with untreated males and during mating and gestation resulted in 8/27 females with total litter loss compared with 3/27 in controls; the difference between the two groups was not statistically significant (Bell et al. 2007b). However, the number of pups alive on day 1, expressed as a ratio to the number of pups born, was significantly decreased, and the number of pups surviving between days 1 and 4 (as a ratio of number of pups alive on day 1) was also statistically significantly reduced in the exposed group. Decreased neonatal survival was found in the F1 generation of Sprague-Dawley rats exposed via the feed to 0.001 µg/kg/day of 2,3,7,8-TCDD in a 3-generation study (Murray et al. 1979); decreased survival was also observed in the F2 generation at 0.01 µg/kg/day but was not observed in the F3 generation. Significantly reduced neonatal survival was reported in pups from C57BL/6J mice following exposure to a maternal dose of 0.5 µg/kg/day 2,3,7,8-TCDD administered on GDs 0, 7, and 14, and PND 2 (Vorderstrasse et al. 2006). A study in minks in which females were exposed to 2,3,7,8-TCDD in the diet for 35 days before mating with untreated males reported that maternal doses of 0.00003, 0.003, and 0.007 µg/kg/day resulted in 3-week survival rates of 83, 47, and 11%, respectively (Hochstein et al. 2001).

Structural malformations and anomalies. Skeletal malformations have been reported in a number of studies of laboratory animals. The most commonly reported skeletal malformation is cleft palate, which has been reported in rats and mice following acute-duration oral perinatal exposure to 2,3,7,8-TCDD at maternal doses ≥1 µg/kg (see Table 2-24 for citations). The other commonly reported anomaly occurs in the kidney (primarily hydronephrosis) of rats, mice, and hamsters at maternal doses ≥0.5 µg/kg (see Table 2-24 for citations).

Table 2-24. Structural Anomalies in Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, exposure	NOAEL (µg/kg/day)	LOAEL (µg/kg/day)	Effect	Reference
C57BL/6J mouse GD 10		12	Hydronephrosis	Abbott et al. 1987a
C57BL/6N mouse GD 10		12	Impaired function of the Bowman's capsule	Abbott et al. 1987b
C57Bl/6N mouse, GD 10 or 21		24	Cleft palate	Abbott and Birnbaum 1990
C57BL/6N mouse, GD 14		6	Hydronephrosis	Aragon et al. 2008a
Wild-type mouse, GD 12		24	Cleft palate, hydronephrosis	Bryant et al. 2001
CD-1 mouse, GDs 7–16		25	Hydronephrosis	Courtney 1976
CD-1 mouse, GDs 7–16		50	Cleft palate	Courtney 1976
C57BL/6N mouse PND 1 or 4		6	Hydronephrosis	Couture-Haws et al. 1991b
C57Bl/6J mouse, GD 9		15	Cleft palate	Dasenbrock et al. 1992
DBA2 mouse, GD 9		150	Cleft palate	Dasenbrock et al. 1992
ICR mouse, GD 12.5		40	Cleft palate	Fujiwara et al. 2008
CRCD rat, 2 weeks prior to mating	0.5	2	Cystic kidneys	Giavini et al. 1983
Syrian hamster, GD 11		2	Nephrosis	Gray et al. 1995
Long-Evans rats, GD 8	1	5	Cleft palate	Huuskonen et al. 1994
Hans/Wistar rats, GD 8 or 10	1	10	Hydronephrosis	Huuskonen et al. 1994
Golden Syrian hamster, GD 9		3	Hydronephrosis	Kransler et al. 2007
Holtzman rat, GD 10	6	18	Cleft palate	Kransler et al. 2007
C57BL/6J mouse, GD 10		24	Cleft palate	Li et al. 2010
EGFR mouse, GD 10	1.5	4.4	Hydronephrosis	Miettinen et al. 2004
C57BL/6J mouse, GD 12.5		40	Cleft palate, hydronephrosis	Mimura et al. 1997
C57BL/6 mouse, GD 10		1	Hydronephrosis	Moore et al. 1973
C57BL/6 mouse, GDs 10–13		1	Hydronephrosis	Moore et al. 1973

Table 2-24. Structural Anomalies in Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, exposure	NOAEL (µg/kg/day)	LOAEL (µg/kg/day)	Effect	Reference
C57BL/6 mouse, GDs 10–13		3	Cleft palate	Moore et al. 1973
C57BL/6 mouse, once at parturition		1	Hydronephrosis	Moore et al. 1973
NMRI mouse, GDs 6–15	0.3	3	Cleft palate	Neubert and Dillmann 1972
Holtzman rat, GD 15		1	Hydronephrosis	Nishimura et al. 2006
Golden Syrian hamster, GD 7 or 9		1.5	Hydronephrosis	Olson and McGarrigle 1992
C57Bl/6J mouse, GDs 6–15		0.5	Hydronephrosis	Silkworth et al. 1989b
DBA/2J mouse, GDs 6–15		0.5	Hydronephrosis	Silkworth et al. 1989b
C57Bl/6J mouse, GDs 6–15	2	4	Cleft palate	Silkworth et al. 1989b
DBA/2J mouse, GDs 6–15	4	8	Cleft palate	Silkworth et al. 1989b
CF-1 mouse, GDs 6–15	0.1	1	Cleft palate	Smith et al. 1976
C57BL/6N mouse, GD 10		12	Cleft palate	Weber et al. 1985
C57BL/6J mouse, GD 12.5		10	Cleft palate	Yamada et al. 2006
C57BL/6J mouse		28	Cleft palate	Yuan et al. 2017

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

A study on the role of the timing of exposure found that the highest incidence of cleft palate in mice was observed when 2,3,7,8-TCDD was administered on GDs 11.5–12.5, which is just before palatogenesis, as compared to other exposure days (GDs 8.5–14.5 tested) (Yamada et al. 2006). A timing study for hydronephrosis found that the incidence and severity of hydronephrosis was greater in pups exposed *in utero* and/or during lactation, as compared to pups only exposed *in utero* (Nishimura et al. 2006). Mimura et al. (1997) examined the role of the AhR in the development of 2,3,7,8-TCDD-induced cleft palate and hydronephrosis and found that almost all of wild-type (*AhR*+/+) fetuses exhibited cleft palate and hydronephrosis following dosing of dams with 40 µg/kg 2,3,7,8-TCDD on GD 12.5; neither defect was observed in similarly exposed AhR-null mice. In contrast, most of the offspring from heterozygous AhR mutant genotype (*AhR*+/−) exhibited hydronephrosis, but only 24–28% exhibited cleft palate indicating the haplo-insufficiency of the *AhR* gene in the incidence of cleft palate.

Effects on growth. Decreases in offspring body weights were observed in Holtzman rats administered 0.7 or 1 µg/kg on GD 15 (Bjerke and Peterson 1994; Bjerke et al. 1994a; Hattori et al. 2014; Nishimura et al. 2006); however, no effects on body weight were observed in offspring exposed to ≤0.8 µg/kg on GD 15 (Ikeda et al. 2005a; Nishimura et al. 2003). Neonatal weight was significantly reduced in pups from Sprague-Dawley rats administered 1 µg/kg 2,3,7,8-TCDD on GD 15; no significant effects were reported at 0.5 µg/kg (Nayyar et al. 2002). In Wistar rats, fetal weight was significantly reduced on GD 19 following maternal administration of 0.1 µg/kg 2,3,7,8-TCDD on GDs 9– 19 (Nishijo et al. 2007). Significant decreases in body weight on PNDs 7, 21, and 30 were observed in the offspring of C57BL/6 mice administered 1 µg/kg/day on 4 lactation days (Jin et al. 2010); a decrease in body length was also observed on PNDs 30 and 60. Doses of up to 106 µg/kg 2,3,7,8-TCDD given to a strain of mice heterozygous for the epidermal growth factor receptor ($EGFR^{+/-}$) on GD 10 did not significantly affect fetal weight on GD 18 (Miettinen et al. 2004).

Impaired development of respiratory, cardiovascular, skeletal, and gastrointestinal systems. 2,3,7,8-TCDD has been shown to alter lung development in perinatally exposed rats (see Table 2-25). Treatment of Holtzman rats with ≥1.5 µg/kg 2,3,7,8-TCDD on GD 10 resulted in morphological changes in the lungs of GD 20 fetuses and PND 7 pups indicative of immaturity and hypoplasia (Kransler et al. 2009). These changes were associated with alterations in mechanical properties of the lungs examined on PND 7. 2,3,7,8-TCDD-treated rats required more pressure to achieve comparable changes in lung volume than control rats. The study also showed the presence of responsive AhR and aryl hydrocarbon receptor nuclear translocator (ARNT) mRNA and protein in the developing alveolar and bronchiolar epithelium.

Table 2-25. Systemic Effects Observed in the Offspring of Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species/exposure	LOAEL[a] (µg/kg/day)	Effect	Reference
Respiratory system			
Holtzman rat, GD 10	1.5	Altered lung morphology and mechanical properties	Kransler et al. 2009
Cardiovascular system			
C57BL/6N mouse, GD 14	6	↑ relative left ventricle plus septum weight	Aragon et al. 2008a
C57BL/6N mouse, GD 14.5	6	↑ susceptibility to hypertension in adulthood	Aragon et al. 2008b
C57BL/6J mouse, PND 1	20	Hypertrophy of left ventricle	Fujisawa et al. 2019

Table 2-25. Systemic Effects Observed in the Offspring of Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species/exposure	LOAEL[a] (µg/kg/day)	Effect	Reference
C57BL/6J mouse GD 0.5, GD 7.5, and PND 10	1	↑ systolic blood pressure and arterial pressure in response to angiotensin stress	de Gannes et al. 2021
C57BL/6N mouse, GD 14.5	3[b]	↓ relative heart weight	Thackaberry et al. 2005a
Skeletal system			
Sprague-Dawley rat, GD 11	1	↓ bone strength	Finnilä et al, 2010
Line C rat, GD 15	0.03	↓ molar size	Kattainen et al. 2001
C57BL/6N mouse, GD 13	1[c]	Altered molar and mandible shape	Keller et al. 2007
C3H/HeJ mouse, GD 13	0.01	Altered mandible shape	Keller et al. 2008
Line C rat, GD 11	1	Arrested molar development	Miettinen et al. 2002
Line C rat, GD 15	1[d]	Morphological and mechanical alterations in bone	Miettinen et al. 2005
Linc C rat, GD 15	0.03	Enhanced dental caries susceptibility	Miettinen et al. 2006
Gastrointestinal system			
Han/Wistar rat, GD 12	10[e]	Gastrointestinal hemorrhage	Huuskonen et al. 1994
Wistar rat, GDs 6–15	0.25[f]	Gastrointestinal hemorrhage	Khera and Ruddick 1973
Holtzman rat, GD 10	1.5	Intestinal hemorrhage	Kransler et al. 2007
Holtzman rat, GDs 7–19	1	Intestinal hemorrhage	Shiverick and Muther 1983
Sprague-Dawley rat, GDs 6–15	0.125[g]	Intestinal hemorrhage	Sparschu et al. 1971
Endocrine system and metabolic effects			
Wistar rat, GD 1–LD 30	0.2	↓ T3, T4, growth hormone ↑ TSH	Ahmed 2001
Long-Evans rat, GD 15	1	↓ serum TSH levels at PND 25 and 60 ↓ T4 at PND 60	Fenton et al. 2002
Long-Evans rat, GD 15	1	↓ core body temperature	Gordon et al. 1995
Long-Evans rat, GD 15	1	Altered thermoregulation	Gordon and Miller 1998
Holtzman rat, GD 15	0.8[h]	↓ serum T4 and ↑ TSH at PND 21; thyroid hyperplasia	Nishimura et al. 2003
Holtzman rat, GD 15	1	↓ serum T4 and ↑ TSH at PND 21; thyroid hyperplasia	Nishimura et al. 2005b

Table 2-25. Systemic Effects Observed in the Offspring of Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species/exposure	LOAEL[a] (µg/kg/day)	Effect	Reference
Sprague-Dawley rat, GDs 10–16	1[i]	↓ T4	Seo et al. 1995

[a]Unless noted, studies did not identify NOAELs.
[b]NOAEL of 1.5 µg/kg.
[c]NOAEL of 0.1 µg/kg/day.
[d]NOAEL of 0.3 µg/kg.
[e]NOAEL of 1 µg/kg.
[f]NOAEL of 0.125 µg/kg/day.
[g]NOAEL of 0.03 µg/kg/day.
[h]NOAEL of 0.2 µg/kg.
[i]NOAEL of 0.025 µg/kg/day.

↑ = increase; ↓ = decrease; GD = gestation day; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PND = postnatal day; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone

Heart abnormalities have been reported in mice following perinatal exposure to 2,3,7,8-TCDD, as summarized in Table 2-25. In C57BL/6N mice dosed with ≥3 µg/kg 2,3,7,8-TCDD on GD 14.5, relative fetal heart weight on GD 17.5 was significantly decreased (Thackaberry et al. 2005a). Maternal doses ≥6 µg/kg significantly reduced cardiocyte proliferation; this was seen throughout the developing heart but was most evident in the interventricular septum. In offspring examined on PND 21, but not PND 7, maternal doses ≥6 µg/kg 2,3,7,8-TCDD significantly increased relative heart weight, which was found to be associated with increased expression of the cardiac hypertrophy marker, atrial natriuretic factor. An electrocardiogram (EKG) performed in 21-day-old anesthetized pups showed no evidence of cardiac arrhythmias, but gestational plus lactational exposure significantly reduced heart rate. However, responsiveness to isoproterenol stimulation of the heart rate was not changed. Microarray gene analysis of the fetal heart showed that 2,3,7,8-TCDD significantly altered the expression of a number of genes involved in drug metabolism, cardiac homeostasis, extracellular matrix production/remodeling, and cell cycle regulation (Thackaberry et al. 2005b). Left ventricle hypertrophy was observed in the offspring of C57BL/6J mice administered 20 µg/kg on PND 1 (Fujisawa et al. 2019). Other studies showed that the 2,3,7,8-TCDD-induced changes required the AhR since gene expression was not altered in *AhR* knockout fetuses (Aragon et al. 2008a). Furthermore, evaluation of 3-month-old offspring showed that cardiac abnormalities seen in fetuses persisted through adulthood and increased the susceptibility of offspring to hypertension (Aragon et al. 2008a, 2008b). Studies examining blood pressure in adult offspring have found increased systolic blood pressure in rats administered 0.2 µg/kg/day on GDs 14 and 21 and PNDs 7

and 22 (Hsu et al. 2018, 2020) and an increase in systolic blood pressure and arterial pressure in response to angiotensin pathological stress (de Gannes et al. 2021).

Perinatal exposure to 2,3,7,8-TCDD can also affect bone and teeth development, as presented in Table 2-25. A study in a strain of rat with no TCDD-resistant alleles (referred to as "Line C") reported that a single maternal dose of 1 μg/kg 2,3,7,8-TCDD, but not ≤0.3 μg/kg, on GD 15 resulted in the following effects in female pups (males were not monitored) on PND 35: decreased cortical bone mineral density in the tibia and femur, decreased cross-sectional area of the cortex of femur, decreased periosteal and endosteal circumference in the femur, and decreased polar cross-sectional moment of inertia of the femur; bone length was not significantly affected (Miettinen et al. 2005). To determine a critical time of exposure, male and female pups were examined on PND 40 after dosing the dams with 1 μg/kg 2,3,7,8-TCDD at various times from GD 11 to PND 4. Effects varied somewhat between males and females and, in general, earlier exposures caused more severe effects and decreases in bone mineral density were not observed in offspring only receiving postnatal exposure. In a separate experiment, the investigators showed that at 1 year of age, most of the effects induced by gestational and lactational exposure to 1 μg/kg on GD 15 were reversed (Miettinen et al. 2005). A maternal dose of 1 μg/kg 2,3,7,8-TCDD administered to Sprague-Dawley rats on GD 11 significantly decreased parameters of mineralization, geometry, and strength in the tibias from pups on PNDs 35 and 70 (Finnilä et al. 2010). Results of nanoindentation tests showed that exposure to 2,3,7,8-TCDD disturbs the age-dependent maturation process causing the tibias of pups to be more ductile, softer, and less able to store energy than control bone. The results suggested that the reduced bone strength is associated more with the mineralization level and altered bone geometry than with changes in bone material properties.

Dosing rats of a strain with no TCDD-resistant alleles with 1 μg/kg 2,3,7,8-TCDD on GD 15 completely prevented the development of the lower third molar in 50% of female pups and 60% of male pups sacrificed on PNDs 35 and 70, respectively (Kattainen et al. 2001). 2,3,7,8-TCDD also reduced the size of the lower third molar at ≥0.03 μg/kg in females and ≥0.3 μg/kg in males. Further studies by the same group of investigators showed that effects were limited to third molars and that maternal exposure on GD 11 resulted in more missing molars than exposure at later times (Miettinen et al. 2002). 2,3,7,8-TCDD also decreased eruption frequency of developed third molars and effects were more marked in pups exposed *in utero* plus lactation than only *in utero* or only during lactation. The results suggested that the critical window for the third molar is during early morphogenesis, from tooth initiation to the early bud stage, and that the dental epithelium is the likely target for 2,3,7,8-TCDD. In a more recent study, it was shown that *in utero* exposure to 2,3,7,8-TCDD rendered rat molars more susceptible

to caries and this could not be explained by changes in mineral composition (Miettinen et al. 2006). 2,3,7,8-TCDD has also been shown to affect mandible size and shape in mice. Exposure on GD 13 of five different strains of mice, all containing the sensitive b allele at the AhR locus, showed that 2,3,7,8-TCDD affected mandible size and shape in the offspring, but the sensitivity differed among the inbred strains (Keller et al. 2007, 2008). A significant association between mandible size and 2,3,7,8-TCDD exposure was observed in male C3H/HeJ mice. Mandible shape was also affected significantly in male C3H/HeJ mice at 0.01 µg/kg and in C57BL/6J and C57BL/10J mice at higher doses. The investigators hypothesized that beyond AhR-related effects, variation in response to 2,3,7,8-TCDD reflects differences in the genetic architecture controlling the trait being evaluated.

Gastrointestinal hemorrhage was observed in the offspring of Wistar, Han/Wistar, or Holtzman rats at doses ≥0.125 µg/kg/day during GDs 6–15 or GD 8, 12, or 20 (see Table 2-25 for citations and summaries).

Impaired thyroid function and metabolic effects. Several studies examined thyroid hormone levels in 2,3,7,8-TCDD exposed offspring and reported conflicting results; see Table 2-25 for a summary of results. Fenton et al. (2002) reported significant increases in serum TSH levels in 25-day-old female pups from Long-Evans rats exposed once to 1 µg/kg 2,3,7,8-TCDD on GD 20 or PND 1, 3, 5, or 10; no effects were observed when maternal exposure occurred on GD 15; serum T3 and T4 levels were not significantly altered. However, in 60-day-old offspring (exposed on GD 15), serum TSH was significantly elevated and T4 was significantly decreased. In contrast, Seo et al. (1995) reported decreased T4 levels in weanling offspring of rats exposed to 0.1 µg/kg/day 2,3,7,8-TCDD on GDs 10–16, but no alterations in T3 or TSH levels. Decreased serum T3 and T4 levels and increased TSH levels were observed in the offspring of Wistar rats administered 0.2 µg/kg/day 2,3,7,8-TCDD from GD 1 to lactation day (LD) 30 (Ahmed 2011); hormone levels were measured in fetuses on GDs 16 and 19 and in the pups on LDs 10, 20, and 30. Significantly increased serum TSH levels were reported in 21- and 49-day-old offspring from Holtzman rats dosed with 0.8 µg/kg 2,3,7,8-TCDD on GD 15 (Nishimura et al. 2003). The increases in TSH were more pronounced in male pups. At 0.2 µg/kg, significant decreases in T4 levels and increases in T3 levels were observed in 21-day-old offspring, but not in 49-day-old offspring. Microscopic examination of the thyroid on PND 49 showed that exposure to 0.8 µg/kg 2,3,7,8-TCDD induced diffuse hyperplasia of follicular cells in males. Immunocytochemistry showed a significant increase in the number of proliferating cell nuclear antigen-positive cells indicating the ability of 2,3,7,8-TCDD to induce proliferation. In a subsequent study, cross-fostering experiments revealed that serum total and free T4 levels were reduced significantly, mostly due to lactational exposure (dams were

dosed with 1 µg/kg on GD 15); serum total T3 levels were not significantly altered by exposure to 2,3,7,8-TCDD (Nishimura et al. 2005b). Additionally, serum TSH levels were significantly elevated due to lactational exposure to 2,3,7,8-TCDD. Microscopic examination of the thyroid on PND 49 revealed proliferative lesions of follicular cells including hyperplasia in pups exposed via the milk but not in those exposed only *in utero*. In another study in which AhR-null mouse pups were evaluated, the same group of investigators showed that the disruption of thyroid homeostasis is mediated entirely via AhR (Nishimura et al. 2005a).

A decrease in core body temperature was observed in the offspring of Long-Evans rats exposed to 1 µg/kg on GD 15; no effect on metabolic rate or evaporative heat loss was observed (Gordon et al. 1995). A follow-up study showed that exposure to 2,3,7,8-TCDD affected the 24-hour pattern of core temperature by reducing nocturnal temperature, particularly at 7 and 11 months of age (Gordon and Miller 1998). Motor activity was reduced in a parallel manner. The hypothermic effects of 2,3,7,8-TCDD were more pronounced at cooler ambient temperatures. Behavioral thermoregulation was not affected by 2,3,7,8-TCDD. The investigators noted that the normal behavioral regulation of core temperature suggested that hypothalamic thermoregulatory centers are not permanently altered by gestational exposure to 2,3,7,8-TCDD.

Impaired development and functional alterations of the immune system. The immune system is a sensitive target following gestational and/or lactational exposure to 2,3,7,8-TCDD; a summary of studies examining immune endpoint is presented in Table 2-26. The observed effects include decreases in lymphoreticular organ weight (particularly the thymus and spleen), decreases in thymic cellularity, alterations in the T cell and mature B cell phenotypes, and functional impairment.

Table 2-26. Immunological Effects in the Offspring of Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	Dose (µg/kg/day): effect			
Species, exposure	Thymus	Thymocyte	Function	Reference
C57BL/6 mouse GDs 6–14	1.5: atrophy	1.5: delayed maturation		Blaylock et al. 1992
C57BL/6 mouse, GD 15.5			10: ↓ decreased resistance to infection	Ding et al. 2018
F344 rat, LD 0, 7, and 14	5: ↓ weight (44–52% on PND 25)		5: ↓ response to PHA and ConA	Faith and Morre 1977
BALB/cGa mouse, GD 14	10: atrophy			Fine et al. 1989

Table 2-26. Immunological Effects in the Offspring of Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	Dose (µg/kg/day): effect			
Species, exposure	Thymus	Thymocyte	Function	Reference
Fischer 344 rat, GD 14	1: ↔ 3: ↓ weight (38% on GD 19)	3: ↑ $CD4^-/CD8^+$ and ↓ $CD4^+/CD8^+$		Gehrs et al. 1997a
Fischer 344 rat, GD 14	3: ↓ weight (27%)	3: ↓ $CD4^-/CD8^-$	3: delayed-type hypersensitivity to BSA	Gehrs et al. 1997b
Fischer 344 rat, GD 14	1: ↔ weight	1: ↓ $CD4^-/CD8^-$	1: delayed-type hypersensitivity to BSA	Gehrs et al. 1997b
Sprague-Dawley rat, LD 1	10: Atrophy			Håkansson et al. 1987
C57BL/6 mouse, GD 0, 7, and 14 and LD 2			0.17: ↓ CD8+ response to viral infection	Hogaboam et al. 2008
B6C3F1 mouse, GDs 6–14	1.5: atrophy	1.5: ↓ $CD4^+CD8^+$ and ↑ $CD4^-/CD8^-$	1.5: ↓ cytotoxic T lymphocytes 1.5: ↔ response to PHA, ConA, or LPS	Holladay et al. 1991
Long-Evans rat, GD 8	1: ↔ 5: atrophy			Huuskonen et al. 1994
Han/Wistar rat, GD 8	1: ↔ 10: atrophy			Huuskonen et al. 1994
B6C3F1 mouse, GD 14, LDs 1, 7, and 14	1: ↔ 5: ↓ weight (41%)		1: ↔ 5: Impaired response to *Listeria monocytogenes* challenge and to PHA	Luster et al. 1980
C57BL/5 mouse GD 12	2.5: ↓ weight (14%)	5: ↓ $CD4^+CD8^+$		Mustafa et al. 2008
Holtzman rat, GD 15		0.8: ↔ CD4 CD8		Nohara et al. 2000
C57BL/6NCji mouse, LDs 0–17	0.011: ↔ weight	0.001: ↔ 0.011: ↑ $CD4^+$	0.001: ↔ 0.011: impaired response to *Listeria* challenge	Sugita-Konishi et al. 2003
Swiss-Webster mouse, 4 weeks prior to mating and during gestation and lactation	0.13: ↔ 0.325: atrophy		0.13: ↔ 0.325: ↓ response to sRBC	Thomas and Hinsdill 1979
C57BL/6J mouse, GD 0,7, and 14 and LD 2			0.04: ↔ 0.1: ↓ response to influenza virus	Vorderstrasse et al. 2006

↑ = increase; ↓ = decrease; ↔ = no change; BSA = bovine serum albumin; ConA = concanavalin A; GD = gestation day; LD = lactation day; LPS = lipopolysaccharide; PHA = phytohemagglutinin: sRBC = sheep red blood cell

Decreased thymus weights were observed in the offspring of rats and mice orally exposed to ≥1 µg/kg/day for acute durations (Faith and Moore 1977; Gehrs et al. 1997b; Luster et al. 1980; Mustafa et al. 2008) or 0.011 µg/kg/day for an intermediate duration (Sugita-Konishi et al. 2003). Thymic atrophy was found in pups of rats and mice exposed to acute doses ≥1.5 µg/kg/day (Blaylock et al. 1992; Fine et al. 1989; Håkansson et al. 1987; Holladay et al. 1991; Huuskonen et al. 1994) and at 0.325 µg/kg/day in the offspring of mice exposed for 4 weeks prior to mating and during gestation and lactation (Thomas and Hinsdill 1979). At lower doses, the thymic atrophy may be transitory; thymic atrophy was observed on GD 19 in the offspring of F344 rats exposed to 3 µg/kg on GD 14 but not on GD 22 (Gehrs et al. 1997a). Similarly, transient thymus atrophy was observed in the neonates of BALB/cGa mice exposed to 10 µg/kg on GD 14 but was not observed on PND 18 (Fine et al. 1989).

Evaluation of 24-week-old offspring from C57BL/6 mice administered a single dose of 5 µg/kg 2,3,7,8-TCDD on GD 12 showed significant changes in thymic T cell differentiation, in T cell phenotypes in the spleen and lymph nodes, in the phenotype of mature B cells in the spleen, and in B lymphoid progenitors in bone marrow; the immune dysregulation often appeared to be gender-specific (Mustafa et al. 2008). This study also reported increased deposition of anti-IgG and anti-C3 immune complexes in the kidneys of both male and female offspring that, according to the investigators, were suggestive of early stages of autoimmune glomerulonephritis. Subsequent studies by the same group of investigators of a strain of mice that spontaneously develop an immune complex-mediated glomerulonephritis showed that gestational exposure to 2,3,7,8-TCDD exacerbated a type III hypersensitivity lupus-like autoimmune disease, which was more severe in males than in females (Mustafa et al. 2009).

Studies have also examined functional alterations in immune response in offspring from dams exposed perinatally to 2,3,7,8-TCDD. Suppressed responses to phytohemagglutinin-P and concanavalin A mitogens and a suppressed delayed hypersensitivity response to oxazolone were observed in the offspring of F344 rats exposed to 5 µg/kg on LDs 0, 7, and 14 or on GD 18 and LDs 0, 7, and 14; no alteration in antibody production in response to bovine gamma globulin was observed (Faith and Moore 1977). Gehrs et al. (1997b) also found a suppression of the delayed hypersensitivity response to bovine serum albumin in 5-month-old male offspring receiving *in utero* and lactational exposure.

An impaired response to sheep red blood cells was observed in the offspring of Swiss Webster mice exposed to 0.325 µg/kg/day for 4 weeks prior to mating and during gestation and lactation (Thomas and Hinsdill 1979). Exposure of C57BL/6NCji mice pups to 0.011 µg/kg/day 2,3,7,8-TCDD via lactation resulted in reduced clearance of *Listeria monocytogenes* from the spleen 2 days after infection (Sugita-

Konishi et al. 2003). Decreased survival in response to a *Streptococcus agalactiae* infection was observed in the pups of C57BL/6 mice administered 10 µg/kg 2,3,7,8-TCDD on GD 15.5 (Ding et al. 2018). Exposure of C57BL/6J mice on GDs 0, 1, and 14 and PND 2 to a time-weighted average (TWA) dose of 0.1 µg/kg/day suppressed the increase in total cellularity and significantly reduced the number of $CD8^+$ cytotoxic T lymphocytes recovered from the mediastinal lymph node from female pups in response to infection to influenza A virus; no significant alterations were observed in the male pups (Vorderstrasse et al. 2006). To rule out that the observed effects in functional immunity resulted from overt toxicity to the immune organs rather than altered responsiveness following infection, the investigators examined the percentage and number of specific immune cell populations in the bone marrow, thymus, and spleen in 2,3,7,8-TCDD-treated mice not exposed to virus. No changes were detected in total cellularity of these tissues or in the percentage or number of any cell subpopulation. In another study in C57BL/6 mice that used the same exposure protocol, exposure to a TWA dose of 0.17 µg/kg/day 2,3,7,8-TCDD (only dose tested) resulted in a 66% reduction in the number of virus-specific $CD8^+$ cells in the mediastinal lymph node 9 days after infection, relative to unexposed offspring (testing was conducted at the age of 6–12 weeks) (Hogaboam et al. 2008). Nine days after infection of dams, the number of $CD8^+$ cells in the mediastinal lymph node was equivalent to control dams. Antibodies in response to immunization with ovalbumin also were reduced in offspring exposed during development, but not in treated dams. These results suggested that AhR activation in adults does not cause long-lasting deregulation of the mature immune system; however, inappropriate activation of the AhR during ontogeny of the hematopoietic system results in long-lasting functional deregulation. Furthermore, results of cross-fostering experiments showed that $CD8^+$ production in response to viral infection was significantly reduced in all adult offspring groups except those exposed only during gestation. Increased neutrophils were found in pups of B6C3F1 mice exposed to 1 µg/kg/day 2,3,7,8-TCDD on GD 14 and LDs 1, 7, and 14 (Luster et al. 1980). Furthermore, increased lymphocytes and decreased erythrocytes and hematocrit were recorded in groups exposed to 5 µg/kg/day. Alterations in thymocyte phenotypes have also been observed following *in utero* and/or lactational exposure. A decrease in the percentage of $CD3^-/CD4^-CD8^-$, $CD3^+/CD4^-CD8^-$, and $CD3^+/CD4^+$ $CD8^+$ thymocytes and an increase in $CD3^+/CD4^-CD8^+$ thymocytes were observed in the offspring of F344 rats exposed to 1 or 3 µg/kg on GD 14 (Gehrs et al. 1997a). A decrease in $CD4^-/CD8^-$ thymocytes was observed following *in utero*, lactation only, or *in utero* and lactational exposure to 1 µg/kg (administered on GD 14) (Gehrs et al. 1997b). *In utero* and lactational exposure also resulted in an increase in the percentage of $CD4^-/CD8^+$ lymphocytes; this was not observed in the *in utero* only or lactation only groups.

Impaired development and functional alterations of the nervous system. Numerous studies have reported neurological effects (morphological and neurobehavioral) in offspring following perinatal exposure to 2,3,7,8-TCDD. For example, Moran et al. (2004) reported morphological alterations in the neural tube of Cynomolgus monkeys following a maternal dose of 4 μg/kg 2,3,7,8-TCDD on GD 15. The investigators suggested that alterations in critical fatty acid mobilization during pregnancy, which were documented, may have played a role in the morphological effects observed. A lower dose of 0.7 μg/kg 2,3,7,8-TCDD (only dose tested) administered to pregnant rats on GD 18 resulted in delayed myelination in several areas in the pups' brain, some of which persisted until adulthood (Fernández et al. 2010). Treatment of Sprague-Dawley rats with 0.18 μg/kg 2,3,7,8-TCDD on GD 8 shifted hemispheric dominance from right to left in male pups examined on PND 90 (Hojo et al. 2006). The shift in hemispheric dominance was judged by changes in cell numbers and size distribution in the cerebral cortex. A much higher dose of 20 μg/kg 2,3,7,8-TCDD administered to pregnant C57BL/6N mice on GD 7 induced a significant reduction (15%) in the thickness of the somatosensory cortex (Mitsuhashi et al. 2010); the thickness of the deeper cortical layers was reduced by 24%, whereas no significant changes were seen in the superficial layers.

Delays in negative geotaxis and cliff avoidance reflexes were observed in the offspring of Sprague-Dawley rats administered 0.2 μg/kg/day on GDs 8–14 (Zhang et al. 2018b). Doses of up to 1 μg/kg 2,3,7,8-TCDD given on GD 15 to Wistar rats did not cause treatment related alterations in tests of learning ability or motor activity or in a functional observation battery conducted on postnatal weeks 12–13 (Bell et al. 2007a). The same group of investigators reported similar observations in the offspring of rats dosed with up to 0.008 μg/kg/day 2,3,7,8-TCDD via the diet for 12 weeks before mating and continued during mating and gestation (Bell et al. 2007b); at 0.046 μg/kg/day, a decrease in motor activity was observed. Dosing of Long-Evans rats with up to 0.8 μg/kg 2,3,7,8-TCDD on GD 15 did not affect spontaneous activity in male offspring on PNDs 100–110 (Kakeyama et al. 2003). Using benchmark methodology to estimate a POD, Markowski et al. (2001) calculated an ED_{10} of 0.007 μg/kg 2,3,7,8-TCDD with a 95% lower bound of 0.005 μg/kg for neurobehavioral alterations that suggested reduced responsiveness to environmental contingencies in offspring of Holtzman rats dosed once on GD 18. The same group reported that a maternal dose of 0.18 μg/kg 2,3,7,8-TCDD on GD 15 caused impaired performance on operant behavior tests in Holtzman rats (Markowski et al. 2002). The investigators noted that rather than a global learning deficit, this effect appeared to be more a function of an inability to inhibit or delay voluntary behavior. Hojo et al. (2002) calculated an ED_{10} of 0.003 μg/kg 2,3,7,8-TCDD with 95% lower bounds of 0.002 μg/kg 2,3,7,8-TCDD for alterations in two different schedule-controlled, food reinforced operant procedures in 80-day-old offspring from Sprague-Dawley

rats dosed on GD 8. Improved performance of 80-day-old offspring of Sprague-Dawley rats administered 0.1 µg/kg/day on GDs 10–16 was observed in a radial arm maze working memory task (Seo et al. 1999). The investigators suggested that the improvement in the spatial task was specific to the radial arm maze and might have been related to response patterning (Seo et al. 1999). This study also reported that 0.1 µg/kg 2,3,7,8-TCDD significantly impaired visual reversal learning in 80-day-old offspring. A follow-up study by this group (Seo et al. 2000) confirmed the finding of improvement performance on the radial arm maze test in rats exposed to 0.1 µg/kg/day on GDs 10–16; however, this improvement was not observed at 0.2 µg/kg/day. A subsequent study by this group found that alterations in spatial and visual reversal learning observed in Sprague-Dawley rats administered 0.1 µg/kg/day on GDs 10–16 was likely due to either attentional or associative processing effects (Widholm et al. 2003). Hojo et al. (2008) reported an increase in response rate on schedule-controlled operant behavior tests in female offspring of Long-Evans rats administered 0.2 µg/kg on GD 15; this effect was not observed at the next highest dose (0.8 µg/kg). The investigators suggested that the increased response rate was likely due to hyperactive behavior rather than enhanced learning performance. Sha et al. (2021) reported alterations in activity in an open field test suggestive of hyperactivity in the offspring of C57BL/6J mice administered 0.1 µg/kg/day 2,3,7,8-TCDD on GD 0.5, GD 12.5, and PND 7.5. Increased motor activity and decreased social activity were observed at 1 µg/kg in the offspring of Wistar rats administered 1 µg/kg on GD 15 (Nguyen et al. 2013a). Similarly, Kakeyama et al. (2007) reported anxiety-like behavior and inhibition of acquisition of paired-associative memory in male offspring of Long-Evans rats administered 0.2 µg/kg during pregnancy; however, these effects were not observed at 0.8 µg/kg. The results of a study in mice with different genotypes suggested that the effects of 2,3,7,8-TCDD on learning as well as on hippocampal morphology are mediated through the AhR since they were absent in *AhR*-knockout mice (Powers et al. 2005). Impaired acquisition and retention of fear memory were observed in the male offspring of C57BL/6J mice administered 3 µg/kg 2,3,7,8-TCDD on GD 12.5 and examined at 25–28 weeks of age (Haijima et al. 2010). In Wistar rats administered 1 µg/kg on GD 15, an impaired response in contextual fear conditioning tests was observed in male offspring, but not in female offspring (Mitsui et al. 2006). In the adult offspring of C57BL/6 mice administered 0.6 µg/kg 2,3,7,8-TCDD on GD 12.5, impaired attainment of rapid behavioral shifts in tests of behavioral flexibility, compulsive repetitive behavior, and low competitive dominance were observed (Endo et al. 2012); the latter two effects were not observed at 3 µg/kg. Delayed habituation and reduced exploration of novel objects were observed in the offspring of C57BL/6 mice administered 0.25 µg/kg/day on GD 7, GD 14, and PND 2 (Sobolewski et al. 2014). Delayed avoidance learning and reduced motor activity were reported in Wistar rat pups following maternal dosing with 0.1 µg/kg/day 2,3,7,8-TCDD on GDs 9–19 (Nishijo et al. 2007). A different type of study examined the effect of gestational exposure to 2,3,7,8-TCDD on sensory cortex

function in rats (Hood et al. 2006). In 45-day-old offspring of Long-Evans rats dosed with 0.7 µg/kg 2,3,7,8-TCDD on GD 15, the mean spontaneous electrical activity of cells assayed in the primary sensory cortex was reduced approximately 50% relative to controls, even after ≥60 days of postnatal recovery. Responses evoked by sensory stimulation were also reduced by 50% at every level of stimulus intensity compared with controls. The reduction in activity was associated with decrements in specific glutamate receptor subunits.

The neurodevelopmental toxicity of 2,3,7,8-TCDD was evaluated in a multi-breeding study in monkeys reported in several papers (Bowman et al. 1989a, 1989b; Schantz and Bowman 1989; Schantz et al. 1986, 1992). The study evaluated three cohorts of offspring of mothers exposed to 2,3,7,8-TCDD in the diet and mated to unexposed males. Cohort I consisted of offspring of mothers mated after 7 months of exposure with an average of 16.2 months of exposure prior to birth; cohort II consisted of offspring of mothers mated after 27 months of exposure with an average of 36 months of exposure prior to birth; and cohort III consisted of infants of mothers exposed for 3.5–4 years and mated 10 months post-exposure and born 18 months post-exposure. Alterations in peer-group behavior (Bowman et al. 1989b; Schantz et al. 1992) and cognitive deficits (Bowman et al. 1989a; Schantz and Bowman 1989) were observed in the cohort I offspring of monkeys exposed to 0.00012 µg/kg/day. Significant alterations were observed in play behavior, displacement, and self-directed behavior. Exposed monkeys tended to initiate more rough tumble play bouts and retreated less from play bouts than controls, were less often displaced from preferred positions in the playroom than the controls, and engaged in more self-directed behavior than controls. Cognitive function was altered as evidenced by impaired-reversal-learning performance in the absence of impaired delayed-spatial-alterations performance; cognitive function was also altered in the cohort II monkeys (Schantz and Bowman 1989). In cohort III, there was increased and prolonged maternal care (increased time in mutual ventral contact and nipple contact) at 0.000012 and 0.00064 µg/kg/day (Schantz et al. 1986) and altered social behavior (rough tumble play) was observed at 0.00064 µg/kg/day (Schantz et al. 1992).

Ototoxicity was observed in the offspring of C57Bl/6 mice administered 0.5 µg/kg 2,3,7,8-TCDD on GD 12 (Safe and Luebke 2016). A 5–20 dB shift in auditory brainstem response was observed at frequencies of 11.3–30 kHz. There was no alteration in distortion-product otoacoustic emissions at the same frequencies suggesting a mild auditory neuropathy. No structural abnormalities in the cochlea. In contrast, no signs of ototoxicity were observed in similarly exposed offspring of CBA or Balb/C mice (Safe and Luebke 2016).

Impaired development and functional alterations of the reproductive system. A large number of studies have found impaired development of the reproductive system in male and female animals exposed to 2,3,7,8-TCDD during gestation and/or lactation.

Studies examining outcomes indicative of impaired development of the reproductive system in the offspring of pregnant animals administered 2,3,7,8-TCDD are summarized in Table 2-27. Gestational (and lactational) exposure resulted in impaired development of the prostate and vagina in male and female offspring. Alterations in the formation of prostatic epithelial buds have been observed in mice at 5 µg/kg (Abbott et al. 2003; Allgeier et al. 2009; Ko et al. 2002). Other alterations in male reproductive tissue include degenerative changes in the testes, decreases in seminiferous tubular diameter and epithelial thickness, and an increase in the percentage of abnormal seminiferous tubules in rats at 0.5 µg/kg (Mai et al. 2020); altered development of the seminal vesicles was also observed at 1 µg/kg (Hamm et al. 2000).

Decreases in testis, prostate, seminal vesicle, and cauda epididymis weights have also been observed in male offspring at ≥0.064 µg/kg (Bjerke and Peterson 1994; Gray et al. 1995; Jin et al. 2010; Lin et al. 2002b; Mably et al. 1992a, 1992c; Ohsako et al. 2002). A cross-fostering study in mice showed that the decrease in relative ventral prostate weight was greater in offspring exposed *in utero* or *in utero* and during lactation than in offspring exposed during lactation only (Lin et al. 2002b). The study also found a greater decrease in ventral prostate weight in offspring exposed on GD 13 compared to those exposed on GD 16.

In female offspring, maternal exposure to 1 µg/kg 2,3,7,8-TCDD on GD 15 resulted in altered vaginal morphogenesis as early as GD 18 (Dienhart et al. 2000; Hurst et al. 2002); observed effects included an increase in the thickness of mesenchymal tissue between the caudal Mullerian ducts, which resulted in a failure of the Mullerian ducts to fuse (a process normally completed before birth) and impaired the regression of the Wolffian ducts by increasing the size of the interductal mesenchyme and by preventing fusion of the Mullerian ducts. Changes in the spatial and temporal expression of growth factors in response to 2,3,7,8-TCDD appeared to be implicated in the pathogenesis of the vaginal thread (Hurst et al. 2002). A vaginal thread has been observed at doses ≥0.2 µg/kg (Flaws et al. 1997; Gray and Ostby 1995; Gray et al. 1997a), but not at 0.05 µg/kg (Gray et al. 1997a). Partial clefting of the phallus was also observed in the female offspring at the same dose levels (Flaws et al. 1997; Gray and Ostby 1995; Gray et al. 1997a). Impaired development of mammary glands, specifically impairment of mammary gland differentiation, was observed in female offspring of dams exposed to 0.5 or 1 µg/kg/day (Brown et al. 1998; Fenton et al. 2002; Filgo et al. 2016; Lewis et al. 2001).

Table 2-27. Impaired Development of Reproductive System in Offspring of Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	Dose (µg/kg/day): effect					
				Puberty		
Species, exposure	Morphological alterations	Organ weights	Anogenital distance (males)	Males	Females	Reference
C57BL/6J mouse, GD 12	5: impaired prostatic bud development					Abbott et al. 2003
C57BL/6J mouse, GD 13.5	5: impaired prostate budding					Allgeier et al. 2009
Han Wistar rat, GD 15				0.2: ↔ 1: ↓		Bell et al. 2007a
Holtzman rat, GD 15			0.7: ↔	0.7: ↓		Bjerke et al. 1994a
Holtzman rat, GD 15		1: ↓, prostate, seminal vesicle, testis, cauda epididymis		1: ↓		Bjerke and Peterson 1994
Sprague-Dawley rat, GD 15	1: impaired mammary gland differentiation					Brown et al. 1998
Holtzman rat, GD 15	1: altered vaginal morphogenesis					Dienhart et al. 2000
Long-Evans rat, GD 15	1: Delayed development of mammary gland					Fenton et al. 2002
Sprague-Dawley rat, GDs 15 and 18	0.5: Delayed development of mammary gland					Filgo et al. 2016
Holtzman rat, GD 11, 15, or 18	1: ↑ vaginal phallus clefting and vaginal thread					Flaws et al. 1997
Holtzman rat, GD 15	1: ↑ vaginal phallus clefting and vaginal thread				1: ↔	Gray and Ostby 1995
Long-Evans rat, GD 15	1: ↑ vaginal phallus clefting and vaginal thread				1: ↔	Gray and Ostby 1995
Long-Evans rat, GD 8	1: ↑ vaginal phallus clefting 1: ↔ vaginal thread				1: ↓	Gray and Ostby 1995

Table 2-27. Impaired Development of Reproductive System in Offspring of Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	Dose (µg/kg/day): effect					
				Puberty		
Species, exposure	Morphological alterations	Organ weights	Anogenital distance (males)	Males	Females	Reference
Holtzman rat, GD 8 or 15		1: ↓, testis, cauda epididymis				Gray et al. 1995
Long-Evans rat, GD 8 or 15				1: ↓		Gray et al. 1995
Golden Syrian hamster, GD 11		1: ↓, testis, cauda epididymis		2: ↓		Gray et al. 1995
Long-Evans rat, GD 15	0.05: ↔ 0.2: ↑ vaginal phallus clefting and vaginal thread					Gray et al. 1997a
Long-Evans rat, GD 15				0.05: ↔ 0.2: ↓		Gray et al. 1997b
Long-Evans rat, GD 15	1: altered development of seminal vesicles					Hamm et al. 2000
Long-Evans rat, GD 15	1: altered vaginal morphogenesis					Hurst et al. 2002
C57Bl/6 mouse, PNDs 1–4		1: ↓, testis, cauda epididymis	1: ↓			Jin et al. 2010
Long-Evans rat, GD 15					0.2: ↔ 0.8: ↑	Kakeyama et al. 2008
C57BL/6J mouse, GD 13	5: inhibition of prostate lobe branching					Ko et al. 2002
Holtzman rat, GD 15	1: impaired mammary gland differentiation					Lewis et al. 2001
C57BL/6J mouse, GD 13	5: inhibition of prostate development					Lin et al. 2002a
C57BL/6J mouse, GD 13 or 16		5: ↓, prostate and seminal vesicle				Lin et al. 2002b

Table 2-27. Impaired Development of Reproductive System in Offspring of Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	Dose (µg/kg/day): effect					
				Puberty		
Species, exposure	Morphological alterations	Organ weights	Anogenital distance (males)	Males	Females	Reference
Holtzman rat, GD 15		0.064: ↓, prostate 0.16: ↓, seminal vesicle	0.064: ↔ 0.16: ↓	0.064: ↔ 0.16: ↓		Mably et al. 1992a
Holtzman rat, GD 15		0.064: ↓, testis, cauda epididymis				Mably et al. 1992c
Wistar rat, GD 15	0.5: alterations in testes and seminiferous tubules					Mai et al. 2020
Holtzman rat, GD 15			0.0125: ↔ 0.05: ↓			Ohsako et al. 2001
Sprague-Dawley rat, GD 15		1: ↓, testis, prostate, epididymis	1: ↓			Ohsako et al. 2002
Sprague-Dawley rat, GD 18			1: ↓			Ohsako et al. 2002
Line C rat, GD 15			0.3: ↔ 1: ↓			Simanainen et al. 2004b
Long-Evans rat, GD 15			0.8: ↔	0.05: ↔ 0.2: ↓	0.2: ↔ 0.8: ↓	Yonemoto et al. 2005
Sprague-Dawley rat, GDs 8–14					1: ↑ (F3)	Yu et al. 2019
Wistar, 12 weeks premating and during gestation and lactation				0.0024: ↓		Bell et al. 2007b

↑ = increase; ↓ = decrease; ↔ = no change; GD = gestation day; PND = postnatal day

Other effects associated with impaired development of the reproductive system include alterations in anogenital distance and onset of puberty. Decreases in anogenital distance has been observed in male rat offspring at 1 µg/kg (Jin et al. 2010; Ohsako et al. 2002; Simanainen et al. 2004b); lower LOAEL values have been reported (Mably et al. 1992a; Ohsako et al. 2001) but these overlap with NOAEL values from other studies (Bjerke et al. 1994a; Simanainen et al. 2004b; Yonemoto et al. 2005). Delays in puberty, as measured by testis descent or date of preputial separation, were observed in rats at doses as low as 0.2 µg/kg (Bell et al. 2007a; Bjerke et al. 1994a; Gray et al. 1995, 1997a; Yonemoto et al. 2005) following acute-duration exposure and 0.0024 µg/kg/day following intermediate-duration exposure (Bell et al. 2007b) and in hamsters at 2 µg/kg (Gray et al. 1995). In one study, a delay in the onset of puberty, as measured by date of vaginal opening, was observed in the female offspring of rats exposed to 1 µg/kg on GD 8, but not in the offspring of rats exposed on GD 15 (Gray and Ostby 1995). Yonemoto et al. (2005) found delays at 0.8 µg/kg in the offspring of dams exposed on GD 15. In contrast, Kakeyama et al. (2008) reported shortened time to vaginal opening at 0.8 µg/kg; this effect was also observed in the F3 generation at 0.5 µg/kg (Yu et al. 2019).

Examination of the offspring after sexual maturity has revealed functional alterations in males and females; summarized in Tables 2-28 and 2-29, respectively. Decreased daily sperm production has been inconsistently observed in several studies. Decreases have been observed in offspring of rats administered ≥0.064 µg/kg 2,3,7,8-TCDD on GD 15 (Mably et al. 1992c; Simmanainen et al. 2004b; Sommer et al. 1996) but not in other studies testing doses as high as 1 µg/kg (Gray et al. 1995; Ohsako et al. 2001, 2002; Rebourcet et al. 2010; Yonemoto et al. 2005). Decreases in cauda epididymal sperm counts have been consistently found at doses ≥0.8 µg/kg (Bruner-Tran et al. 2014; Gray et al. 1995; Jin et al. 2010; Mai et al. 2020; Ohsako et al. 2002; Simanainen et al. 2004b). Studies examining sexual behavior in male offspring have reported demasculinization and feminization. Demasculinized sexual behavior, as measured by decreases number and/or increases in latency of mounts and intromission (in the Ikeda et al. [2005a] study, demasculinization was assessed by measuring brain aromatase levels), was observed at ≥0.2 µg/kg (Bjerke et al. 1994b; Ikeda et al. 2005a; Kakeyama et al. 2003; Mably et al. 1992b; Taura et al. 2014). Feminized sexual behavior, as measured by frequency and intensity of lordotic behavior, was also observed in male offspring castrated and primed with ovarian steroid at maternal doses ≥0.16 µg/kg (Bjerke and Peterson 1994; Bjerke et al. 1994b; Mably et al. 1992b). A small number of studies evaluated male fertility. In males mated with unexposed females an increase in preterm births and decrease in gestation length was observed at 10 µg/kg (Ding et al. 2011), an increase in pre- and post-implantation losses with no effect on mating or fertility indices was observed at ≥0.5 µg/kg (Mai et al.

Table 2-28. Functional Alterations in the Reproductive System of Male Offspring of Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	Dose (µg/kg/day): effect					
Species, exposure	Daily sperm production	Cauda epididymal sperm count	Demasculinization	Feminization	Fertility	Reference
Holtzman rat, GD 15				1: ↑		Bjerke and Peterson 1994
Holtzman rats, GD 15			0.7: ↑	0.7: ↑		Bjerke et al. 1994b
C57BL/6 mouse, GD 15.5		10: ↓				Bruner-Tran et al. 2014
C57BL/6 mouse, GD 15.5					10: ↑, preterm births and ↓ gestation length	Ding et al. 2011
Holtzman rat, GD 8 or 15					1: ↓	Gray et al. 1995
Long-Evans rat, GD 15		1: ↓				Gray et al. 1995
Golden Syrian hamster, GD 11		2: ↓				Gray et al. 1995
Long-Evans rat, GD 15	0.05: ↓ ejaculated sperm count					Gray et al. 1997a
Long-Evans rat, GD 15	0.8: ↔	0.8: ↓				Gray et al. 1997b
Holtzman rat, GD 15			0.2: ↑			Ikeda et al. 2005a
C57BL/6 mouse, PNDs 1–4		1: ↓				Jin et al. 2010

Table 2-28. Functional Alterations in the Reproductive System of Male Offspring of Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	Dose (µg/kg/day): effect					
Species, exposure	Daily sperm production	Cauda epididymal sperm count	Demasculinization	Feminization	Fertility	Reference
Long-Evans rat, GD 15			0.8: ↑			Kakeyama et al. 2003
Holtzman rats, GD 15			1: ↑	0.16: ↑		Mably et al. 1992b
Holtzman rat, GD 15	0. ↓					Mably et al. 1992c
Wistar rat, GD 15		0.5: ↔ 1: ↓			2: ↔ 0.5: ↑, pre- and post-implantation losses	Mai et al. 2020
Holtzman rat, GD 15	0.8: ↔					Ohsako et al. 2001
Sprague-Dawley rat, GD 15	1: ↔	1: ↓				Ohsako et al. 2002
Sprague-Dawley rat, GD 18		1: ↔				Ohsako et al. 2002
Sprague-Dawley rat, GD 15	0.2: ↔				0.2: ↔	Rebourcet et al. 2010
Line C rat, GD 15	0.3: ↔ 1: ↓	1: ↓				Simanainen et al. 2004b
Holtzman rat, GD 15	1: ↓	1: ↓				Sommer et al. 1996
Wistar rat, GD 15			1: ↑			Taura et al. 2014

Table 2-28. Functional Alterations in the Reproductive System of Male Offspring of Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	Dose (µg/kg/day): effect					
Species, exposure	Daily sperm production	Cauda epididymal sperm count	Demasculinization	Feminization	Fertility	Reference
Long-Evans rat, GD 15	0.8: ↔	0.8: ↔				Yonemoto et al. 2005

↑ = increase; ↓ = decrease; ↔ = no change; GD = gestation day; PND = postnatal day

Table 2-29. Functional Alterations in the Reproductive System of Female Offspring of Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	Dose (µg/kg/day): effect				
Species, exposure	Ovarian follicles	Estrous	Fertility	Other effects	Reference
C57BL/6 mouse, GD 15.5			10: ↓, F1, F2, and F3		Bruner-Tran and Osteen 2010
Sprague-Dawley rat, GD 8				1: ↔ endometriotic lesion diameter	Cummings et al. 1999
C57BL/6 mouse, GD 8				3: ↔ endometriotic lesion diameter	Cummings et al. 1999
C57BL/6 mouse, GD 8, PNDs 77, 98, 119, 140, and 161				3: ↑ endometriotic lesion diameter	Cummings et al. 1999
C57BL/6 mouse, GD15.5			10: ↓	10: ↑, preterm births and ↓ gestation length	Ding et al. 2011
Holtzman rat, GD 11, 15, or 18	1: ↔				Flaws et al. 1997
Sprague-Dawley rat, PND 29		10: ↑, premature onset of abnormal or absent cyclicity			Franczak et al. 2006

Table 2-29. Functional Alterations in the Reproductive System of Female Offspring of Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	Dose (µg/kg/day): effect				
Species, exposure	Ovarian follicles	Estrous	Fertility	Other effects	Reference
Long-Evans rat, GD 8		1: ↑, constant estrus	1: ↓		Gray and Ostby 1995
Long-Evans rat, GD 15		1: ↔, constant estrus	1: ↓, litter 5		Gray and Ostby 1995
Long-Evans rat, GD 15			0.8: ↔ 0.8: ↓, time to pregnancy		Gray et al. 1997a
Holtzman rat, GD 15	1: ↓, antral and preantral follicles				Heimler et al. 1998
Long-Evans rat, GD 15		0.2: ↔, first day of estrus 0.8: ↑, first day of estrus 0.8: ↔, estrus cyclicity			Kakeyama et al. 2008
Sprague-Dawley rat, GD 15		1: ↓, days in estrous			Salisbury and Marcinkiewicz 2002
Syrian hamster, GD 11.5			2: ↓		Wolf et al. 1999
Long-Evans rat, GD 15		0.8: ↔, estrus cyclicity			Yonemoto et al. 2005
Sprague-Dawley rat, GDs 8–14	0.1: ↓, primordial follicles 0.1: ↑, primary and secondary follicles				Yu et al. 2020
Sprague-Dawley rat, GDs 8–14	0.1: ↓, primordial follicles 0.1: ↑, primary and secondary follicles				Zhang et al. 2018b
Lewis-Furth rat, GDs 14 and 21, PNDs 7 and 14, and PNDs 21–24		0.007: ↑, onset of acyclicity			Jablonska et al. 2010

↑ = increase; ↓ = decrease; ↔ = no change; GD = gestation day; PND = postnatal day

2020), a decrease in the number of implants was observed at 1 µg/kg (Gray et al. 1995), and no effect on pregnancy rate was observed in rats at 0.2 µg/kg (Rebourcet et al. 2010).

A smaller number of studies have examined functional alterations in female offspring (summarized in Table 2-29). A study by Yu et al. (2020) in the offspring of Sprague-Dawley rats administered 0.1 µg/kg on GDs 8–14 found decreased primordial follicles and increased primary and secondary follicles and Heimler et al. (1998) reported decreased antral and preantral follicles in the offspring of Holtzman rats administered 1 µg/kg on GD 15. In contrast, Flaws et al. (1997) found no alterations in primordial follicles in the offspring of Holtzman rats administered 1 µg/kg on GD 11, 15, or 18. Studies examining the estrus cycle have reported a delay in the first day of estrus at 0.8 µg/kg (Kakeyama et al. 2008), no effect on estrus cyclicity at 0.8 µg/kg (Kakeyama et al. 2008; Yonemoto et al. 2005), a decrease in days in estrous at 1 µg/kg (Salisbury and Marcinkiewicz 2002), and premature onset of abnormal or absent cyclicity at 0.007 or 10 µg/kg/day (Franczak et al. 2006; Jablonska et al. 2010). Exposure to 1 or 3 µg/kg on GD 8 followed by surgically induced endometriosis on PND 98, did not result in an increase in endometriotic lesions in Sprague-Dawley rats or C57BL/6 mice, respectively (Cummings et al. 1999). However, an increase in lesions were observed in mice prenatally exposed to 2,3,7,8-TCDD and receiving a 3 or 10 µg/kg dose of 2,3,7,8-TCDD on PNDs 77, 98, 119, 140, and 161. Several studies have reported decreases in transgenerational fertility in female rats, mice, and hamsters. Decreases in fertility were observed in the female offspring exposed to ≥1 µg/kg 2,3,7,8-TCDD *in utero* and mated to unexposed males (Bruner-Tran and Osteen 2011; Ding et al. 2011; Gray and Ostby 1995; Wolf et al. 1999); no alteration in fertility was observed in rats exposed to 0.8 µg/kg (Gray et al. 1997a). Bruner-Tran and Osteen (2011) also demonstrated decreased pregnancy rates in the F2 and F3 generations (only the P0 generation was administered 10 µg/kg 2,3,7,8-TCDD). Increased preterm births and decreased gestation length were observed in the offspring of mice exposed *in utero* to 10 µg/kg (Ding et al. 2011). Increased preterm births were also observed in another study of mice (Bruner-Tran and Osteen 2011); however, this was only observed in a colony contaminated with mouse parvovirus and in mice exposed to 2,3,7,8-TCDD and injected with lipopolysaccharide. The results suggest that TCDD-induced increased sensitivity to inflammation negatively impacted gestation length as the mouse parvovirus or lipopolysaccharide did not affect the rate of preterm births in controls.

Several studies have evaluated reproductive hormone levels in male offspring of rats orally administered 2,3,7,8-TCDD during pregnancy; the results of these studies are summarized in Table 2-30. Decreased plasma testosterone levels were observed at 1 µg/kg in the fetuses of Hans/Wistar and Long Evans rats (Haavisto et al. 2001) and 90-day-old rats (Sanabria et al. 2016), but were not observed in the male

Table 2-30. Alterations in Reproductive Hormones in the Male Offspring of Laboratory Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, exposure	Age	Plasma testosterone	Testicular testosterone	Plasma luteinizing hormone	Pituitary luteinizing hormone	Follicle stimulating hormone	Reference
Sprague-Dawley rat, GD 11	19-day fetuses		0.3: ↓				Adamsson et al. 2008
Han/Wistar rat, GD 13.5	19.5-day fetuses	0.1: ↔ 0.5: ↓	1: ↔		0.5: ↔ 1: ↓		Haavisto et al. 2001
Sprague-Dawley rat, GD 13	PND 14		1: ↔	1: ↔		1: ↔	Haavisto et al. 2006
Holtzman rat, GD 15	17-, 18-, 19-, 20-, or 21-day fetuses	1: ↓					Mably et al. 1992a
Holtzman rat, GD 15	PND 32					1: ↓	Mably et al. 1992c
Holtzman rat, GD 15	PND 42, 63, or 120					1: ↔	Mably et al. 1992c
Sprague-Dawley rat, GD 15	PND 28, 40, 67, or 145		0.2: ↔				Rebourcet et al. 2010
Wistar rat, GD 15	PND 90	1: ↓		1: ↔		1: ↔	Sanabria et al. 2016

↓ = decrease; ↔ = no change; GD = gestation day; PND = postnatal day

offspring of Holtzman rats exposed to 1 µg/kg/day (Mably et al. 1992a). Three of four studies examining testicular testosterone levels did not find significant alterations at ≤1 µg/kg (Haavisto et al. 2001, 2006; Rebourcet et al. 2010). Haavisto et al. (2006) and Sanabria et al. (2016) did not find alterations in plasma LH or FSH levels. Mably et al. (1992c) found decreases in FSH levels in rats on PND 32, but not on PND 42, 63, or 120. In the female offspring of Holtzman rats administered 1 µg/kg 2,3,7,8-TCDD on GD 15, a decrease in serum estrogen levels was observed (Chaffin et al. 1996) and no alterations in serum FSH, LH, or progesterone levels were observed (Chaffin et al. 1997).

Other CDD Congeners—Animal Studies. Other CDD congeners have also been found to induce developmental toxicity. Khera and Ruddick (1973) reported edematous separation of the cardiac myofibrils in rat offspring exposed *in utero* to 2,000 µg/kg/day 2,7-DCDD (Khera and Ruddick 1973); however, the study did not include statistical analysis. Schwetz et al. (1973) found no developmental effects in fetuses of rats exposed to 100,000 µg/kg/day 2,7-DCDD during gestation, but histological examinations of soft tissues were not performed. Decreased thymic weight was found in the offspring of rats exposed once on GD 16 to 0.125 µg/kg 1,2,3,7,8-PeCDD (Madsen and Larsen 1989). Subcutaneous edema was found in the offspring of Sprague-Dawley rats exposed to 1 µg/kg/day of mixed HxCDD isomers during GDs 6–15 (Schwetz et al. 1973). Furthermore, decreased fetal body weight, reduced crown-rump length, delayed ossification, and dilated renal pelvis were observed at 10 µg/kg/day and an increased incidence of cleft palate was found at 100 µg/kg/day. The NOAEL for the mixture of HxCDD isomers was 0.1 µg/kg/day. Subcutaneous edema was also reported in fetuses of rats exposed to 5×10^5 µg/kg/day of OCDD during GDs 6–15; however, the incidence was not significant when evaluated on a litter basis (Schwetz et al. 1973). No developmental effects were observed in mice exposed to 20 µg/kg/day of OCDD during GDs 7–16 (Courtney 1976). In contrast to most experiments with 2,3,7,8-TCDD, the 1,2,3,4-TCDD isomer did not induce developmental effects in the offspring of Wistar rats treated on GDs 6–15 with 800 µg/kg/day (Khera and Ruddick 1973) or CD-1 mice exposed to 1,000 µg/kg/day during gestation (Courtney 1976). No developmental effects were seen in the offspring of Wistar rats exposed to 2,000 µg/kg/day 2,3-DCDD or 2-MCDD on GDs 6–15 (Khera and Ruddick 1973).

Developmental Mechanisms. Many of the health effects of CDDs share a common initiating event in AhR binding. Section 2.21, Mechanisms of Toxicity, provides a discussion of this initiating event and its physiological sequelae. In this subsection, an overview of the mechanisms involved in developmental effects is provided. Detailed mechanistic explanations are beyond the scope of this profile.

Hydronephrosis. Hydronephrosis has been induced by 2,3,7,8-TCDD in both rats and mice exposed in utero or during the neonatal period (Yoshioka and Tohyama 2019). While the AhR is necessary for both fetal and neonatal 2,3,7,8-TCDD-induced hydronephrosis, two distinct mechanisms have been elucidated, differing on the developmental stage of exposure (fetal or neonatal) (Yoshioka and Tohyama 2019). Fetal hydronephrosis is obstructive: a direct hyperplastic action of 2,3,7,8-TCDD on the uretic epithelium results in occlusion of the ureter (Abbott et al. 1987a) leading to accumulation of urine, expansion of the ureter and pyelocaliceal space of the kidney, and destruction of the renal parenchyma (Yoshioka and Tohyama 2019). In contrast, anatomical obstruction has not been observed in neonatal hydronephrosis, which has been shown to be associated with increased urine production (Yoshioka and Tohyama 2019).

In addition to AhR, neonatal hydronephrosis in 2,3,7,8-TCDD exposed animals also requires cyclooxygenase-2 (COX-2) and microsomal prostaglandin E synthase-1 (mPGES-1), both of which are upregulated in the kidneys of exposed animals. Inhibition of COX-2 and genetic ablation of mPGES-1 can each block the development of neonatal hydronephrosis in 2,3,7,8-TCDD exposed animals (Yoshioka and Tohyama 2019). The increased expression of COX-2 and mPGES-1, which are key enzymes in the production of prostaglandin E2 (PGE2), leads to increased excretion of PGE2. Yoshioka and Tohyama (2019) suggested that higher levels of PGE2 in the renal tubules could interfere with water reabsorption, resulting in an increase in urine volume and backpressure on the renal pelvicalyceal space. In adult mice exposed to 2,3,7,8-TCDD, no increase in COX-2 or mPGES-1 expression was seen, urine volume was not affected, and hydronephrosis did not occur (Yoshioka and Tohyama 2019).

Both rats and mice are susceptible to hydronephrosis, and the AhR is necessary in both species. However, while AhR-null mice do not develop 2,3,7,8-TCDD-induced hydronephrosis, the AhR is required for normal development of the rat urinary tract, and AhR-null rats develop abnormalities in the absence of 2,3,7,8-TCDD (Yoshioka and Tohyama 2019).

Cleft palate. AhR binding is also necessary for 2,3,7,8-TCDD-induced cleft palate. Cleft palate was observed in nearly all wild-type ($AhR^{+/+}$) fetuses, in 24–28% of heterozygous AhR mutant genotype ($AhR^{+/-}$) fetuses, and not in any AhR-null fetuses after dosing of maternal mice with 40 µg/kg 2,3,7,8-TCDD on GD 12.5 (Mimura et al. 1997).

Jacobs et al. (2011) showed that, in addition to AhR, all-trans-retinoic acid (atRA) signaling was necessary for the development of cleft palate after 2,3,7,8-TCDD exposure in mice, and that the atRA signaling controlled AhR expression in the nasal mesenchyme. In mice bearing null mutations for

enzymes that synthesize atRA or for retinoic acid receptor G (RARG), gestational exposure to 2,3,7,8-TCDD (30 µg/kg on GD 10.5) did not result in cleft palates in the offspring. Further, in mice lacking the RALDH3 enzyme (the only retinoic acid synthesizing enzyme in the nasopalatal region during the critical developmental period, and transduced by RARG), Ahr mRNA levels were significantly decreased relative to wild-type mice (Jacobs et al. 2011).

Several mechanisms have been proposed to explain the development of cleft palate in animals exposed to 2,3,7,8-TCDD, including: (1) 2,3,7,8-TCDD may induce palatal split after fusion of the palatine processes; (2) 2,3,7,8-TCDD may inhibit the development of the palatine processes so that they do not make contact; or (3) 2,3,7,8-TCDD may inhibit palatal fusion by impairing the apoptosis of epithelial cells and mesenchymal tissues in the medial epithelium seam. Post-fusion split was demonstrated by Yamada et al. (2014), who examined the palatal forms of E14–E18 mouse fetuses after 2,3,7,8-TCDD exposure (40 µg/kg on E12.5). Yamada et al. (2014) observed palatal fusion in 3–18% of fetuses between days E14 and E16, but by E18, all of the palates were separated, suggesting that, in some instances, the split occurred after fusions.

Other studies have shown that 2,3,7,8-TCDD can alter the proliferation, migration, and apoptosis of epithelial and mesenchymal cells involved in palate development. Immunohistochemistry showed that 2,3,7,8-TCDD exposure decreased cell proliferation (bromodeoxyuridine [BrdU]-positive cells) in fetal palatal mesenchyme when pregnant mice were given 64 µg/kg by gavage on GD 10 and sacrificed on GD 13, 14, or 15 (Tao et al. 2020). 2,3,7,8-TCDD also altered apoptosis (terminal deoxynucleotidyl transferase dUTP nick end labeling [TUNEL]-positive cells) in the palatal mesenchyme, but the effect differed by GD. Decreased apoptosis was observed at sacrifice on GD 13, while on GD 15, apoptosis was increased by 2,3,7,8-TCDD exposure, and no difference from control was observed on GD 14 (Tao et al. 2020). In an *in vitro* study, Chen et al. (2020) compared the effects of 2,3,7,8-TCDD on primary epithelial and mesenchymal cells from GD 14 mouse embryo palatal tissue. At a lower exposure level (10 nmol/L), 2,3,7,8-TCDD increased cell proliferation and migration in mesenchymal cells, while decreasing epithelial cell proliferation with no effect on motility (Chen et al. 2020). At a higher exposure level (100 nmol/L), 2,3,7,8-TCDD exposure resulted in decreased proliferation of both cell types, decreased motility of mesenchymal cells, and increased apoptosis of mesenchymal cells (with no effect on epithelial cell motility or apoptosis). The study authors proposed that the mechanism for cleft palate formation by 2,3,7,8-TCDD may differ with dose, consistent with the observed dose-dependence seen *in vitro*.

Male reproductive tract development. Johnson et al. (2020) outlined a proposed adverse outcome pathway for effects of 2,3,7,8-TCDD on the developing male reproductive tract via influence on the pituitary. In this proposed scheme, absorption of 2,3,7,8-TCDD into the fetal pituitary and testis leads to binding and activation of the AhR, which triggers alterations in intracellular signaling pathways in the pituitary that result in reductions in the secretion of LH and FSH. Decreased LH secretion reduces the expression of steroidogenic genes and subsequently the production of androgens in Leydig cells. In the testes, AhR is proposed to downregulate the expression of cholesterologenic genes in Leydig cells, which also reduces the production of androgens. Coupled with a decrease in FSH secretion, the diminished production of androgens leads to impaired proliferation of Sertoli cells, which are necessary for spermatogenesis: the result is decreased sperm production (Johnson et al. 2020).

Transcriptomic studies in male rats exposed to 2,3,7,8-TCDD *in utero* have shown effects of exposure on the expression of pituitary hormone genes. Takeda et al. (2014) observed decreases in LH subunit β [*Lhb*] mRNA in rat offspring exposed *in utero* to 1 μg/kg 2,3,7,8-TCDD on GD 15 and removed on GD 20, GD 21, or PND 0. Johnson et al. (2020) reported decreased pituitary expression of Fshb, but not Lhb in GD 20 male fetuses after *in utero* exposure to 6 or 10 μg/kg on GDs 8–20 or 10 μg/kg on GD 15. Testicular expression of inhibin subunit alpha (*Inha*), a glycoprotein that suppresses FSH secretion, was also decreased at the same doses (Johnson et al. 2020).

2,3,7,8-TCDD exposure during gestation leads to feminization of sexual behavior in male offspring. Mably et al. (1992b) suggested that the demasculinization/feminization of sexual behavior might result from impaired sexual differentiation of the central nervous system, which is dependent on the presence of androgens during early development. However, Bjerke et al. (1994b) observed no effects of 2,3,7,8-TCDD exposure on the volume of the sexually dimorphic nucleus in the preoptic area of the hypothalamus or on the sexual differentiation of ER concentrations in brain nuclei, which exhibit sexual dimorphism, suggesting that the 2,3,7,8-TCDD-induced alterations in sexual behavior were not due to 2,3,7,8-TCDD acting as an estrogen antagonist or altering ER capacities of hypothalamic nuclei. More recently, Del Pino Sans et al. (2016) showed that exposure of male pups to 2,3,7,8-TCDD via lactation (maternal exposure on PND 1) resulted in a significant increase in the number of gamma-aminobutyric acid (GABA)/glutamate neurons in the anteroventral periventricular nucleus of the brain (compared to untreated male pups). During normal development of male pups, these estradiol-sensitive dual-phenotype neurons are lost, preventing them from responding to estradiol signals to induce the female LH surge release pattern. Exposure to 2,3,7,8-TCDD via lactation prevented the loss of these neurons in male pups and resulted in GABA/glutamate neuron content in the anteroventral periventricular nucleus (AVPV)

more similar to female pups. Del Pino Sans et al. (2016) also observed that 2,3,7,8-TCDD exposure downregulated the expression of *cugpbp2* (CUG triplet repeat, ribonucleic acid [RNA] binding protein 2). This gene encodes a protein that is proapoptotic, may be involved in signaling sexual differentiation of neural structures, and is usually upregulated in the AVPV of males.

Takeda et al. (2014) demonstrated that direct injection of equine chorionic gonadotropin (eCG, a hormone that mimics LH) into rat fetuses reversed the inhibition of masculine sexual behavior induced by 2,3,7,8-TCDD. When evaluated at sexual maturity, male rats exposed *in utero* to 2,3,7,8-TCDD exhibited reduced mount frequency and prolonged latency to mount, while those receiving eCG 2 days after maternal 2,3,7,8-TCDD exposure on GD 15 exhibited behavior similar to controls (not treated with 2,3,7,8-TCDD) (Takeda et al. 2014). This finding suggests that the effects of 2,3,7,8-TCDD on sexual behavior may stem from reductions in LH or gonadotropin-releasing hormone (GnRH), which stimulates the production of LH.

These studies also showed that 2,3,7,8-TCDD exposure alters the testicular expression of several genes important to steroidogenesis (including steroidogenic acute regulatory protein [*Star*], scavenger receptor class B member 1 [*Scarb1*], *Cyp17a1*, and *Cyp11a1*). Administration of 1 µg/kg 2,3,7,8-TCDD on GD 15 to pregnant Wistar rats resulted in decreased mRNA levels of *Star* and *CYP17* in the testes of offspring removed between GD 19 and PND 2 (Takeda et al. 2014). Similarly, repeated exposures of maternal rats to doses of 6 or 10 µg/kg on GDs 8–20 resulted in decreased mRNA levels of *Star*, *Cyp17a1*, *Cyp11a1*, and *Scarb1* mRNA in fetal testes collected on GD 20 (Johnson et al. 2020). A single 10 µg/kg dose on GD 15 resulted in decreases in *Star* and *Scarb1* expression, but not *Cyp17a1* or *Cyp11a1* (Johnson et al. 2020). In contrast to these results, steroidogenesis measured by testosterone production and expression of *Star* was not impacted by 2,3,7,8-TCDD exposure in cultures of primary mouse Leydig cells (Naville et al. 2011).

Abnormal prostate development (smaller dorsolateral and anterior prostate, fewer main ducts and ductal tips, and agenesis or smaller size of ventral prostate) has been demonstrated in mice exposed to 2,3,7,8-TCDD *in utero* or during lactation (Yoshioka and Tohyama 2019). Like other effects of 2,3,7,8-TCDD, AhR expression is necessary for effects on the developing prostate; AhR-null mice exhibit resistance to prostate abnormalities. The role of AhR in 2,3,7,8-TCDD-induced prostate effects is not simple, however, because a functional AhR is required for normal development of the prostate. There is some evidence that AhR-mediated changes in the Wnt/β-catenin signaling pathway may be involved in ventral prostate agenesis mediated by 2,3,7,8-TCDD. Specifically, organ culture experiments showed

that 2,3,7,8-TCDD-induced reductions in prostatic buds can be reversed by treatment with an antibody against Wnt5a (Yoshioka and Tohyama 2019).

Developmental neurotoxicity. *In utero* and lactational exposure to 2,3,7,8-TCDD has been associated with neurobehavioral effects in laboratory rodents. Efforts to investigate the mechanisms underlying these changes have been focused on neuromorphology, GABA/glutamate neurotransmission, and gene expression. Kimura et al. (2015) showed that 14-day-old offspring of pregnant mice given 0.6 or 3.0 μg/kg 2,3,7,8-TCDD on GD 12.5 exhibited altered dendritic branch lengths in pyramidal neurons of the hippocampal CA1 and BLA regions. Dendritic branch length differences were not seen in groups of offspring evaluated at 16 months of age; however, at this time point, dendritic spine density in the hippocampal CA1 was significantly decreased in treated compared with control offspring. Excitatory synapses expressing glutamate receptors occur in dendritic spines and are important in neuronal transmission; furthermore, decreased spine density is thought to be involved in memory impairments (Kimura et al. 2015).

Studies in neonatal rats have suggested that 2,3,7,8-TCDD may alter GABA and glutamate neurotransmission in the developing brain. In cerebral cortical neurons obtained from rat pups treated *in utero* on GD 18, both basal and potassium-evoked glutamate transmission were reduced, as was cellular uptake of ^{3}H glutamate (Tomasini et al. 2012). This effect was seen in cells obtained from 1-day-old rats and also in cerebral cortical slices from 14- and 60-day-old rats, indicating the persistence of the change. Nguyen et al. (2013b) treated rats with 2,3,7,8-TCDD during gestation and analyzed the numbers of parvalbumin (PV)- and calbindin (Calb)-immunoreactive neurons (GABAergic neurons) in the brains of the offspring at 14 weeks of age. The effects of 2,3,7,8-TCDD varied by sex of the pups and by region of the brain. Increases in the numbers and sizes of PV-immunoreactive neurons were noted in the medial prefrontal cortex of female pups, but not male pups. In exposed offspring of both sexes, decreases in the numbers of immunoreactive neurons were observed in the basolateral amygdala (PV-immunoreactive only) and hippocampus (both PV- and Calb-immunoreactive). In the superior colliculus, decreases in PV-immunoreactive neurons were seen in both sexes, while only females exhibited a decrease in Calb-immunoreactive neurons (Nguyen et al. 2013b). The study authors suggested that impaired functioning of GABAergic neurotransmission could be a factor in the neurobehavioral effects of 2,3,7,8-TCDD.

Kimura et al. (2016) identified two genes upregulated in the olfactory bulb of neonatal mice treated *in utero* under the same regimen. These genes, *Sema3b* and *Sema3g*, which encode proteins that control axonal projections, were upregulated in groups sacrificed on PNDs 3, 7, and 14. The study authors showed that these genes were selectively upregulated in the brain; expression of these genes in the kidney, liver, lung, and spleen was not affected by exposure (Kimura et al. 2016). The study authors noted that the olfactory bulb, along with the hippocampus and amygdala, has been shown to be involved in behavioral changes.

In microarray analysis subsequently confirmed with reverse transcriptase polymerase chain reaction (RT-PCR), Mitsui et al. (2011) observed upregulation of the chemokine genes *Cxcl4* and *Cxcl7* in GD 18.5 whole brains of both male and female mice. *In situ* hybridization was used to determine that the *Cxcl4* mRNA was located on the surface of the cerebral cortex (Mitsui et al. 2011). Mitsui et al. (2011) noted that chemokines in the brain have been suggested to play roles in neuronal regeneration and apoptosis, hippocampal structure formation, blood-brain barrier disruption, and disorders of the central nervous system.

Using an *in vitro* blood:brain barrier model, Miyazaki et al. (2016) showed that 2,3,7,8-TCDD exposure prior to adult developmental function of the barrier resulted in increased permeability as measured by transendothelial electrical resistance (TEER), as well as decreased expression of the tight junction proteins ZO-1 and claudin-5. These effects were shown to be mediated by suppressed expression of glial cell line-derived neurotrophic factor (GDNF), as the effects were mitigated when exogenous GDNF was added to the culture medium (Miyazaki et al. 2016).

2.18 OTHER NONCANCER

No data were located on other noncancer effects in humans or animals following inhalation, oral, or dermal exposure to CDDs.

2.19 CANCER

The carcinogenicity of CDDs has been evaluated in a number of cohorts of workers at chlorophenoxy herbicide or trichlorophenol manufacturing facilities and phenoxy herbicide applicators, Vietnam War veterans exposed to Agent Orange, Seveso residents, communities living near municipal incinerators, and the general population. Meta-analysis of the occupational exposure cohorts has found increased risks of all cancers associated with serum CDD TEQ levels. IARC concluded that there was consistent evidence of associations between CDDs and several specific cancer types: lung cancer, soft tissue sarcoma, and non-Hodgkin lymphoma.

Several animal studies have evaluated the carcinogenicity of 2,3,7,8-TCDD and found increases in several tumor types including hepatocellular carcinoma, thyroid follicular cell adenoma, squamous cell carcinoma in the lungs, squamous cell carcinoma in hard palate and tongue, and gingival squamous cell carcinoma in oral mucosa. Hepatocellular carcinomas were also observed in mice orally exposed to a mixture of HxCDD congeners or 2,7-DCDD.

Epidemiological Studies. The carcinogenicity of 2,3,7,8-TCDD in humans has been assessed in numerous case-control and mortality cohort studies of chemical manufacturing and processing workers and phenoxy herbicide and chlorophenols applicators, Vietnam War veterans exposed to Agent Orange, residents of Seveso exposed to high levels of 2,3,7,8-TCDD resulting from an industrial accident, communities living near a municipal incinerator, and the general population. A major weakness in many of these studies is the lack of adequate exposure data. Most studies did not measure exposure levels or 2,3,7,8-TCDD body burdens; rather, surrogates of exposure such as exposure to chemicals contaminated with 2,3,7,8-TCDD or chloracne were used to identify subjects likely exposed to 2,3,7,8-TCDD. Another major weakness of most of the human cancer data is concomitant exposure to other compounds. The focus of this discussion on the carcinogenic potential of 2,3,7,8-TCDD and other CDDs will be on studies that have documented exposure by measuring blood levels or in which exposure can be reasonably presumed.

Increases in the overall cancer risk were observed in a number of large cohort mortality studies of chemical manufacturing workers and phenoxy herbicide applicators; these studies are briefly summarized in Table 2-31. Most of the subjects in these studies were males working in chlorophenoxy herbicide or trichlorophenol manufacturing facilities.

Table 2-31. Cancer Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Occupational			
Becher et al. 1996 Retrospective cohort mortality study of 2,479 workers at four phenoxy acid herbicides and chlorophenols production facilities in Germany (1,144 male workers in subcohort 1); one facility was also examined by Manz et al. (1991)	2,3,7,8-TCDD blood level: 3–2,252 pg/g lipid in subcohort 1 (samples from 120 workers)	All cancer deaths	↔, whole cohort ↑, subcohort 1
		Lung cancer deaths	↑, whole cohort ↑, subcohort 1
		Lymphatic and hematopoietic cancer deaths	↔, whole cohort ↑, subcohort 1
		Non-Hodgkin lymphoma deaths	↑, whole cohort ↑, subcohort 1
		Leukemia	↔, subcohort 1
Boers et al. 2010 Retrospective cohort mortality study of 1,021 male workers (in factory A) in the Netherlands; follow-up to the Bueno de Mesquita et al. (1993) and Hooiveld et al. (1998) studies	Not reported	All cancer deaths	↔
		Respiratory cancer deaths	↔
		Lymphatic and hematopoietic cancer deaths	↔
		Non-Hodgkin lymphoma	↔
		Leukemia	↔
Boers et al. 2012 Retrospective cohort study; follow-up to the Bueno de Mesquita et al. (1993), Hooiveld et al. (1998), and Boers et al. (2010) studies	Predicted serum 2,3,7,8-TCDD level: high-exposure group ≥20.1 pg/g	All cancer deaths	↔, high exposure
		Respiratory cancer deaths	↔, high exposure
		Lymphatic and hematopoietic cancer deaths	↔
		Non-Hodgkin lymphoma deaths	↑, high exposure
		Leukemia	↔
Bueno de Mesquita et al. 1993 Retrospective cohort mortality study of 549 male workers at 2,4,5-T production facility (factory A) in the Netherlands	Not reported	All cancer deaths	↔
		Respiratory tract cancer deaths	↔
		Non-Hodgkin lymphoma	↔
		Hodgkin lymphoma	↔

Table 2-31. Cancer Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Coggon et al. 2015 Retrospective cohort mortality study of 8,036 male workers at five phenoxy herbicide facilities or were contract sprayers in the United Kingdom (facilities part of the IARC cohort)	Workers ever potentially exposed to phenoxy acids	All cancer deaths	↔
		Soft tissue sarcoma	↔
		Hodgkin lymphoma	↔
		Non-Hodgkin lymphoma	↑
		Leukemia	↔
Collins et al. 2016 Retrospective cohort study of 1,615 trichlorophenol and 2,4,5-T production workers in the United States	Mean serum 2,3,7,8-TCDD levels: 16 pg/g; high-exposure group: 1,500–112,272 pg/g-months	All cancer deaths	↔, high exposure
		Lung cancer deaths	↔, high exposure
		Non-Hodgkin lymphoma deaths	↔, high exposure
Eriksson et al. 1981 Case-control study of 110 cases with soft tissue sarcoma and 219 controls in Sweden	Exposure to phenoxyacetic acid herbicides and/or chlorophenols	Soft tissue sarcoma	↔, high exposure
Eriksson et al. 1990 Case-control study of 237 cases with soft tissue sarcoma and 237 controls in Sweden	Exposure to phenoxyacetic acid herbicides and/or chlorophenols	Soft tissue sarcoma	↑
Fingerhut et al. 1991 Retrospective mortality study of 5,172 workers at 12 facilities in the United States involving exposure to chemicals contaminated with 2,3,7,8-TCDD (NIOSH cohort)	Mean 2,3,7,8-TCDD serum level: 233 pg/g lipid (range of 2–3,400 pg/g) (samples from 253 workers at two facilities)	All cancer deaths	↑
		Respiratory tract cancer deaths	↔
		Lymphatic and hematopoietic cancer deaths	↔
		Soft-tissue sarcoma deaths	↑
		Non-Hodgkin lymphoma deaths	↔
		Hodgkin lymphoma deaths	↔

Table 2-31. Cancer Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Flesch-Janys et al. 1998 Retrospective mortality study of 1,189 male workers at facility producing trichlorophenol, 2,4,5-T, and other herbicides contaminated with 2,3,7,8-TCDD in Germany (follow-up to Manz et al. 1991 study)	Mean serum 2,3,7,8-TCDD serum level: 108.6 pg/g lipid (samples from 275 workers)	All cancer deaths	↑
		Lung cancer deaths	↑
		Lymphatic and hematopoietic cancer deaths	↑
Hardell and Eriksson 1988 Case-control study of 54 males with soft tissue sarcoma (18 alive and 36 dead), 311 population-based referents (208 alive and 103 dead) and 179 cancer referents (73 alive and 106 dead) in Sweden	Employment in industries associated with phenoxyacetic acids and chlorophenols (forestry, agriculture, horticulture, carpentry, saw mills)	Soft tissue sarcoma	↑,exposure to phenoxyacetic acids ↔, exposure to chlorophenols
Hardell and Sandström 1979 Case-control study of 52 males with soft tissue sarcoma and 208 controls in Sweden	Exposure to phenoxyacetic acids or chlorophenols	Soft tissue sarcoma	↑,exposure to phenoxyacetic acids ↑, exposure to chlorophenols
Hardell et al. 1995 Meta-analysis of Eriksson et al. (1981, 1990), Hardell and Eriksson (1988), and Hardell and Sandström (1979) studies	Phenoxyacetic acid herbicide or chlorophenol exposure	Soft-tissue sarcoma	↑
Hooiveld et al. 1998 Retrospective cohort mortality study of 549 male workers at 2,4,5-T production facility in the Netherlands (follow-up to Bueno de Mesquita et al. 1993 study)	Mean 2,3,7,8-TCDD serum levels: 96.3 pg/g lipid in 14 workers exposed to high levels during an accident and 16.6 in 17 workers not exposed during accident	All cancer deaths	↑
		Lung cancer deaths	↔
		Non-Hodgkin lymphoma deaths	↔
		Hodgkin lymphoma	↔
		Leukemia	↔

Table 2-31. Cancer Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Kogevinas et al. 1995 Nested case-control study of 11 cases of soft-tissue sarcoma (55 controls) and 32 cases of non-Hodgkin lymphoma (158 controls)	Phenoxy herbicide, chlorophenols, CDD/CDF, or 2,3,7,8-TCDD exposure	Soft-tissue sarcoma	↑, any phenoxy herbicide ↔, chlorophenols ↑, CDD/CDF ↔, 2,3,7,8-TCDD
		Non-Hodgkin lymphoma	↔, any phenoxy herbicide ↔, chlorophenols ↔, CDD/CDF ↔, 2,3,7,8-TCDD
Kogevinas et al. 1997 Retrospective mortality study of the IARC cohort expanded to 21,863 phenoxy herbicide or chlorophenol workers (20,851 males and 1,012 females) in 36 facilities in 12 countries; 13,831 workers exposed to phenoxy herbicides contaminated with 2,3,7,8-TCDD or higher chlorinated dioxins	Mean serum 2,3,7,8-TCDD levels in 573 workers in 10 cohorts: 17–401.7 pg/g lipid	All cancer deaths	↑, males only ↔, females only
		Lung cancer deaths	↔, phenoxy herbicide workers
		Soft-tissue sarcoma deaths	↑, phenoxy herbicide workers
		Non-Hodgkin lymphoma deaths	↔, phenoxy herbicide workers
Mannetje et al. 2005 Cross-sectional study of a total of 813 producers and 699 sprayers classified as exposed to dioxin and phenoxy herbicides in a New Zealand study	Job codes were used for exposure evaluation	All cancer deaths	↔, producers, sprayers
		Respiratory cancer deaths	↔, producers, sprayers
		Non-Hodgkin lymphoma deaths	↔, producers, sprayers
Manuwald et al. 2012 Retrospective cohort mortality study of 1,589 workers at an herbicide and insecticide (including 2,4,5-T) production facility in Germany; follow-up to the Manz et al. (1991), Flesch-Janys et al. (1998), and Becher et al. (1996) studies	Median serum cumulative job exposure level: 77.4 pg/g lipid for men and 19.5 ppt for women	All cancer deaths	↑, men ↔, women
		Respiratory cancer deaths	↑, men
		Lymphatic and hematopoietic tissue cancer deaths	↔, men, women
		Non-Hodgkin lymphoma	↔

Table 2-31. Cancer Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Manz et al. 1991 Retrospective cohort mortality study of 1,583 workers (1,184 males and 399 females) at a facility producing trichlorophenol, 2,4,5-T, and other herbicides contaminated with 2,3,7,8-TCDD in Germany	Mean serum 2,3,7,8-TCDD level: 296 pg/g lipid in 37 workers in high- exposure group and 83 pg/g lipid in 11 workers in medium-/low-exposure groups	All cancer deaths, compared to gas worker reference cohort	↑, total cohort ↑, high exposure cohort
		Lung cancer deaths, compared to gas worker reference cohort	↑, total cohort
McBride et al. 2009 Retrospective cohort mortality study of 1,754 workers at a phenoxy herbicide production facility in New Zealand	Not measured	All cancer deaths	↔
		Respiratory tract cancer deaths	↔
		Lymphatic and hematopoietic cancer deaths	↔
		Non-Hodgkin lymphoma deaths	↔
		Hodgkin lymphoma deaths	↔
		Soft tissue sarcoma deaths	↔
McBride et al. 2018 Retrospective cohort mortality study of 1,134 workers at a facility producing 2,4,5-trichlorophenol in New Zealand; follow-up to the McBride et al. (2009) study	Mean serum 2,3,7,8-TCDD level in samples from 241 workers in 2005: 9.9 pg/g lipid	All cancer deaths	↔
		Lung cancer deaths	↔
		Lymphatic and hematopoietic cancer deaths	↔
		Non-Hodgkin lymphoma deaths	↔
		Hodgkin lymphoma deaths	↔
Ott and Zober 1996 Retrospective cohort study; follow-up to the Zober et al. (1990) study	Half-life extrapolated 2,3,7,8-TCDD body burdens of <0.1, 0.1–0.99, and ≥1 µg/kg body weight	All cancer deaths	↔, high body burden group ↑, high body burden and 20-year lag
		Respiratory cancer deaths	↔, high body burden group ↑, high body burden and 20-year lag
		Lymphatic or hemopoietic tissue cancer deaths	↔, high body burden group

Table 2-31. Cancer Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Saracci et al. 1991 Retrospective mortality study of the IARC cohort of 18,875 in 20 facilities in 10 countries	Exposed workers sprayed chlorophenoxy herbicides or worked in factories producing chlorophenoxy herbicides or chlorinated phenols; probably exposed workers worked at facilities producing PCP or 2,4-D, 2,4-(dichlorophenoxy)butanoic acid, (4-chloro-2-methyl-phenoxy)acetic acid, and (4-chloro-2-methyl)propanoic acid	All cancer deaths	↔, exposed workers
		Trachea, bronchus, and lung cancer deaths	↔, exposed workers ↑, probably exposed workers
		Hodgkin lymphoma deaths	↔, exposed workers
		Soft-tissue sarcoma deaths	↑, exposed workers
Steenland et al. 1999 Retrospective mortality study of U.S cohort of 5,132 workers; follow-up to the Fingerhut et al. (1991) study	Cumulative exposure score	All cancer deaths	↑, total cohort
Zober et al. 1990 Retrospective cohort mortality study of 247 male workers exposed to 2,3,7,8-TCDD during an accident in a German 2,4,5-TCP production facility	Median serum 2,3,7,8-TCDD level: 24.5 pg/g lipid in 11 highly exposed workers	All cancer deaths	↔, highly exposed ↔, workers with chloracne ↑, workers with chloracne and exposure lagged 20 years
		Trachea, bronchus, lung cancer deaths	↔, highly exposed ↔, workers with chloracne
Vietnam veterans and Operation Ranch Hand veterans			
USAF 1991 Cross-sectional report of 866 Operation Ranch Hand personnel and a comparison group of 1,198	Not reported	All malignant cancers	↔
		Hodgkin lymphoma	↔
		Non-Hodgkin lymphoma	↔
		Soft tissue sarcoma	↔
Wolfe et al. 1985 Retrospective study of 1,278 Operation Ranch Hand personnel	Not reported	All malignant cancers	↔

Table 2-31. Cancer Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Yi and Ohrr 2014 Retrospective cohort study of Vietnam War veterans participating in the Korean Veterans Health Study (n=180,251 men)	Exposure to Agent Orange evaluated using data on the proximity of the military unit to area sprayed with Agent Orange	All cancers	↑
		Non-Hodgkin lymphoma	↔
		Hodgkin lymphoma	↔
		Soft tissue sarcoma	↔
		Lymphoid leukemia	↔
Seveso, Italy			
Bertazzi et al. 1993 Retrospective cohort study of adults living in Seveso aged 20–74 years (n= 724 in zone A, n=4,824 in zone B, and n=31,647 in zone R; referent population of 181,579)	Not measured	All cancers	↔, zone A, B, or R
		Soft-tissue sarcoma	↑, zone R, males
Bertazzi et al. 1997 Retrospective cohort mortality study of Seveso residents (n=805 in zone A, n=5,943 in zone B, and 38,625 in zone R); follow-up to Bertazzi et al. (1993) study	Not measured	All cancer deaths	↔, zone A, B, or R
		Lymphohemopoietic cancer deaths	↑, zone B, males
		Leukemia deaths	↑, zone B, males
Bertazzi et al. 2001 Retrospective cohort mortality study of Seveso residents (n=804 in zone A and n=5,941 in zone B); follow-up to the Bertazzi et al. (1993, 1997) studies	Not reported	All cancer deaths	↔
		Lung cancer deaths	↔
		Lymphatic and hemopoietic cancer deaths	↔, zone A ↑, zone B
		Non-Hodgkin lymphoma deaths	↑, 15–20 since first exposure
Consonni et al. 2008 Retrospective cohort mortality study of Seveso residents (n=804 in zone A, n=5,941 in zone B, and n=36,623 in zone R)	Not reported	All cancer deaths	↔
		Lung cancer deaths	↔
		Lymphatic and hematopoietic tissue cancer deaths	↑, zone B
		Non-Hodgkin lymphoma deaths	↑, zone A

Table 2-31. Cancer Effects in Humans Exposed to TCDD/CDDs

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Pesatori et al. 2009 Retrospective cohort study of Seveso residents (n=723 in zone A, n=4,821 in zone B, and n=31,643 in zone R)	Serum 2,3,7,8-TCDD in samples collected from some participants in 1976: 447.0 pg/g (n=296), 94.0 (n=80), and 48.0 (n=48) in zones A, B, and R, respectively	All cancers	↔, zone A
		Lung cancer	↔, zone A
		Lymphatic and hematopoietic cancers	↔, zone A ↑, zone B
		Non-Hodgkin lymphoma	↔, zone A
		Lymphatic leukemia	↔, zone A
Warner et al. 2011 Retrospective cohort study of female Seveso residents (n=981) residing in zone A or B at the time of the accident	Median 2,3,7,8-TCDD serum level: 55.9 pg/g lipid	All cancers	↑, per 10-fold increase in 2,3,7,8-TCDD serum level
Communities living near a municipal incinerator			
Floret et al. 2003 Case-control study of 222 residents in France living near a solid waste incinerator with non-Hodgkin lymphoma and 2,220 controls	Modeled CDD/CDF ground level concentration; high-exposure group: 0.0004–0.0016 pg/m^3	Non-Hodgkin lymphoma	↑, high dioxin exposure group
Viel et al. 2011 Case-control study of 34 men and women with non-Hodgkin lymphoma and 34 controls living near a solid waste incinerator in France	Serum CDD/CDF levels (values not reported)	Non-Hodgkin lymphoma	↑, CDD TEQ

↑ = association; ↓ = inverse association; ↔ = no association; 2,4-D = 2,4-dichlorophenoxyacetic acid; 2,4,5-T = 2,4,5-trichlorophenoxyacetic acid; CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; PCP = pentachlorophenol; TCDD = tetrachlorodibenzo-*p*-dioxin; TEQ = toxic equivalency

The occupational exposure database consists of several large cohort studies, which are presented in Table 2-32. Mixed results were found for associations between 2,3,7,8-TCDD exposure and deaths from all cancers. Associations were found in the some of the cohorts (Becher et al. 1996; Fingerhut et al. 1991; Flesch-Janys et al. 1998; Hooiveld et al. 1998; Kogevinas et al. 1997; Manuwald et al. 2012; Manz et al. 1991; Ott and Zober 1996; Steenland et al. 1999; Zober et al. 1990) and no associations were found in other cohorts (Boers et al. 2010, 2012; Bueno de Mesquita et al. 1993; Collins et al. 2016; McBride et al. 2009, 2018; Saracci et al. 1991). Steenland et al. (2001) reported a dose-response relationship between estimated cumulative serum 2,3,7,8-TCDD levels and cancer mortality for the NIOSH cohort. A meta-analysis of the NIOSH cohort (Fingerhut et al. 1991; Steenland et al. 1999), German accident cohort (Ott and Zober 1996; Zober et al. 1990), and German cohort (Becher et al. 1996; Flesch-Janys et al. 1998) was conducted by Crump et al. (2003). The analysis found an increased risk of all cancer deaths (SMR=117, 95% CI: 104–130); a linear model predicted an increased relative risk of $6.3x10^{-6}$ (95% CI: $8.8x10^{-7}$–$1.3x10^{-5}$) per 1 ppt-year of cumulative lipid concentration.

Table 2-32. Occupational Cohort Studies Examining the Carcinogenicity of Chlorinated Dibenzo-*p*-Dioxins (CDDs)

Cohort	References
National Institute for Occupational Safety and Health (NIOSH) cohort	Fingerhut et al. 1991; Steenland et al. 1999
U.S. cohort	Collins et al. 2016
German cohort	Becher et al. 1996; Flesch-Janys et al. 1998; Manuwald et al. 2012; Manz et al. 1991
German accident cohort	Ott and Zober 1996; Zober et al. 1990
Dutch cohort	Boers et al. 2010, 2012; Bueno de Mesquita et al. 1993; Hooiveld et al. 1998
New Zealand cohort	McBride et al. 2009, 2018
International Agency for Research on Cancer (IARC) multi-nation cohort	Kogevinas et al. 1997; Saracci et al. 1991

Studies of Seveso residents have not found increased risk of all cancers (Bertazzi et al. 1993, 1997, 2001; Consonni et al. 2008). However, the most recent study of this cohort (Warner et al. 2011) did find an increase in all cancers among women. A number of studies have looked at cancer incidences among Vietnam veterans to determine if exposure to Agent Orange with its 2,3,7,8-TCDD contamination resulted in a higher cancer risk. Many of these studies compared cancer incidences in Vietnam veterans to Vietnam-era veterans stationed outside of Vietnam. Limitations of this study design include that not all veterans in Vietnam were exposed to Agent Orange and exposure was lower than that of occupational workers. CDC (1988) found that the levels of 2,3,7,8-TCDD in Vietnam veterans were usually similar to

a comparison group. Thus, studies that examined cancer incidences in "Vietnam veterans" may not be adequate to assess the carcinogenicity of 2,3,7,8-TCDD. Two studies of Operation Ranch Hand personnel did not find increases in the risk of all malignant cancers (USAF 1991; Wolfe et al. 1985); a third study of veterans stationed near areas sprayed with Agent Orange found an increased risk of all cancers (Yi and Ohrr 2014).

A large number of studies have evaluated possible associations between CDD exposure and specific tumor types. The National Academy of Sciences (NAS) review of the health of effects in Vietnam veterans from exposure to herbicides concluded that there was sufficient evidence of an association between the chemicals of interest (2,4-D, 2,4,5-T, picloram, dimethylarsinic acid, and 2,3,7,8-TCDD) and soft tissue sarcomas, B-cell lymphomas (Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, hairy cell leukemia), and monoclonal gammopathy of undetermined significance (NAS 2018). IARC (2012) concluded that the most consistent evidence was for lung cancer, soft tissue sarcoma, and non-Hodgkin lymphoma. Increases in lung (or respiratory tract) cancer have been observed in the German cohort and German accident cohort, but not in the Dutch, U.S., NIOSH, IARC, or the New Zealand cohorts; see Tables 2-31 and 2-32 for citations. Increases in lung cancer risk was not observed in the Seveso cohort (Bertazzi et al. 2001; Consonni et al. 2008; Pesatori et al. 2009).

The possible association between 2,3,7,8-TCDD exposure and soft tissue sarcoma was first suggested by the results of a series of case-control studies that found increases in the risk of soft-tissue sarcomas in Swedish agricultural, forestry, and horticultural workers (Eriksson et al. 1981, 1990; Hardell and Eriksson 1988; Hardell and Sandström 1979), workers involved in manufacturing and application of phenoxy herbicides (Kogevinas et al. 1995), and New Zealand farmers (Smith et al. 1984). Increased risk of soft tissue sarcomas has also been reported in the NIOSH cohort (Fingerhut et al. 1991), IARC cohort (Kogevinas et al. 1997; Saracci et al. 1991), and Seveso cohort (Bertazzi et al. 1993); it has not been found in Operation Ranch Hand veterans (USAF 1991) or Korean Vietnam veterans (Yi and Ohrr 2014).

Increases in the risk of several types of lymphohematopoietic cancers have been associated with 2,3,7,8-TCDD exposure. Increases in deaths or incidences of non-Hodgkin lymphoma have been reported in the German cohort (Becher et al. 1996), Dutch cohort (Boers et al. 2012), U.K. cohort (Coggon et al. 2015), and Seveso cohort (Bertazzi et al. 2001; Consonni et al. 2008); it was also found in two case-control studies of residents living near a solid waste incinerator (Floret et al. 2003; Viel et al. 2011). No increases in non-Hodgkin lymphoma risk were found in the U.S. cohort (Collins et al. 2016), NIOSH cohort (Fingerhut et al. 1991), IARC cohort (Kogevinas et al. 1995, 1997), New Zealand cohort

(Mannetje et al. 2005; McBride et al. 2009), German cohort (Manuwald et al. 2012), or Vietnam veterans (USAF 1991; Yi and Ohrr 2014). No increases in Hodgkin lymphoma were found in large occupational exposure studies (Bueno de Mesquita et al. 1993; Coggon et al. 2015; Fingerhut et al. 1991; Hooiveld et al. 1998; McBride et al. 2009, 2018) or in Operation Ranch Hand veterans (USAF 1991).

A meta-analysis of five studies of workers involved in chlorophenol pesticide production found a risk of prostate cancer deaths (standard mortality rate of 1.2, 95% CI of 1.02–1.42) (Kabir et al. 2018).

2,3,7,8-TCDD—Animal Studies. The carcinogenicity of 2,3,7,8-TCDD has been demonstrated in several experiments in animals; the cancer sites include the liver, lungs, oral cavity, and thyroid. A summary of these studies is presented in Table 2-33. Hepatocellular carcinomas and neoplastic nodules have been observed in rats and mice chronically exposed to ≥0.01 µg/kg/day (Della Porta et al. 1987; Kociba et al. 1978; NTP 1982b, 2006; Toth et al. 1979). In Sprague-Dawley rats, females were more affected than males (Kociba et al. 1978). Cholangiocarcinomas have also been observed in female Sprague-Dawley rats exposed to 0.071 µg/kg/day for 2 years (NTP 2006). In the thyroid, follicular cell adenomas were observed in rats and mice (NTP 1982b) and c-cell adenomas were reported in rats (NTP 2006). Lung lesions in rats include squamous cell carcinoma and cystic keratinizing epithelioma (Kociba et al. 1978; NTP 2006). Chronic-duration oral exposure also resulted in squamous cell carcinoma in the hard palate or nasal turbinates and oral mucosa gingiva (Kociba et al. 1978; NTP 2006). NTP (2006) also found a nonsignificant increase in the combined incidence of adenoma or carcinoma in the pancreas in rats exposed to 0.071 µg/kg/day; however, the incidence was higher than historical controls and there was a significant positive trend. The study also found an increased incidence of squamous cell carcinoma of the uterus at 0.032 µg/kg/day, but not at 0.0711 µg/kg/day.

Table 2-33. Carcinogenic Effects in Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, duration	Dose (µg/kg/day)	Tumor type	Reference
Liver			
B6C3 mouse, 1 year	0.36	Hepatocellular carcinomas (males and females) and adenomas (females)	Della Porta et al. 1987
Female Sprague-Dawley rat	0.1	Hepatocellular carcinoma	Kociba et al. 1978
Female Sprague-Dawley rat, 2 years	0.01	Hepatocellular hyperplastic nodules	Kociba et al. 1978

Table 2-33. Carcinogenic Effects in Animals Orally Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

Species, duration	Dose (µg/kg/day)	Tumor type	Reference
Female Osborne-Mendel rat, 2 years	0.071	Neoplastic nodules in liver and hepatocellular carcinoma	NTP 1982b
Male B6C3F1 mouse, 2 years	0.071	Hepatocellular carcinoma	NTP 1982b
Female Sprague-Dawley rat, 2 years	0.071	Hepatocellular adenomas, cholangiocarcinomas	NTP 2006
Swiss mouse, 1year	0.1	Hepatomas and hepatocellular carcinomas	Toth et al. 1979
Thyroid			
Male Osborne-Mendel rat, 2 years	0.0071	Thyroid follicular cell adenoma	NTP 1982b
Female B6C3F1 mouse, 2 years	0.3	Thyroid follicular cell adenoma and histiocytic lymphoma	NTP 1982b
Female Sprague-Dawley rat, 2 years	0.071	c-cell adenoma in thyroid gland	NTP 2006
Lung			
Female Sprague-Dawley rat, 2 years	0.1	Squamous cell carcinoma in lungs	Kociba et al. 1978
Female Sprague-Dawley rat, 2 years	0.071	Cystic keratinizing epithelioma in lungs	NTP 2006
Oral cavity			
Sprague-Dawley rat, 2 years	0.1	Squamous cell carcinoma in hard palate or nasal turbinates	Kociba et al. 1978
Female Sprague-Dawley rat, 2 years	0.071	Gingival squamous cell carcinoma in oral mucosa	NTP 2006

Dermal application of ≥0.036 µg/kg 2,3,7,8-TCDD 3 times/week for 26 weeks (equivalent to 0.015 µg/kg/day) to the shaved skin of groups of 20 female Tg.AC transgenic mice (genetically initiated, tumor promoter-sensitive epidermal tumorigenesis model) resulted in significant increases in the incidence of skin squamous cell papillomas (Wyde et al. 2004); an increase in squamous cell carcinomas was observed at ≥0.052 µg/kg/day. No significant alterations were observed at lower doses (0.0021 or 0.0073 µg/kg/day).

Acute- and intermediate-duration studies in animals investigated the interactions of 2,3,7,8-TCDD with known carcinogens. A single dermal pretreatment of CD-1 mice with 0.01 µg 2,3,7,8-TCDD inhibited the development of skin papillomas otherwise initiated by 7,12-dimethylbenzathracene (DMBA) (Berry et al. 1979). In intermediate-duration experiments, 2,3,7,8-TCDD did not promote skin tumors initiated by

DMBA (Berry et al. 1978, 1979). In contrast, the promoting ability of 2,3,7,8-TCDD at 0.0025 µg/day (and higher), 2 days/week, for 20 weeks, was reported in HRS/J hairless mice following the initiation with N-methyl-N-nitro-N-nitrosoguanidine in intermediate-duration experiments (Hebert et al. 1990; Poland et al. 1982). The effect was not observed in mice heterozygous for the hairless trait (Poland et al. 1982). No ovarian tumors were observed in Sprague-Dawley rats administered 0.125 µg/kg 2,3,7,8-TCDD in corn oil via gavage biweekly for 14, 30, or 60 weeks (Davis et al. 2000); however, in rats administered a single dose of diethylnitrosamine (175 mg/kg, intraperitoneal) and followed by biweekly doses of 2,3,7,8-TCDD for 60 weeks (administered 2 weeks after initiation), there was a significant increase in ovarian tumors. Similarly, no observable tumors were observed in female Sprague-Dawley rats administered 1.25 µg/kg/day 2,3,7,8-TCDD in corn oil biweekly for up to 60 weeks (Walker et al. 2000). Initiation with diethylnitrosamine and biweekly exposure to 1.25 µg/kg/day 2,3,7,8-TCDD for 60 weeks resulted in a non-statistically significant increase in the incidence of liver tumors. In a chronic-duration study, significantly increased incidence of fibrosarcoma of the integumentary system was found in Swiss Webster female mice following dermal exposure to 2,3,7,8-TCDD at 0.005 µg, 3 days/week for 2 years (NTP 1982a).

Initiation with 100 µg DMBA applied to the dorsal shaved skin of male ICR mice followed by application of 0.0025, 0.025, and 0.125 µg 2,3,7,8-TCDD in 100 µL acetone 2 times/week for up to 20 weeks did not result in skin papillomas (Wu et al. 2004).

Other Congeners—Animal Studies. Experiments with other congeners showed that chronic-duration exposure to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD by gavage induced hepatocellular carcinoma, adenoma, and neoplastic nodules at 0.34 µg/kg/day in female Osborne-Mendel rats and at 0.71 µg/kg/day in male B6C3F1 mice (NCI/NTP 1980). Furthermore, chronic-duration exposure to $6.5x10^5$ µg/kg/day of 2,7-DCDD in the feed caused leukemias, lymphomas, hemangiosarcomas, hemangiomas, and dose-related increased incidences of hepatocellular adenomas and carcinomas in male B6C3F1 mice (NCI/NTP 1979). In contrast, no cancer effects were observed following chronic-duration exposure of Osborne-Mendel rats to $5x10^5$ µg/kg/day of 2,7-DCDD (NCI/NTP 1979) in the feed.

Rozman et al. (2005) reported an increase in the prevalence of lung tumors (squamous cell carcinoma) in female Sprague-Dawley rats receiving a single dose of 2.8 mg/kg 1,2,3,4,6,7,8-HpCDD in corn oil; an increased prevalence of liver tumors (hepatocarcinoma and cholangiocarcinoma) was observed at 3.4 mg/kg. Similarly, increases in the prevalence of lung tumors and liver tumors were observed in rats repeatedly exposed to a TWA dose of 0.0065 or 0.012 mg/kg/day, respectively.

Cancer Classification. HHS has classified 2,3,7,8-TCDD as known to be a human carcinogen (NTP 2021). EPA (IRIS 2012) has not established a cancer classification for 2,3,7,8-TCDD. IARC (2012) has determined that 2,3,7,8-TCDD is carcinogenic to humans (Group 1) based on limited evidence in humans and sufficient evidence in animals.

EPA (1987) categorized the mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD as a probable human carcinogen (Group B2) based on sufficient evidence of carcinogenicity in animals. IARC (1997) concluded that other CDDs are not classifiable as to their carcinogenicity in humans (Group 3) based on limited evidence for a mixture of 1,2,36,7,8-HxCDD and 1,2,3,7,8,9-HxCDD in animals and inadequate evidence for 1,2,3,7,8-PeCDD in animals.

Cancer Mechanisms. Information pertaining to the mechanisms of carcinogenicity for CDDs is primarily from studies of 2,3,7,8-TCDD. As with many other effects of 2,3,7,8-TCDD, its carcinogenicity is expected to result from AhR activation. Section 2.21, Mechanisms of Toxicity, provides more information on the interaction between 2,3,7,8-TCDD and the AhR as well as the diversity of gene expression changes and cellular events that ensue from this interaction. This section provides an overview of the proposed mechanism(s) by which 2,3,7,8-TCDD induces carcinogenic effects based on published reviews (Chen et al. 2023; IARC 2012; Knerr and Schrenk 2006; Opitz et al. 2023; Patrizi and Siciliani de Cumis 2018; Schwarz and Appel 2005). Detailed mechanistic explanations are beyond the scope of this profile.

Studies to date have indicated that 2,3,7,8-TCDD does not act as a direct genotoxic carcinogen (see Section 2.20), but acts primarily by perturbing cellular growth, differentiation, and programmed death mechanisms (IARC 2012; NTP 2006). These changes are believed to result from persistent AhR activation due to the long half-life of 2,3,7,8-TCDD in the body (Chen et al. 2023; IARC 2012; Schwarz and Appel 2005). Sustained cell proliferation may increase the frequency of spontaneous mutations, induce the accumulation of epigenetic changes, and promote the growth of initiated cells.

Increases in cell proliferation have been observed in several tissues (including liver and skin), after both *in vivo* and *in vitro* exposure to 2,3,7,8-TCDD (Chen et al. 2023; IARC 2012). While activation of AhR is known to be an initial step leading to proliferation, it is likely that several key events follow from AhR activation. Downstream effects of 2,3,7,8-TCDD-liganded AhR activation include modulation of growth factors, cytokines, hormones, and metabolic pathways related to cell proliferation or differentiation,

including (for example): epidermal growth factor (EGF), vitamin A, tumor necrosis factor-α, interleukin-1-β, gonadotrophin-releasing hormone, testosterone, plasminogen activator inhibitor-2, and many others (Knerr and Schrenk 2006; NTP 2006; see also Section 2.21). 2,3,7,8-TCDD also inhibits cellular apoptosis and senescence (Knerr and Schrenk 2006; NTP 2006; Ray and Swanson 2009; Schwarz and Appel 2005), effects that may foster the clonal expansion of initiated cells.

In addition to its effects on cell growth and proliferation, 2,3,7,8-TCDD is believed to indirectly increase oxidative stress and oxidative DNA damage via prolonged upregulation of metabolic enzymes (IARC 2012). Induction of cytochrome P450 (CYP) can lead to uncoupling of the P40 catalytic cycle, with concomitant production of excess reactive oxygen species (ROS) and oxidative DNA damage (IARC 2012; Knerr and Schrenk 2006; Veith and Moorthy 2018). Increases in oxidative stress, along with DNA damage and mutations, have been observed in rats and mice exposed *in vivo* to 2,3,7,8-TCDD, as well as in *in vitro* studies (IARC 2012; Knerr and Schrenk 2006).

Upregulation of CYPs leads to increased levels of reactive intermediates from the metabolism of both exogenous and endogenous compounds (IARC 2012; Knerr and Schrenk 2006; Veith and Moorthy 2018). For example, estrogen has been shown to markedly increase oxidative DNA damage in the livers of female rats, an effect postulated to result from redox cycling of the CYP-generated estradiol metabolite, 4-hydroxyestradiol (IARC 2012; Knerr and Schrenk 2006). CYP-mediated metabolism of estrogen and the related production of ROS has been proposed as a mechanism for the greater sensitivity of female rats to the hepatocarcinogenic effects of 2,3,7,8-TCDD (IARC 2012; Knerr and Schrenk 2006).

Enhanced metabolism may also perturb retinoid homeostasis in the liver. Exposure to 2,3,7,8-TCDD depleted hepatic stores of retinyl acid in several species, an effect that was demonstrated to depend on intact AhR (Knerr and Schrenk 2006). NTP (2006) noted that disruption of hepatic retinoid homeostasis leads to aberrant differentiation of epithelial cells in the lung to a keratinized squamous phenotype, proposing that this change could progress to squamous metaplasia and cystic keratinizing epitheliomas, a lung tumor observed at increased incidences in rats in their 2-year study.

As reviewed by Patrizi and Siciliani de Cumis (2018) and Opitz et al. (2023), 2,3,7,8-TCDD induces a variety of epigenetic changes that may contribute to its carcinogenic action. Experiments both *in vivo* and *in vitro* have shown that 2,3,7,8-TCDD exposure alters the expression of large non-coding RNAs (lncRNAs) that act as regulators of chromatin remodeling (including DNA methylation and histone modifications). In mice, alterations in DNA methylation (both demethylation and hypermethylation) have

been observed after exposure to 2,3,7,8-TCDD. Finally, histone modifications have been observed in human breast and hepatic cancer cell lines exposed to 2,3,7,8-TCDD (Patrizi and Siciliani de Cumis 2018). These epigenetic changes may play a role in the regulation of the AhR or its target genes and thereby modify carcinogenic action (Opitz et al. 2023). For example, regulation of expression of some CYPs (and therefore metabolic changes that may relate to cancer) is dependent on DNA methylation (Opitz et al. 2023). In addition, AhR hypomethylation has been associated with reduced survival in some cancers (Opitz et al. 2023).

A stop-exposure component in the NTP (2006) cancer bioassay of 2,3,7,8-TCDD demonstrated that protracted exposure was a requirement for its liver carcinogenicity in this animal model. Female rats exposed to 100 ng/kg 2,3,7,8-TCDD for 30 weeks developed significantly fewer liver tumors (cholangiocarcinomas and hepatocellular adenomas) than rats exposed to the same dose for 2 years (NTP 2006).

In summary, the carcinogenic effects of 2,3,7,8-TCDD are strongly linked to sustained AhR activation and its pleiotropic sequelae, rather than from a direct genotoxic action. As discussed further in Section 2.21, Mechanisms of Toxicity, there are marked differences in 2,3,7,8-TCDD-mediated AhR activation and ensuing changes across species, strains, sexes, and tissues. The variability in AhR activation and cellular responses to 2,3,7,8-TCDD exposure likely contributes to the diversity of tumor types seen in animals exposed *in vivo*. Further, the activation of AhR is a plausible mechanism for the carcinogenicity of other CDDs, especially those with physiological half-lives similar to that of 2,3,7,8-TCDD, but data with which to evaluate this potential mechanism were not located.

2.20 GENOTOXICITY

Information on studies regarding genotoxic effects in humans is provided in Table 2-34. The studies do not provide conclusive data regarding dioxin genotoxicity.

Table 2-34. Genotoxic Effects in Humans Exposed to 2,3,7,8-TCDD/CDDs

Reference	Design and population	TCDD/CDD concentrations	Effects
Baccarelli et al. 2004	20 years after the Seveso, Italy (1976) incident, 62 randomly selected individuals from the exposed zone and 59 controls from the noncontaminated area	2,3,7,8-TCDD in plasma (lipid adjusted) ranged from 3.5 to 90 pg/g (ppt)	AhR mRNA levels in uncultured lymphocytes were negatively correlated with plasma TCDD
Baccarelli et al. 2006	Among 144 healthy individuals from the previously exposed population in Seveso, there were 50 of the t(14,18)-translocation-positive subjects (34.7%)	TCDD in plasma: <10 ppt 10–50 ppt 50–475 ppt	The frequency of non-Hodgkin lymphoma-related t(14,18)-translocations (but not the prevalence) was associated with increased plasma levels in previously exposed individuals; clinical impact is not clear; similarly, increased frequency was detected in smokers.
Rowland et al. 2007	24 New Zealand Defense Force Vietnam War veterans and 23 matched controls	Not applicable	Significant increase in SCE (mean 11.05 versus 8.18).
Valic et al. 2004	A case-control study; two occupationally exposed workers (suspected oral exposure); 30 employees from the same workplace were in the normal TCDD range (1.2–8.6 pg/g blood lipids, average 3.0 pg/g), with the exception of three other employees with moderately increased TCDD levels of 93, 149, and 856 pg/g blood lipids and no clinical signs	2,3,7,8-TCDD at a concentration of 144,000 pg/g blood lipids in patient 1 and 26,000 pg/g blood lipids in patient 2 at first examination after manifestation of chloracne; 2 months later, when TCDD levels were 85,600 and 17,700 pg/g blood lipids, respectively, second examination	First examination: normal values (2.4 and 2.5 MN/500 binucleated cells; 6.7±2.2 and 6.0±2.5 SCEs/metaphase); second examination: MN had increased to 16 and 21.8 MN/500 binucleated cells, SCE remained within normal range. Within a period of 13 months, MN had returned to a nearly normal range in both patients. The comet assay tail factor (DNA damage level) in peripheral lymphocytes showed a very high value of 33.5% (at the time of 2nd evaluation).
Yoshida et al. 2006	Occupational exposure, municipal waste incinerator workers; concentrations of serum dioxins and lymphocytic 8-OH-dG were measured in 57 male workers; from the cohort, urinary 8-OH-dG and urinary mutagenicity was tested in 29 males	Mean CDD, CDF, and coplanar-PCB levels were 12.9, 12.4, and 13.6 pg TEQ/g lipids	Oxidative DNA damage and urinary mutagenicity tested. The lymphocytic 8-OH-dG level showed a negative association with the serum dioxin level (total TEQs). Dioxin did not increase the urinary 8-OH-dG level by oxidative DNA damage.

8-OH-dG = 8-hydroxydeoxyguanosine; AhR = aryl hydrocarbon receptor; CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; DNA = deoxyribonucleic acid; MN = micronuclei; mRNA = messenger ribonucleic acid; PCB = polychlorinated biphenyl; SCE = sister chromatid exchange; TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ = toxic equivalency

Data regarding genotoxic effects in humans exposed to CDDs are inconclusive. *In vivo* genotoxicity studies are summarized in Table 2-35. Human studies have been conducted on populations exposed to 2,3,7,8-TCDD. An increased incidence of chromosomal aberrations was found in the fetal tissues, but not in the maternal tissues, following induced abortions in a group of women exposed to 2,3,7,8-TCDD in the Seveso accident (Tenchini et al. 1983). The results from cytogenetic analysis of maternal tissues were comparable to those of the control group. Furthermore, no increase in the frequency of chromosomal aberrations was found in 17 individuals who were treated for chloracne following the Seveso accident (Reggiani 1980). An increased incidence of chromosomal aberrations was found in a group of 10 Vietnam veterans (Kaye et al. 1985); however, in another study, no increases in chromosomal aberrations or sister chromatid exchanges were reported in 15 Vietnam veterans (Mulcahy 1980). None of these studies included 2,3,7,8-TCDD dosimetry and all were limited by using exposed groups that were relatively small (<20 individuals) to have the statistical power to reliably assess the cytogenetic damage. Fewer birth defects due to chromosomal abnormalities in children of Vietnam veterans were reported in another study (Erickson et al. 1984).

Table 2-35. Genotoxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) *In Vivo*

Species (test system)	Endpoint	Results	Reference
Drosophila melanogaster	Recessive lethals	–	Zimmering et al. 1985
Rat, bone marrow	Chromosomal aberrations	–	Loprieno et al. 1982
Mouse, bone marrow	Chromosomal aberrations	+	Loprieno et al. 1982
Rat, bone marrow	Chromosomal aberrations	+	Green et al. 1977
Mouse, bone marrow	Chromosomal aberrations, SCE, micronucleus test	–	Meyne et al. 1985
Monkey, peripheral lymphocytes	Chromosomal aberrations, SCE	–	Lim et al. 1987
Rat	Dominant lethals	–	Khera and Ruddick 1973
Rat, liver	DNA adducts	–	Randerath et al. 1989
Rat, liver	DNA-single strand breaks	+	Wahba et al. 1989
Rat, liver	DNA adducts	–	Poland and Glover 1979
Human, aborted tissues	Chromosomal aberrations	+	Tenchini et al. 1983
Human, peripheral lymphocytes	Chromosomal aberrations	–	Reggiani 1980
Human, peripheral lymphocytes	Chromosomal aberrations	+	Kaye et al. 1985
Human, peripheral lymphocytes	Chromosomal aberrations	–	Mulcahy et al. 1980

Table 2-35. Genotoxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) *In Vivo*

Species (test system)	Endpoint	Results	Reference
Human, peripheral lymphocytes	Chromosomal aberrations, SCE	–	Zober et al. 1993

– = negative result; + = positive result; DNA = deoxyribonucleic acid; SCE = sister chromatid exchange

One study examined the incidence of chromosomal aberrations and of sister chromatid exchanges in human lymphocytes in 27 workers with current 2,3,7,8-TCDD concentrations in blood >40 ppt and in 28 age-comparable referents (Zober et al. 1993). The results showed no statistically significant differences between the two groups in the percentages of gaps, chromatid or chromosome exchanges, chromatid or chromosome breaks/fragments/deletions, multiple aberrations, or overall percentage of aberrations including or excluding gaps. In the exposed group, there was an increased rate of sister chromatid exchanges per cell and a higher percentage of cells with >10 sister chromatid exchanges. However, these associations were no longer significant when smoking status was included as a covariate. Moreover, neither current nor back-calculated 2,3,7,8-TCDD concentration was a significant predictor of these parameters. Zober et al. (1993) indicated that some limitations, such as the small number of individuals studied, a possible selection effect, and the possibility that some effects were transient, should be considered in the interpretation of the results.

The human data on the genotoxicity of 2,3,7,8-TCDD are inconsistent and inconclusive. Human studies cited above were limited by several factors. Generally, the levels of exposure to 2,3,7,8-TCDD were not known and co-exposure to other potentially active compounds occurred in all studies. In the case of Vietnam veterans, a long postexposure period passed before the cytogenetic analysis was done. Furthermore, most of the studies used groups that were too small (<20 individuals) to have the statistical power to detect any changes. The lack of exposure data, small sample sizes, and inconsistent results preclude drawing conclusions from these studies.

Animal studies on the genotoxicity of CDDs are inconclusive. When Osborne-Mendel rats were given 2,3,7,8-TCDD (0.25, 0.5, 1, 2, or 4 µg/kg) by gavage twice a week for 13 weeks, an increased incidence of chromosomal aberrations was observed in the highest-exposure group (Green et al. 1977). Increased incidences of gaps and chromatid aberrations were observed in bone marrow cells of CD-1 mice following an intraperitoneal injection of 10 µg/kg 2,3,7,8-TCDD (Loprieno et al. 1982). Positive results were obtained at 96 hours, but not at 24 hours, post treatment. In contrast, no induction of structural

chromosomal changes was found in CD-COBS rats orally exposed to 1.0, 0.1, or 0.01 µg/kg 2,3,7,8-TCDD once a week for 45 weeks (Loprieno et al. 1982). In addition, no differences in the frequency of sister chromatid exchanges or chromosomal aberrations in peripheral lymphocytes were observed in a group of Rhesus monkeys receiving 0.001 µg/kg 2,3,7,8-TCDD in the feed for 4 years and their matching controls (Lim et al. 1987). Furthermore, no induction of chromosomal aberrations or sister chromatid exchanges, or increases in the frequency of micronuclei, were found in bone marrow cells of C57BL/6J (with high-affinity 2,3,7,8-TCDD receptor) or DBA/2J mice (with low-affinity 2,3,7,8-TCDD receptor) following a single intraperitoneal injection of 2,3,7,8-TCDD at doses of 50, 100, or 150 µg/kg (Meyne et al. 1985). The samples were examined within 8–48 hours. The negative results may, however, have been due to the time-dependent detectability of chromosomal changes after CDD exposure reported earlier (Loprieno et al. 1982).

In addition to studies dealing with structural chromosomal changes, effects on DNA were also investigated. Oral exposure to 1 µg/kg/week of 2,3,7,8-TCDD or 1,2,3,7,8-PeCDD for up to 6 months did not increase the formation of DNA adducts in Sprague-Dawley rats (Randerath et al. 1989). A single oral dose of 2,3,7,8-TCDD (25–100 µg/kg) caused time-dependent increases in the induction of DNA single-strand breaks (and lipid peroxidation) in hepatic cells of Sprague-Dawley rats terminated within 3–14 days after the treatment (Wahba et al. 1989).

Negative results were obtained in reproductive tests including a dominant-lethal test following seven daily oral doses of 2,3,7,8-TCDD (4, 8, or 12 µg/kg/day) to male Wistar rats (Khera and Ruddick 1973) and a sex-linked recessive-lethal test with 2,3,7,8-TCDD in *Drosophila melanogaster* (Zimmering et al. 1985).

In vitro genotoxicity studies are summarized in Table 2-36. Eukaryotic cell systems were used for detecting the effects of 2,3,7,8-TCDD exposure on DNA. Exposure to 2,3,7,8-TCDD did not stimulate the unscheduled DNA synthesis in cultural human cells (Loprieno et al. 1982), but inhibited DNA, ribonucleic acid (RNA), and protein synthesis in mouse lymphocytes (Luster et al. 1979); caused gene mutations in mouse lymphoma cells (Rogers et al. 1982); and induced sister chromatid exchanges in Chinese hamster cells (Toth et al. 1984).

Table 2-36. Genotoxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium				
TA1530	Reverse mutations	NA	–	Hussain et al. 1972
TA1532	Reverse mutations	NA	+	Hussain et al. 1972
TA1535	Reverse mutations	NA	–	Seiler 1973
TA1531	Reverse mutations	NA	–	Seiler 1973
TA1532	Reverse mutations	NA	(+)	Seiler 1973
TA1537	Reverse mutations	NA	(+)	Seiler 1973
TA1535	Reverse mutations	–	NA	Geiger and Neal 1981
TA100	Reverse mutations	–	NA	Geiger and Neal 1981
TA1537	Reverse mutations	–	–	Geiger and Neal 1981
TA1538	Reverse mutations	–	NA	Geiger and Neal 1981
TA98	Reverse mutations	–	NA	Geiger and Neal 1981
TA100	Reverse mutations	–	NA	Mortelmans et al. 1984
TA1535	Reverse mutations	–	NA	Mortelmans et al. 1984
TA1537	Reverse mutations	–	NA	Mortelmans et al. 1984
TA98	Reverse mutations	–	NA	Mortelmans et al. 1984
TA1530	Reverse mutations	–	NA	Gilbert et al. 1980
TA1535	Reverse mutations	–	NA	Gilbert et al. 1980
TA100	Reverse mutations	–	NA	Gilbert et al. 1980
TA1537	Reverse mutations	–	NA	Gilbert et al. 1980
TA1538	Reverse mutations	–	NA	Gilbert et al. 1980
TA98	Reverse mutations	–	NA	Gilbert et al. 1980
TA1535	Reverse mutations	–	–	Toth et al. 1984
TA100	Reverse mutations	–	–	Toth et al. 1984
TA1537	Reverse mutations	–	–	Toth et al. 1984
TA1538	Reverse mutations	–	–	Toth et al. 1984
TA98	Reverse mutations	–	–	Toth et al. 1984
Escherichia coli	Reverse mutations	NA	–	Hussain et al. 1972
Saccharomyces cerevisiae	Reverse mutations	+	–	Bronzetti et al. 1983
S. cerevisiae	Gene conversion	+	–	Bronzetti et al. 1983
S. cerevisiae	Host mediated assay	+	–	Bronzetti et al. 1983

Table 2-36. Genotoxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Eukaryotic organisms:				
EUE human cells	UDS	NA	–	Loprieno et al. 1982
Mouse lymphocytes	DNA, RNA synthesis inhibition	NA	–	Luster et al. 1979
L51784 mouse lymphoma cells	Gene mutations	NA	+	Rogers et al. 1982
Chinese hamster cells	SCE	–	+	Toth et al. 1984

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid; NA = not applicable; RNA = ribonucleic acid; SCE = sister chromatid exchange; UDS = unscheduled DNA synthesis

Several researchers used the Ames test with *Salmonella typhimurium* to assess the mutagenicity of 2,3,7,8-TCDD in prokaryotic organisms. Predominantly negative results were obtained with tester strains G46, TA1530, TA1535, TA100, TA1950, and TA1975, revealing base pair substitutions; and with strains TA1531, TA1532, TA1534, TA1538, TA98, and TA1978, revealing frame shift mutations (Geiger and Neal 1981; Gilbert et al. 1980; Mortelmans et al. 1984; Toth et al. 1984). However, some of the studies were limited by using 2,3,7,8-TCDD concentrations in excess of its solubility in water. Only two early studies reported positive results (Hussain et al. 1972; Seiler 1973). However, the results were limited by failure to demonstrate a dose-response relationship and by low bacterial survival rates. In addition, 2,3,7,8-TCDD exposure induced reverse mutations in *Escherichia coli* (Hussain et al. 1972) and in *Saccharomyces cerevisiae* (Bronzetti et al. 1983). The conflicting data obtained in the above studies may result from technical difficulties in testing 2,3,7,8-TCDD rather than from a lack of biological activity. Testing difficulties arise from an extreme insolubility of this compound and a high toxicity observed in some test systems, which would be anticipated to result in a very narrow window for effective genotoxic doses.

Considering the inconclusive results reported above and the severe limitations of some studies, there is no strong evidence for 2,3,7,8-TCDD genotoxicity. The information regarding the mutagenic potential of other CDDs is even more limited.

Inconclusive results were obtained regarding genotoxicity of CDDs in human studies as well as in animal studies. Structural chromosomal changes were found in some groups of exposed individuals (Kaye et al.

1985). However, the studies were confounded by small cohorts and unknown exposures. Positive and negative results at the chromosomal level (Green et al. 1977; Loprieno et al. 1982; Meyne et al. 1985) as well as at the gene level (Randerath et al. 1989; Wahba et al. 1989) were reported in animal studies. Furthermore, negative results were obtained in dominant-lethal tests (Khera and Ruddick 1973) and sex-linked recessive-lethal tests in rats and *Drosophila* (Zimmering et al. 1985), respectively. In addition, mostly negative results were obtained in prokaryotic organisms (Geiger and Neal 1981; Gilbert et al. 1980; Toth et al. 1984). Some studies indicated that the covalent binding of 2,3,7,8-TCDD to DNA is low, and that this mechanism does not operate in CDD genotoxicity. Further studies on the mechanism of CDDs would be useful to evaluate the best possible method for detecting CDD genotoxicity.

2.21 MECHANISMS OF TOXICITY

Overview. 2,3,7,8-TCDD and structurally related compounds induce a wide range of biological responses, including alterations in metabolic pathways, body weight loss, thymic atrophy, impaired immune responses, hepatotoxicity, chloracne and related skin lesions, developmental and reproductive effects, and neoplasia. The expression of these responses has been shown to be initiated by the binding of individual congeners (or ligands) with the AhR. The role of AhR binding in the toxicity of 2,3,7,8-TCDD was first discovered in the 1970s. Since that time, the extraordinary binding affinity of 2,3,7,8-TCDD for the AhR has led to its extensive use in experiments aimed at determining the mechanisms through which AhR binding influences physiological systems. As a result, the scientific literature on this topic is voluminous. It is beyond the scope of this profile to discuss these studies in detail. Instead, this section provides a brief overview of the role of the AhR in inducing gene expression changes and epigenetic effects believed to be involved in many of the diverse effects seen in humans and animals exposed to 2,3,7,8-TCDD. For more detailed discussions, there are numerous reviews on this topic, including some recent reviews that were used for this section: Denison et al. (2011); Gasiewicz et al. (2008); Patrizi and Siciliani de Cumis (2018); Xu et al. (2022); Wright et al. (2017).

The AhR is a cytosolic protein in the basic helix-loop-helix-Per-ARNT-Sim family of transcription factors. The AhR exists as a multimeric complex with a 90 KDa heat-shock protein (hsp-90) chaperone protein and the co-chaperones, x-associated protein 2 (XAP2) and p23. When 2,3,7,8-TCDD diffuses into the cytoplasm, it binds to inactive (unliganded) AhR. Upon ligand activation, the AhR undergoes a transformational change to expose a nuclear localization sequence(s) resulting in translocation of the complex into the nucleus. Within the nucleus, the AhR:ligand, released from the complex, forms a heterodimer complex with ARNT (also known as hypoxia inducible factor 1β or HIF-1β). The

ligand:AhR:ARNT heterodimer complex binds to specific DNA recognition sites within target genes, referred to as AhR responsive elements or AhREs, also called dioxin-responsive elements [DREs] or xenobiotic responsive elements [XREs]). Target genes include genes coding for phase I and II biotransformation enzymes and genes involved in regulation of development, proliferation, and differentiation. This is the canonical pathway for AhR signal transduction and is exemplified by the induction of CYP1A1.

In addition to induction of CYP1A1, the canonical liganded AhR-ARNT pathway leads to changes in gene expression that trigger a myriad of cellular level changes. Table 2-37 below shows some of the genes known to have functional AhRE sequences, and Table 2-38 shows examples of cellular level changes associated with TCDD-mediated induction of some of these genes. These tables demonstrate the wide distribution of the AhRE across the genome and the diversity of cellular-level effects that are induced by the AhR-ARNT pathway.

Table 2-37. Genes with Functional Aryl Hydrocarbon Response (AhR) Responsive Elements (AhREs)

Aldehyde dehydrogenase 3A1	HES-1
Aryl hydrocarbon receptor repressor (AhRR)	Hsp27
Bax	Insulin-like growth factor binding protein
c-jun	IgM μ gene
c-myc	Interleukin-2
Cathepsin D	junD
Cyclooxygenase-2	NAD(P)H-quinone oxidoreductase-1
CYP1A1	NF-E2 p45 –related factor (NRF2)
CYP1A2	$p21^{CIP1}$
CYP1B1	$p27^{KIP1}$
CYP2A5	pS2
CYP2S1	Slug
Epiregulin	Suppressor of cytokine signaling 2 (Socs2)
Gluthathione-S-transferase Ya	U=Uridine 5'-diphospho-glucuronosyltransferase (UDP)-glucuronosyltransferase 1A1
Filaggrin	UDP-glucuronosyltransferase 1A6

Source: Gasiewicz et al. 2008

Table 2-38. Examples of AhR:ARNT Canonical Pathway Effects

Gene expression change	Cellular level effect
CYP1A1 induction	• Generation of ROS/oxidative stress • Oxidative DNA damage • Activation of intracellular kinase signaling pathways (c-Jun, NFκB, etc.) • Endothelial dysfunction
TiPARP induction	• Suppression of hepatic gluconeogenesis
Nedd1/Hef1/Cas-L induction	• Changes in cell adhesion and shape • Cytoskeletal reorganization • Increased cell migration
SOS1 induction	• Activated Ras-GTP • Activation of extracellular signal related kinase • Accelerated cell proliferation
CYP1A1/1B1 induction	• Catabolism of estrogen
$p27^{kip1}$ and $p21^{Waf1/Cip1}$ induction	• Inhibition of CDKs • Inactivation of Rb • Repression of cell cycle

Source: Denison et al. 2011

CDK = cyclin-dependent kinase; DNA = deoxyribonucleic acid; NFκB = nuclear factor κB; Rb = retinoblastoma protein; ROS = reactive oxygen species

More recent studies have indicated that AhR can also mediate effects on genes that lack an identifiable AhRE. These changes in gene expression are postulated to occur via AhR-ARNT interaction with transcription sites other than the AhRE (Wright et al. 2017). Table 2-39 provides some examples of non-canonical AhR signaling pathways as reviewed by Denison et al. (2011).

Table 2-39. Examples of Non-canonical AhR Signaling

Signal pathway	Effects
AhR and ER crosstalk	• Binding of liganded AhR:ARNT complex to inhibitory DREs blocking gene activation by ER • Competitive sequestration of coactivators or DNA binding partners (p300, cAMP, CREB-binding protein, SRC1/2, ARNT) leading to repression of ER signaling • Direct binding of liganded AhR to ER leading to repression of ER signaling and ubiquitination/degradation of ER
Liganded AhR binding to hyperphosphorylated Rb	• Repression of cell cycle • Decreased cell proliferation
Interaction between AhR and E2F	• Recruitment of positive regulatory factors • Increased cell proliferation

Table 2-39. Examples of Non-canonical AhR Signaling

Signal pathway	Effects
AhR and NFkB crosstalk	• Binding to RelA dimer forming transcriptionally inactive dimer • Competition for coactivators • Binding to RelB forming transcriptionally active dimer • Alterations in immune and inflammatory responses
Opening plasma membrane calcium channels and inducing release of intracellular calcium via action on ryanodine receptors	• Rapid and sustained calcium influx into cells • Stimulation of protein kinase C activity and cAMP production • Enhanced transcriptional activity of ligand-activated AhR
Interaction with KLF6	• Induction of PAI1 • Induction of sustained p21Cip1 expression

Source: Denison et al. 2011

AhR = aryl hydrocarbon receptor; ARNT = aryl hydrocarbon receptor nuclear translocator gene; cAMP = cyclic AMP; CREB = cAMP response element-binding; DNA = deoxyribonucleic acid; DRE = dioxin-responsive element; E2F = E2 promotor-binding factor; ER = estrogen receptor; KLF6 = Kruppel-like factor 6; PAI1 = plasminogen activator inhibitor 1; SRC1/2 = steroid receptor coactivators 1/2

Species Differences. The AhR is present in essentially all tissues and is well conserved across species, with only a few amino acid differences in the ligand binding domain (LBD) (Denison et al. 2011; Xu et al. 2022). However, even small alterations in amino acid residues result in differing binding affinities for 2,3,7,8-TCDD. For example, when the Ala 375 residue in the mouse AhR LBD is replaced with Val (by mutation, or as seen in different mouse strains), binding affinity for 2,3,7,8-TCDD is reduced, and its toxicity is substantially decreased (Xu et al. 2022). Other species and strain differences have been identified in the AhR transactivation domain (TAD) and in the structure, distribution, location, and number of dioxin-responsive elements (Xu et al. 2022). Specifically, there appear to be important species differences in the C terminal region of the TAD, while the N terminal is well conserved across species (Wright et al. 2017; Xu et al. 2022). Xu et al. (2022) noted that the C terminus of the AhR TAD of humans is only 58% similar to that of mice. The Q-rich subdomain of the AhR TAD is an important determinant of AhR activation by TCDD, as shown by the observation that 2,3,7,8-TCDD LD_{50} values show a clear correlation with the number of glutamine residues in Q rich subdomain of the transactivation domain (Xu et al. 2022).

Variations in DNA sequences adjacent to the AhRE also contribute to species differences, as induction of Ah-responsive genes also depends on the presence of binding sites for coactivators or other transcription factors near the AhRE (Xu et al. 2022). As a result of these and potentially other variations, gene expression and physiological responses to 2,3,7,8-TCDD vary widely across species and strains. For

example, the number and spectrum of genes whose expression was up- or down-regulated by 2,3,7,8-TCDD differed markedly between mouse hepatocytes expressing the mouse Ahr and those expressing a human AhR (Denison et al. 2011). Furthermore, the potencies and targets of 2,3,7,8-TCDD toxicity differ by species and even by strain. The oral LD_{50} for 2,3,7,8-TCDD in hamsters is 5,000 µg/kg, ~5,000 times higher than the LD_{50} in guinea pigs (0.6–2.1 µg/kg) (Denison et al. 2011; Xu et al. 2022). Marked strain differences in lethality have also been demonstrated; the oral LD_{50} for 2,3,7,8-TCDD in Han/Wistar rats is >10,000 µg/kg while the LD_{50} in Long-Evans rats is only 17.7 µg/kg. Target organs also differ across species. Among the effects of acute-duration exposure to 2,3,7,8-TCDD, which include thymus, liver, nervous system, skin, and developmental effects, only thymic atrophy is consistently observed across all mammals (Xu et al. 2022). As an example, 2,3,7,8-TCDD is teratogenic in hamsters and rats, but not in guinea pigs (Xu et al. 2022).

Evidence from epidemiology studies and *in vitro* experiments suggests that humans may be less sensitive to the toxic effects of 2,3,7,8-TCDD than other mammals, due in part to the lower binding affinity of the human AhR compared with other mammals (Denison et al. 2011). For example, rat hepatocytes are 30 times more sensitive than human hepatocytes to 2,3,7,8-TCDD induction of CYP1A2 and 5 times more sensitive to induction of CYP1A1 (Xu et al. 2022). However, there also appears to be wide variability in the binding affinity of individual human AhR for 2,3,7,8-TCDD, as shown by experiments using human placental samples showing differences of more than 10-fold (Denison et al. 2011). The variability in AhR binding may help to explain why serum 2,3,7,8-TCDD levels in humans exposed to 2,3,7,8-TCDD in Seveso, Italy did not correlate with development of chloracne (Denison et al. 2011).

While the AhR is widely distributed in the body of mammals, there are tissue differences in levels of expression. The organs with the highest AhR expression are the liver, thymus, lung, kidney, spleen, and placenta (Wright et al. 2017).

Structure-Activity Relationships. Studies using *AhR* and *ARNT* knockout mice have demonstrated that these molecules are necessary for most, but not all, of 2,3,7,8-TCDD's toxic effects. 2,3,7,8-TCDD's remarkable potency for inducing AhR-mediated effects is attributed both to its relative affinity for the AhR as well as its stability. AhR ligands that are readily metabolized (for example, polycyclic aromatic hydrocarbons [PAHs]) remain in the cell only transiently because the induction of metabolic enzymes leads to their degradation. In contrast, 2,3,7,8-TCDD binding to AhR induces its persistent activation and leads to a wide spectrum of toxic effects (Denison et al. 2011).

While most of what is known about the mechanisms of CDD toxicity is from studies of 2,3,7,8-TCDD, there is abundant evidence that toxic effects of other CDDs are also mediated through AhR binding. For this reason, relative AhR binding has been used as one method to estimate the potency of other CDDs relative to 2,3,7,8-TCDD. To date, AhR binding affinity has been shown to correlate well with *in vivo* effects of CDDs on mortality, body weight loss, thymic atrophy, dermal effects, immunosuppression, and teratogenicity. TEFs used to estimate risks from CDDs other than 2,3,7,8-TCDD make use of relative AhR binding affinity in addition to relative potency estimates from *in vivo* data for a variety of endpoints (Ring et al. 2023). Section 2.1 provides a summary of existing TEF values for CDDs.

Exposure to TCDD has been shown to induce dose-dependent increases in neutrophils (the most abundant type of granulocyte) in the blood, peritoneal cavity, spleen, and lungs of mice (Kerkvliet 2009). In addition, TCDD alters the oxidative burst and cytolytic activity of neutrophils in a context-dependent fashion; under different circumstances, experiments have demonstrated suppression, enhancement, and absence of an effect of TCDD on this function (Kerkvliet 2009). Similarly, the cytolytic activity of NK cells after TCDD exposure varies from no response to either suppression or enhancement. The mechanisms by which TCDD affects neutrophils and NK cells are not known; however, several genes for neutrophil cytosolic factors and NK receptor subunits have AhRE sequences and may play a role (Kerkvliet 2009).

In mice exposed to TCDD, a decrease in dendritic cell counts in the spleen was shown to occur a week after exposure and *in vitro* studies showed that TCDD enhanced both maturation and apoptosis of dendritic cells (Kerkvliet 2009). The mechanisms for these effects may include altered expression of apoptotic genes or upstream signaling pathways. For example, *in vitro* data show that TCDD increased the expression of *Fadd*, a gene that mediates apoptosis and also suppressed NFkB signaling (Kerkvliet 2009).

In summary, the mechanisms and pathways by which TCDD modulates immune responses are complex and depend upon the physiological milieu in which the exposure occurs. Most of the data on immune mechanisms are from studies in mice, and there are well-known differences in the responses of various species to TCDD exposure, suggesting the need for studies in other species to better evaluate species differences in immune effects.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Data regarding toxicokinetics of CDDs in humans are limited to information derived from exposures that occurred after industrial accidents, exposures of Vietnam veterans, and ingestion of large doses of 2,3,7,8-TCDD.

- Humans can absorb CDDs by the inhalation, oral, and dermal routes of exposure. CDDs, when administered orally, are well absorbed by experimental animals, but they are absorbed less efficiently when administered by the dermal route. Limited data in rats showed that transpulmonary absorption of 2,3,7,8-TCDD may be at least as efficient as oral absorption. In a volunteer, >86% of the administered single oral dose appeared to have been absorbed. In general, absorption is vehicle-dependent and congener-specific. Passage across the intestinal wall is predominantly limited by molecular size and solubility. These parameters are most significant for hepta- and octachlorinated congeners, which exhibit decreased absorption in mammals.

- The predominant CDD carriers in human plasma are serum lipids and lipoproteins, but chlorine substitution plays a role in the distribution in these fractions. For most mammalian species, the liver and adipose tissue are the major storage sites of CDDs; in some species, skin and adrenals also can act as primary deposition sites. 2,3,7,8-Substituted CDDs are the predominant congeners retained in tissues and body fluids. Tissue deposition is congener-specific and depends on the dose, the route of administration, and age.

- CDDs are very slowly metabolized by the microsomal monooxygenase system to polar metabolites that can undergo conjugation with glucuronic acid and glutathione.

- The major routes of excretion of CDDs are the bile and the feces; smaller amounts are excreted via the urine. In mammalian species, lactation is an effective way of eliminating CDDs from the liver and other extrahepatic tissues.

- Physiologically based pharmacokinetic (PBPK) models have been developed to describe disposition of 2,3,7,8-TCDD in humans and animals. Some of these models included parameters to describe complex interactions of 2,3,7,8-TCDD with cellular proteins that lead to specific biological responses.

3.1.1 Absorption

Inhalation Exposure. No quantitative data were located regarding absorption of CDDs in humans following inhalation exposure. Data on levels of CDDs in blood from populations with above-background exposures (occupational, accidental) suggest that transpulmonary absorption occurs in humans.

Systemic effects (hepatic aryl hydrocarbon hydroxylase [AHH] and CYP induction, hepatic histological alterations) were observed in rats following a single intratracheal instillation of 2,3,7,8-TCDD in a corn oil vehicle or as a laboratory-prepared contaminant of gallium oxide particles (Nessel et al. 1990). In a subsequent study, the same group of investigators (Nessel et al. 1992), using a similar protocol, found that the relative pulmonary bioavailability of 2,3,7,8-TCDD on respirable soil particles was 100% as compared to the gallium oxide vehicle. At 1- and 7-days post-treatment, 13.9 and 11.9% of the administered dose were detected in the liver, respectively, and this was similar to the percentage found after instillation of contaminated gallium oxide particles. Twenty-eight days after treatment, 5.2% of the administered dose was detected in the liver from soil-treated rats and 2.9% of the administered dose was detected in the liver from gallium oxide-treated rats, suggesting that redistribution and retention of 2,3,7,8-TCDD differed in the two treatment groups. Diliberto et al. (1996) reported that 3 days after intratracheal application of a single dose of 0.32 μg 2,3,7,8-TCDD/kg to male Fischer-344 rats, 95% of the applied dose was absorbed, suggesting that inhalation can be an effective route of exposure. The extent of inhalation absorption was higher than when the same dose was administered orally (88%) or dermally (40%). The available data suggest that inhaled CDDs will be absorbed. However, the degree of absorption and the rate will depend on the media on which the CDDs are adsorbed and the degree of chlorination.

Oral Exposure. The absorption of 2,3,7,8-TCDD was estimated to be >87% in a volunteer following ingestion of a single radioactively labeled dose of 0.00114 μg 2,3,7,8-TCDD/kg in corn oil (Poiger and Schlatter 1986). Absorption of several CDDs (2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD; 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,9-HpCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD) from food was examined in seven volunteers using a mass balance protocol, collecting food (normal diet; not controlled) and feces over a 3-day period (Schlummer et al. 1998). Volunteers did not have any history of occupational or accidental exposure to CDDs. The highest net absorption observed for an individual volunteer was 62% for 2,3,7,8-TCDD in a 28-year-old male. However, estimates of absorption were highly variable and, in some individuals, net excretion rather than net absorption was observed. The study authors suggested that variability was related, in part, to the variability of food content of CDDs. Using a similar study design, the absorption of several CDDs (same as those evaluated by Schlummer et al. 1998) was estimated in five volunteers for both low- and high-CDD intake diets (Moser and McLachlan 2001). For high-intake diets, the net absorption of 2,3,7,8-TCDD, PeCDD, and HxCDD was >80%, with lower net absorption for HpCDDs (approximately 70%) and OCDD (approximately 50%). For low-intake diets, the net absorption of most CDDs could not be detected; findings are consistent with

net excretion of CDDs from body stores under low-intake conditions. Data regarding absorption of CDDs from human milk in nursing infants are provided in Section 3.1.4.

Gastrointestinal absorption of radiolabeled 2,3,7,8-TCDD has been investigated in rodents. About 73.5% of the total dose of 2,3,7,8-TCDD (administered by gavage in corn oil vehicle) was absorbed in Syrian hamsters, the species most resistant to acute 2,3,7,8-TCDD toxicity (Olson et al. 1980b). In Sprague-Dawley rats given a single gavage dose of 50 μg/kg 2,3,7,8-TCDD in corn oil, at least 70% was absorbed (Piper et al. 1973). Rose et al. (1976) found a mean of 84% of a single gavage dose of 1 μg/kg absorbed within a day in a similar study and a steady-state body burden was achieved after dosing with 0.01, 0.1, or 1 μg/kg in corn oil, 5 days/week for 7 weeks. When [^{14}C]-2,3,7,8-TCDD was fed to Sprague-Dawley rats at 0.35 or 1 μg/kg/day in the diet for 42 days, about 60% of the consumed dose was absorbed (Fries and Marrow 1975). Intestinal absorption of 2,3,7,8-TCDD did not vary with age of Fischer-344 rats (13 weeks, 13 or 26 months) when *in vivo* absorption was studied with an *in situ* intestinal perfusion technique (Hebert and Birnbaum 1987). When ICR/Ha Swiss mice were given a single dose of radioactively labeled 2,3,7,8-TCDD, 67–76% of the administered dose was excreted in feces and 1–2% was excreted in urine within the first 24 hours (Koshakji et al. 1984). The study authors concluded that most of the dose was not absorbed.

Gastrointestinal absorption of 2,3,7,8-TCDD may differ depending on the vehicle used. When hepatic concentrations were used as a measure of absorbed dose, the levels observed in rats 24 hours after 2,3,7,8-TCDD administration in 50% ethanol were higher than in an aqueous suspension of soil (Poiger and Schlatter 1980). Use of activated carbon as a vehicle almost completely eliminated 2,3,7,8-TCDD absorption. It was further demonstrated that the absorption of 2,3,7,8-TCDD from the gastrointestinal tract of rats was ≈50% less from contaminated soil than from corn oil (Lucier et al. 1986), which is supported by the finding that 2,3,7,8-TCDD-contaminated soil was less toxic to guinea pigs than an equivalent amount of 2,3,7,8-TCDD in oil (Umbreit et al. 1985). The more highly chlorinated CDD congeners are absorbed from the gastrointestinal tract to a lesser extent than 2,3,7,8-TCDD. Gastrointestinal absorption of OCDD was <10% of the administered dose in Sprague-Dawley and Fischer-344 rats following single or repeated (3-week) exposures by gavage in an oil vehicle (Birnbaum and Couture 1988; Norback et al. 1975). Low doses (50 μg/kg) in a *o*-dichlorobenzene:corn oil (1:1) vehicle were found to give the best oral bioavailability for this extremely insoluble compound (Birnbaum and Couture 1988). The bioavailability of CDDs (2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, and 1,2,3,7,8,9-HxCDD) to rats was lower on fly ash (0.4% for 2,3,7,8-TCDD) as compared to extracts of the same fly ash administered in an oily vehicle (45% for 2,3,7,8-TCDD) (Van den Berg et al. 1983,

1987a). The differences in hepatic levels between fly ash- and extract-treated rats were greater for the more highly chlorinated congeners.

Additional studies have evaluated the oral bioavailability of CDDs in soil relative to bioavailability in a reference material (relative bioavailability or RBA), such as corn oil, has been evaluated using several animal models, including rats (Budinsky et al. 2008; Finley et al. 2009; Lucier et al. 1986; Shu et al. 1988), guinea pigs (McConnell et al. 1984; Umbreit et al. 1986a; Wendling et al. 1989), rabbits (Bonaccorsi et al. 1984), and swine (Budinsky et al. 2008; Wittsiepe et al. 2007). Results of all studies show that the RBA of CDDs in soil is <100%, indicating that bioavailability of CDDs in soil is reduced compared to bioavailability of CDDs in the reference material. Relative bioavailability values for CDDs in soil were highly variable, ranging from <1 to 66% (Budinsky et al. 2008; Umbreit et al. 1986a). Variability in RBA values may be related to several factors, including differences in soil characteristics, CDD congener composition of soil, experimental protocol, and/or species differences.

Dermal Exposure. No quantitative data were located regarding absorption of CDDs in humans following dermal exposure. However, based on data from studies with structurally related chemicals, it is reasonable to assume that CDDs are absorbed by this route. Furthermore, data on levels of CDDs in blood from populations with above-background exposures (i.e., occupational, accidental) also suggest that dermal absorption occurs in humans. Due to the relatively low vapor pressure and high lipid solubility, dermal uptake of 2,3,7,8-TCDD in the workplace may be a significant source of occupational exposure (Kerger et al. 1995).

Kerger et al. (1995) examined the potential contribution of dermal exposure to 2,3,7,8-TCDD for three different occupational exposure scenarios: (1) trichlorophenoxy herbicide manufacturing worker (20-year exposure); (2) contract maintenance mechanic exposed by repairing a trichlorophenol reactor after an explosion accident (6-week exposure); and (3) trichlorophenoxy applicator handling only diluted trichlorophenoxy herbicides (seasonal exposure for 20 years). In their evaluation, the study authors used a conceptual model of workplace exposure, dermal bioavailability/uptake calculations, and simple pharmacokinetic modeling techniques (details of the model were not provided). The contribution of background uptake of 2,3,7,8-TCDD from dietary sources in the United States was accounted for in the estimates of steady-state adipose concentrations. The results of the modeling showed that considerable occupational uptake can occur following both long-term continuous exposure and short-term high exposure. In the former case, occupational uptake can be distinguished from background exposures when

body burden is measured within a 10-year period following cessation of exposure. In contrast, seasonal exposure to dilute 2,3,7,8-TCDD residues may result in little or no change in 2,3,7,8-TCDD body burden.

The *in vitro* penetration of [^{3}H]-labeled 2,3,7,8-TCDD into human cadaver skin was studied at concentrations of 6.5 and 65 ng 2,3,7,8-TCDD/cm^2 of skin (Weber et al. 1991a). Two vehicles were used: (1) acetone to simulate exposure to 2,3,7,8-TCDD as a dry material and (2) mineral oil to simulate exposure in an oily medium. The experiments were conducted in intact skin and in skin with stripped stratum corneum, and penetration was monitored for 30, 100, 300, and 1,000 minutes. The results showed that acetone as a vehicle allowed 2,3,7,8-TCDD to penetrate deeply into the loose surface of the lamellae of the stratum corneum, but there was little further penetration. On the other hand, mineral oil appeared to compete with lipophilic constituents of the stratum corneum for 2,3,7,8-TCDD, thus slowing its penetration even more. Removal of the stratum corneum increased the amount of 2,3,7,8-TCDD absorbed into layers of the skin. Rates of absorption were calculated in two ways: (1) a worst-case scenario where 2,3,7,8-TCDD absorbed into any layer of skin, including the stratum corneum, was used for analysis and (2) a physiological approach where only the amount of 2,3,7,8-TCDD that had penetrated beyond the epidermis into the region of dermal vascularization was considered absorbed. In the former case, the stratum corneum appeared to mediate dermal absorption of 2,3,7,8-TCDD since the rates decreased when stripped skin was exposed to 2,3,7,8-TCDD. With the physiological approach, the rate of absorption was a function of the amount applied, suggesting that the rate of absorption per unit time was a first-order function. The amount of 2,3,7,8-TCDD that penetrated the skin also correlated with exposure duration. The rates of 2,3,7,8-TCDD penetration with acetone as vehicle were 100–800 pg 2,3,7,8-TCDD per hour-cm^2 (worst-case scenario), or 6–170 pg per hour-cm^2 with the physiological approach. The corresponding values with mineral oil as a vehicle were 20–220 and 1.4–18 pg per hour-cm^2, respectively.

Data regarding dermal absorption of CDDs in animals are limited. Dermal absorption of 2,3,7,8-TCDD (70 mg total dose in acetone or in a low organic soil) was evaluated following application to shaved skin of female Sprague-Dawley under occluded conditions (Roy et al. 2008). After 96 hours, dermal absorption of 2,3,7,8-TCDD was 77.6 and 16.3% for acetone and soil applications, respectively. When 200 pmol 2,3,7,8-TCDD was applied to the skin of Fischer-344 rats, absorption followed first-order kinetics with an absorption rate constant of 0.005 hour^{-1} (Banks and Birnbaum 1991). Within 120 hours postexposure, about 0.026 µg 2,3,7,8-TCDD was absorbed (<50% of the applied dose); at each interval of measurement, about 70% of detected radioactivity on the skin could be removed by swabbing with acetone. About 15% of the dose was detected in the liver of rats 24 hours after dermal exposure to 26 ng of 2,3,7,8-TCDD in 50% methanol (Poiger and Schlatter 1980). It was estimated that the amount

absorbed from the dermal exposure represents ≈40% of the amount absorbed from an equivalent oral dose. Absorption of 2,3,7,8-TCDD was significantly reduced by application in Vaseline or polyethylene glycol and practically eliminated in soil or activated carbon. Dermal absorption of radioactively labeled 2,3,7,8-TCDD in soil vehicle was reported to be only 1% of the administered dose during a 24-hour contact in rats (Shu et al. 1988). The dermal absorption of 2,3,7,8-TCDD after 4 hours of contact was about 60% of that after 24-hour contact. The uptake was not influenced by the 2,3,7,8-TCDD concentration in soil, nor were there any differences between normal and hairless rats.

Dermal absorption in rats was found to be age-related. Banks et al. (1990) found that in Fischer-344 rats, percutaneous absorption was decreased in middle-aged (36-week-old) and senescent (120-week-old) rats compared to that in young adults (10-week-old) 72 hours after application of a dose of 40 nmol (approximately 12.9 μg) of [^{3}H]-labeled 2,3,7,8-TCDD. The study authors suggested a decrease in blood flow through the skin between 3 and 4 months of age as a possible explanation for their findings. In a subsequent and similar study, the same group of investigators examined the dermal absorption of 2,3,7,8-TCDD in 3-, 5-, 8-, 10-, and 36-week-old Fischer-344 rats 72 hours after application of 200 pmol 2,3,7,8-TCDD in acetone (Anderson et al. 1993). Dermal absorption was greatest in 3-week-old rats (approximately 64% of the applied dose) and decreased to about 40% of the applied dose in 5-, 8-, and 10-week-old rats and to about 22% in 36-week-old rats. In each age group, 70–80% of the radioactivity remaining at the application site 72 hours after dosing could be removed with acetone swabs.

3.1.2 Distribution

As discussed in Section 2.1, occupational or environmental human exposure to CDDs is not readily classifiable as to route of exposure. However, it has been estimated that food contributes over 90% of background exposure to CDDs. Human data regarding distribution obtained at autopsy indicated that accumulation in the liver following low levels of exposure is based, in part, on lipid solubility (Leung et al. 1990a; Watanabe et al. 2013). However, this may not be the case with higher exposure levels that cause hepatic enzyme induction. When human hepatic and adipose tissues were examined for the presence of 2,3,7,8-TCDD, the concentration detected in the liver was about 1/10 of that in the adipose tissue on a whole-tissue-weight basis. However, on the basis of the total tissue lipid, the concentration in adipose tissue lipid was one-half that in the liver lipid (Thoma et al. 1990). Watanabe et al. (2013) measured TEQs (CDDs, CDFs, PCBs) in human adipose and liver autopsy samples. TEQ concentrations (per g lipid) in adipose and liver samples were similar and were 1.3 and 1.5 times higher in males compared to females. In this same study, liver/adipose concentration ratios for OCDD and

1,2,3,6,7,8-HxCDF increased with increasing levels of hepatic CYP1A2. It was further demonstrated that over a wide range of concentrations, the serum 2,3,7,8-TCDD levels highly correlated with adipose tissue 2,3,7,8-TCDD levels when both were expressed on a lipid weight basis (Patterson et al. 1988). Adipose tissue serves as a storage depot for 2,3,7,8-TCDD in the body, and detectable levels (up to 20.2 ppt) were found in the general population with no known risk of high exposure to CDDs (Andrews et al. 1989). Studies conducted in mice have shown that 2,3,7,8-TCDD stored in adipose tissue grafts can be released and distributed to other tissues (Joffin et al. 2018). An average concentration of 2,3,7,8-TCDD in serum lipid of 5.38 pg/g has been estimated for the U.S. population (Orban et al. 1994). The distribution of highly chlorinated CDDs among tissue lipid fractions is not equal. For example, the distribution of OCDD is 12:1 (Thoma et al. 1990) between liver and adipose tissue lipid factions and 2:1 between serum and adipose tissue lipid fractions (Schecter et al. 1990b). A study conducted in Norway found that men and women who had similar dietary congener profiles had different serum congener profiles (Knutsen et al. 2011). In this study, the results of a regression analysis of factors influencing congener profiles suggested that being female was associated with lower levels of 1,2,3,7,8-PeCDD, 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, and 1,2,3,4,7,8,9-HpCDF.

Increased adipose tissue levels of CDDs were reported in populations with known high residential or occupational exposure (Beck et al. 1989b; Fingerhut et al. 1989; Patterson et al. 1989b; Schecter et al. 1994c). For example, high levels of 2,3,7,8-TCDD were found in fat (42–750 ppt) and serum lipid (61–1,090 ppt) of Missouri chemical workers (Patterson et al. 1989b). Measurable CDDs and CDFs levels were reported in the liver tissue of human stillborn neonates, suggesting that the transplacental intrauterine transfer of these persistent chemicals resulted from environmentally exposed mothers (Schecter et al. 1990b). In addition, CDDs are distributed to human milk (i.e., Fürst et al. 1994; Schecter et al. 1987a, 1987b, 1989e) and numerous studies have published concentrations of various congeners in human milk samples (see Section 5.6). Levels of CDDs in human milk have been found to be significantly and positively associated with proximity of residence to waste sites and to dietary fat intake per week (Schlaud et al. 1995).

Inhalation Exposure. The tissue distribution of 2,3,7,8-TCDD-derived radioactivity was examined in male Fischer-344 rats 3 days after intratracheal application of a single dose of 0.32 µg 2,3,7,8-TCDD/kg (Diliberto et al. 1996). The liver and adipose tissue were the major tissue depots for 2,3,7,8-TCDD-derived radioactivity, with 32.9 and 14.9% of the applied dose distributing to these respective tissues. The skin (ear) and muscle followed with 4.3 and 1.3%, respectively. All other tissues had <0.5% of the

administered dose. The 2/1 liver/adipose ratio was in contrast to the approximately 1/1 ratio found after gavage administration of the same dose.

Oral Exposure. Following an ingested dose of [^{3}H]-2,3,7,8-TCDD of 0.00114 µg/kg by a volunteer, the concentrations of 2,3,7,8-TCDD in the adipose tissue were 3.09 and 2.86 pg/g at 13 and 69 days following exposure, respectively (Poiger and Schlatter 1986). The study authors estimated that about 90% of the body burden was distributed to the fatty tissue. Increased radioactivity was detected in the blood only during the first 2 days postexposure; no radioactivity was detected in serum lipid after 5 days, but was in the feces for several months.

Studies in animals have shown that 2,3,7,8-TCDD distributes preferentially to the liver and adipose tissue. Following single gavage administration of 50 or 100 ng/kg of 2,3,7,8-TCDD in corn oil to female Harlan Sprague-Dawley rats, TCDD tissue concentrations in blood, lung, liver, and adipose were measured at several time intervals up to 150 days (NTP 2006). The highest peak tissue concentration (per gram of tissue) was observed in liver, followed by adipose > lung ≈ blood. Peak blood levels of 2,3,7,8-TCDD were observed within 24 hours of dosing, decreasing to nondetectable levels after 15 days; results were consistent with rapid distribution to tissues. Peak liver concentration was observed within 24 hours of dosing, whereas peak adipose concentration was observed in 20–40 days. In Sprague-Dawley rats, the highest levels of radioactivity (expressed as percentage of dose per gram of tissue) were located in the liver (3.18, 4.49, and 1.33% at days 3, 7, and 21 post-exposure, respectively) and adipose tissues (2.6, 3.22, and 0.43% at days 3, 7, and 21, respectively) following a single oral dose of labeled 2,3,7,8-TCDD at 50 µg/kg (Piper et al. 1973). Much smaller amounts were found in muscles, testes, lungs, stomach, and other organs. In male Fischer-344 rats administered a single gavage dose of 0.32 µg 2,3,7,8-TCDD/kg, 24.4 and 26.2% of the administered dose was found in the liver and adipose tissue, respectively, 3 days after dosing (Diliberto et al. 1996); skin and muscle had 7.3 and 1.8%, respectively. 2,3,7,8-TCDD accumulated mainly in the liver and adipose tissue, with smaller amounts in the brain of pregnant Wistar rats after 10 daily doses of 2 µg/kg (Khera and Ruddick 1973). Similarly, the highest levels of radioactivity were found in the liver, adipose tissue, and adrenals of Golden Syrian hamsters after a single gavage dose of 650 µg/kg labeled 2,3,7,8-TCDD (Olson et al. 1980b). In addition, about 36% of the total radioactivity administered remained in the adipose tissue by day 45 postexposure in Hartley guinea pigs; only about 7% (each) was found in the liver, pelt, and skeletal muscles and carcass (Olson 1986). When pregnant NMRI mice were exposed to a single oral, intraperitoneal, or subcutaneous dose of 2,3,7,8-TCDD, hepatic levels were about the same, indicating that there is no major first-pass effect after oral 2,3,7,8-TCDD exposure (Nau and Bass 1981). Liver, then adipose tissue and skin, were

the major depots of OCDD in Fischer-344 rats treated with single oral doses of this congener (Birnbaum and Couture 1988). One day following a single oral dose of [^{3}H]-labeled 2,3,7,8-TCDD (12.5 ng/kg) administered to female Long-Evans rats, the largest percentages of the administered radioactivity dose were found in liver (46%) adrenal gland (20%), adipose (24%), lung (14%) and thymus (10%) (Yonemoto et al. 2005). In this same study, the distribution of radioactivity following a single dose of [^{3}H]-labeled 2,3,7,8-TCDD administered to pregnant rats late in gestation was similar to that of non-pregnant rats, with the largest percentages of dose found in liver (11.8%) and adipose tissue (3.65%). A similar distribution of radiolabelled 2,3,7,8-TCDD was found in pregnant and adult male rats following a single dose of [^{14}C]-2,3,7,8-TCDD (10 μg/kg), with the largest percentage of the dose found in liver (Ishida et al. 2010).

The dose- and time-dependent tissue distribution of 2,3,7,8-TCDD in mice has been examined (Diliberto et al. 1995, 1998, 1999, 2000; Hakk et al. 2009; van Birgelen et al. 1996). Results show that distribution to liver and adipose tissue is dose-dependent; at lower doses, distribution (as a percentage of the administered dose) to adipose tissue is greater than to liver, whereas at higher doses, distribution to liver is greater than to adipose tissue. A typical example of the patterns for dose- and time-dependent distribution of 2,3,7,8-TCDD is provided in a study by Diliberto et al. (1995). In this study, female B6C3F1 mice were administered a single dose of 0.1, 1, or 10 μg [^{3}H]-2,3,7,8-TCDD/kg by gavage in corn oil and the distribution of radioactivity was followed in 18 tissues for up to 35 days after dosing. The results showed dose-dependent distribution of 2,3,7,8-TCDD-derived radioactivity in all tissues. The highest concentrations of radioactivity were found in liver and adipose tissues, and both tissues accounted for 50% of the body burden. Relatively high concentrations of 2,3,7,8-TCDD-derived radioactivity were also found in skin, adrenal glands, thyroid, pancreas, olfactory epithelium, spleen, mesenteric lymph nodes, thymus, lung, and bone marrow. The liver concentration of radioactivity increased disproportionally with increasing doses, whereas relative concentration and percentage dose/total tissue in extrahepatic tissues decreased with increasing dose and over time. Liver/adipose tissue concentration ratios were shown to be dose- and time-dependent. At the low, mid-, and high dose, the ratios were 0.6–0.2, 2.3–0.5, and 3.1–1.4 over time, respectively. This variation over time was thought to have been due to redistribution of 2,3,7,8-TCDD between the two storage sites and/or hepatic metabolism and subsequent excretion. Dose-dependence of distribution of 2,3,7,8-TCDD and TEQ to liver and adipose tissue appears to be related to induction of CYP1A2, a protein that is under AhR transcriptional regulation and binds to 2,3,7,8-TCDD (Diliberto et al. 1998, 1999, 2000; Hakk et al. 2009; Watanabe et al. 2010).

The effect of age of the animal on 2,3,7,8-TCDD tissue distribution has also been examined. Pegram et al. (1995) administered a single dose of 0.015, 0.5, or 15 µg [^{3}H]-2,3,7,8-TCDD/kg to 10-week-old and 28-month-old male C57BL/6N mice and monitored 2,3,7,8-TCDD-derived radioactivity in blood, liver, skin, kidney, and muscle 7 days after dosing. The results showed that in young mice given the low and high dose, the concentration of 2,3,7,8-TCDD in blood relative to all other tissues was significantly greater than in older mice. Also, in older mice, the concentration of 2,3,7,8-TCDD in skin and the percentage of the dose in the skin were greater than in the young mice. The same trend was observed in kidney and muscle. The concentration of 2,3,7,8-TCDD in liver, as well as the percentage of the dose in the liver, were greater in younger animals as compared to older animals at both the mid- and high doses. In both younger and older mice, the ratios of liver to adipose tissue increased with increasing doses. According to the study authors, the higher hepatic concentration of 2,3,7,8-TCDD in younger mice could be due to the older mice having a larger fat compartment, such that the hepatic 2,3,7,8-TCDD sequestering action of CYP1A2 or other inducible binding factors may have been less effective in the more obese older mice. In addition, decreased perfusion in the liver and adipose compartments in the older mice may have limited the effectiveness of hepatic 2,3,7,8-TCDD accumulation. The greater accumulation of 2,3,7,8-TCDD in the skin, muscle, and kidney from older mice was attributed to altered perfusion and possibly greater lipid infiltration in these tissues.

The subcellular distribution of 2,3,7,8-TCDD-derived radioactivity in the liver, lungs, and kidneys from female Sprague-Dawley rats and B6C3F1 mice was studied by Santostefano et al. (1996). In the liver of rats given a single oral dose of 0.1, 1, or 10 µg [^{3}H]-2,3,7,8-TCDD/kg, radioactivity accumulated equally in the supernatant (S9, cytosol, and microsomes) and pellet (P9, nucleus, lysosomes, and mitochondria) fractions; within the S9 fraction, accumulation was predominantly in the microsomal fraction. In contrast, in kidneys and lungs, radioactivity accumulated preferentially in P9, but radioactivity detected in S9 was mostly in the cytosolic fraction. The pattern of distribution of radioactivity in liver and lungs from mice was similar to that found in rats, but in mice kidneys, 2,3,7,8-TCDD detected in S9 was equally distributed between the microsomal and cytosolic fractions. Accumulation of 2,3,7,8-TCDD in the various fractions in this single-dose study was not dose-dependent. The investigators also conducted a 17-week oral dosing study in B6C3F1 mice given 1.5 or 150 ng/kg that showed that increasing the dose resulted in equal accumulation between liver S9 and P9 fractions, whereas the kidney P9 had the most radioactivity regardless of the dose. In addition, liver S9 accumulated 2,3,7,8-TCDD in the microsomal fraction, whereas kidney S9 accumulated predominantly in the cytosol. These results are consistent with the hypothesis that hepatic microsomal sequestration of 2,3,7,8-TCDD is mediated by CYP1A2, a dioxin-inducible protein. This hypothesis was subsequently confirmed by experiments in transgenic mice

lacking expression of Cyp1a2 (Cyp1a2$^{-/-}$) (Diliberto et al. 1997). These mice, as judged by 2,3,7,8-TCDD liver/fat concentration ratios, failed to sequester 2,3,7,8-TCDD in the liver after administration of a single dose of 2,3,7,8-TCDD.

The distribution of CDDs under steady-state or near steady-state conditions has been studied in intermediate-duration oral exposure studies (Birnbaum and Couture 1988; Birnbaum et al. 1989a; DeVito et al. 1998; Diliberto et al. 2001; Fries and Marrow 1975; Laurent et al. 2005; Norback et al. 1975). In female B6C3F1 mice administered via gavage [^{3}H]-2,3,7,8-TCDD (1.5 or 150 ng/kg/day) in corn oil 5 days/week for 13 weeks, radioactivity was detected in all tissues examined (blood, adipose tissue, liver, kidneys, lungs, skin, muscle, spleen, and thymus), with the highest tissue concentrations in liver and adipose tissue (Diliberto et al. 2001). As demonstrated in single-dose studies (discussed above), at the lower dose, distribution (as a percentage of the administered dose) to adipose tissue was greater than to liver, whereas at the higher dose, distribution to liver was greater than to adipose tissue. In female B6C3F1 mice administered 2,3,7,8-TCDD (1.5–150 ng/kg/day) or 1,2,3,7,8-PeCDD (90–9,000 ng/kg/day) in corn oil by gavage 5 days/week for 13 weeks, dose-dependent increases in tissue concentrations were observed for liver, adipose tissue, skin, and blood (DeVito et al. 1998). After 13 weeks of treatment, tissue concentrations of CDDs were highest in liver, followed by adipose tissue, skin, and blood. The study authors suggested that high liver concentrations of CDDs are consistent with an inducible hepatic binding protein for dioxin-like compounds. Liver and adipose levels of CDDs were monitored in male Sprague-Dawley rats fed diets containing a mixture of CDDs (TCDD, PeCDD, HxCDD, HpCDD, and OCDD) from contaminated milk for 120 days (Laurent et al. 2005). Liver and adipose tissue levels of CDDs remained constant after approximately 1.5 months, with greater amounts found in the liver compared to adipose tissue; the ratio of liver:adipose tissue CDD levels ranged from 2.5 for 2,3,7,8-TCDD to 33 for OCDD. Intermediate-duration exposure to 2,3,7,8-TCDD in the feed has been shown to produce higher liver accumulation in male rats (85%) than in female rats (70%) (Fries and Marrow 1975). The percentage retained was related to intake, and at steady state, the total amount retained was about 10.5 times the average daily intake.

Intermediate-duration studies have also been conducted with radioactively labeled OCDD. OCDD had similar patterns of distribution and similar half-lives as 2,3,7,8-TCDD in Sprague-Dawley (Norback et al. 1975) and Fischer-344 rats (Birnbaum and Couture 1988; Birnbaum et al. 1989a). Most of the absorbed amount (50–97%) was found in the liver and was associated with the microsomal fractions. Skin and adipose-tissue levels were much lower. Radioactivity was also detected in the kidneys, heart, testes, skeletal muscle, and serum.

Dermal Exposure. Male Fischer-344 rats absorbed 40% of a single dermal dose of 0.32 µg of radioactive 2,3,7,8-TCDD/kg over a period of 120 hours after dosing (Banks and Birnbaum 1991). The major depots for 2,3,7,8-TCDD-derived radioactivity were the liver and adipose tissue. Seventy-two hours after dosing, the liver and adipose tissue retained approximately 21 and 8% of the administered dose, respectively. Distribution to the liver increased significantly between 4 and 8 hours and between 12 and 72 hours after dosing. Distribution in fat increased significantly between 12 and 120 hours after dosing. Skin and muscle accumulated considerably less 2,3,7,8-TCDD-derived radioactivity than liver and fat. Within 120 hours of dosing, <4% of the administered dose was found in the skin or muscle tissues. When 2,3,7,8-TCDD was dermally applied to HRS/J hairless mice for an intermediate duration, about 5–6% of the total administered dose (0.0025–0.01 µg/kg, 2 days/week, for 20 weeks) was detected in the liver (Hebert et al. 1990).

3.1.3 Metabolism

Little data were located regarding metabolic pathways of CDDs in humans. However, there is some evidence that 2,3,7,8-TCDD is partially excreted in the feces in the form of metabolites (Sorg et al. 2009; Wendling et al. 1990). Two main metabolites, 2,3,7-trichloro-8-hydroxydibenzo-*p*-dioxin and 1,3,7,8-tetrachloro-2-hydroxydibenzo-*p*-dioxin, were identified in feces, urine, and blood serum of an individual poisoned with TCDD (Sorg et al. 2009). The patient's blood serum level of TCDD was 108,000 pg/g lipid 3 months after the poisoning. Results of an *in vitro* study using recombinant yeast microsomes containing human CYP isozymes from human liver show that 2,3,7-TrCDD undergoes sequential metabolism by CYP and UDP-glucuronosyltransferase (Kasai et al. 2004). Using the same *in vitro* model, several mono-, di-, and tri-CDDs have been shown to be metabolized by multiple forms of CYP (Inouye et al. 2002). Metabolites included products of multiple reactions, including several types of hydroxylation reactions. Enzymes CYP1A1 and CYP1A2 exhibited the highest activity for mono-, di-, and tri-CDDs, although other CYP isozymes (PYP2C8, CYP2C9, and CYP3A4) did not show any significant activity for CDDs; none of the CYP isozymes showed any activity toward 2,3,7,8-TCDD.

A study in animals indicates that 2,3,7,8-TCDD is metabolized slowly in mammals (Koshakji et al. 1984). Metabolic transformation by phase I metabolizing enzymes includes oxidation and reductive dechlorination, as well as oxygen bridge cleavage. This is followed by conjugation reactions catalyzed by phase II type enzymes, which facilitate excretion by adding more polar groups to the molecule. A study in guinea pigs showed that only 28% of the radioactivity in the tissues 45 days following exposure to

[^{3}H]-2,3,7,8-TCDD was in the form of metabolites (Olson 1986). Results from high performance liquid chromatography (HPLC) suggested the presence of at least five [^{3}H]-labeled metabolites of 2,3,7,8-TCDD, but their structure was not established. The results indicated that in the guinea pig, the metabolites of 2,3,7,8-TCDD may not leave the body rapidly. In rats and hamsters, metabolism appears to be required for urinary and biliary excretion (Olson et al. 1980a). Metabolites of 2,3,7,8-TCDD are not generally detected in tissues, suggesting that for most species, 2,3,7,8-TCDD is readily eliminated following metabolism.

The role of CYP1A2 in the overall metabolism of CDDs has been studied in *CYP1A2* knockout mice (lacking the *Cyp1a2* gene) following single-dose oral exposure (Hakk and Diliberto 2002, 2003; Hakk et al. 2009). Results show that mice with the *Cyp1a2* gene (wild-type mice) only metabolize slightly more 2,3,7,8-TCDD or 1,2,3,7,8-PeCDD than *Cyp1a2* knockout mice, indicating that sequestration of CDDs by binding to CYP1A2 does not have an important effect on metabolism by other CYP isozymes or other enzymes (Hakk and Diliberto 2002, 2003). Overall metabolism did not exhibit dose-dependence in either wild-type or *CYP1A2* knockout mice (Hakk et al. 2009).

Metabolism of 1,3,6,8-TCDD was studied in hepatic microsomes obtained from male C57BL/6 mice administered a single oral dose of 2,3,7,8-TCDD in corn oil (Aozasa et al. 1996). Metabolites of 1,3,6,8-TCDD included several hydroxylation products, which appear to be further metabolized to other compounds, including quinones, sulfate conjugates, and other smaller compounds (not identified). Metabolites isolated from urine, bile, and feces of Sprague-Dawley rats administered a single dose of [^{14}C]-1,2,7,8-TCDD (8 mg/kg) in corn oil by gavage include hydroxylation products, glucuronide conjugates, and sulfide conjugates (Hakk et al. 2001). Similar metabolic profiles were reported for 1,3,7,8- and 1,4,7,8-TCDD (Huwe et al. 1997, 1998; Petroske et al. 1997).

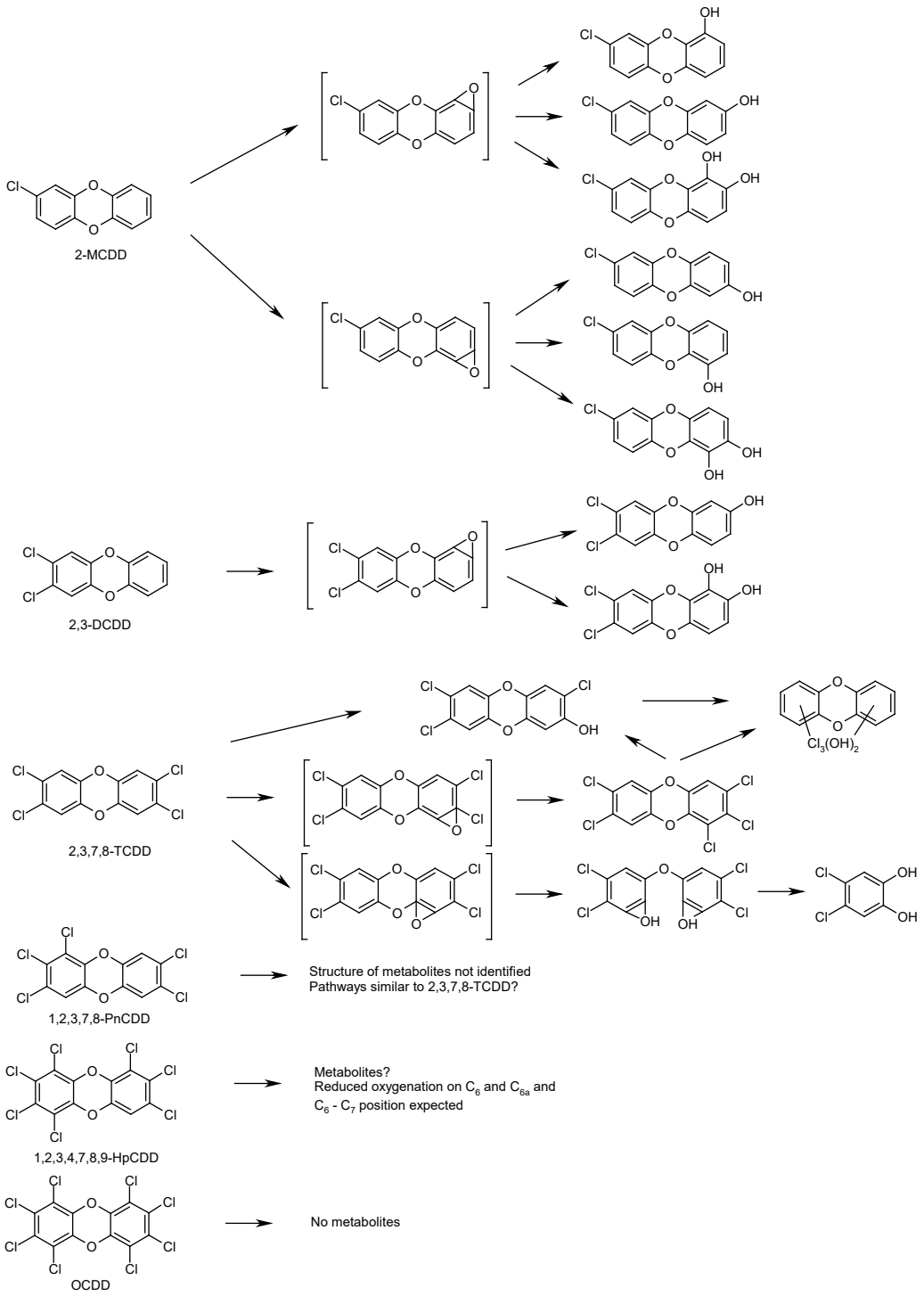
An *in vitro* study with isolated rat hepatocytes identified 1–hydroxy-2,3,7,8-TCDD and 8-hydroxy-2,3,7-TrCDD as metabolites (Sawahata et al. 1982). 2-Hydroxy-1,3,7,8-TCDD was found to be the major metabolite of 2,3,7,8-TCDD in dogs but not in rats (Poiger et al. 1982). The metabolites from dogs administered to rats were eliminated as conjugates in the bile (Weber et al. 1982). Self-induction of 2,3,7,8-TCDD metabolism was reported in both species (Poiger and Schlatter 1985; Weber et al. 1982). A single 10 µg/kg dose of unlabeled 2,3,7,8-TCDD 9 days prior to administration of [^{3}H]-2,3,7,8-TCDD resulted in a doubling of the amount of radioactivity eliminated in the bile of dogs. When the 2,3,7,8-TCDD metabolites, 2-hydroxy-2,3,7-TrCDD and 2-hydroxy-1,3,7,8-TCDD, were synthesized and injected intraperitoneal into Wistar rats, no toxic effects were observed (Mason and Safe 1986). This

supports the observation that the extract from the bile of 2,3,7,8-TCDD-treated dogs is about 100 times less toxic to rats and guinea pigs than pure 2,3,7,8-TCDD (Poiger et al. 1982). The lack of toxicity of the 2,3,7,8-TCDD metabolites suggests that autoinduction of its own metabolism in animals is a detoxification mechanism.

Data regarding other 2,3,7,8-substituted CDDs are limited. Wacker et al. (1986) found at least three phenolic radiolabeled metabolites of [^{14}C]-1,2,3,7,8-PeCDD in rat bile after treatment with glucuronidase and methylation, indicating the probability of formation of hydroxy metabolites. Results from studies in rats revealed no metabolites of OCDD, as expected from the fully chlorinated molecule (Birnbaum and Couture 1988; Tulp and Hutzinger 1978).

CDDs induce both phase I and phase II drug-metabolizing enzymes including AHH, ethoxyresorufin-O-deethylase (EROD), UDP-glucuronosyltransferase, glutathione S-transferase, and DT-diaphorase (Van den Berg et al. 1994). These enzymes are responsible for the metabolism of a variety of exogenous and endogenous substances. Pretreatment of C57BL/6J mice with 2,3,7,8-TCDD increased hepatic accumulation of a subsequent radiolabeled dose (total liver burden increased about 50%), whereas distribution to the kidney, fat, heart, lung, and gastrointestinal tract were reciprocally decreased (Curtis et al. 1990). The data indicated that an inducible, saturable system is involved in 2,3,7,8-TCDD toxicokinetics. The pretreatment, however, did not alter the hepatic metabolism of 2,3,7,8-TCDD in exposed mice. Similarly, the rate of metabolism of 2,3,7,8-TCDD in hepatocytes from 2,3,7,8-TCDD-pretreated (induced) guinea pigs and mice was unchanged from that in untreated animals (Olson and Wroblewski 1985; Shen et al. 1989; Wroblewski and Olson 1985). In contrast, the rate of metabolism in hepatocytes from 2,3,7,8-TCDD-pretreated rats was 3.2-fold greater than the rate in hepatocytes from control rats and about 9 times greater than in hepatocytes from 2,3,7,8-TCDD-pretreated guinea pigs. The difference between the 2,3,7,8-TCDD ability to induce its own rate of metabolism in rats and guinea pigs could be a factor in the difference between the susceptibility to 2,3,7,8-TCDD-induced toxicity in these two species, because the parent compound rather than metabolites is the toxic agent (Poland and Glover 1979). A generalized scheme of metabolic pathways for CDDs based on information from *in vivo* mammalian studies was proposed by Van den Berg et al. (1994) and is presented in Figure 3-1.

Figure 3-1. A Generalized Scheme of Pathways for the Biotransformation of CDDs Based on Information from *In Vivo* Mammalian Studies



CDD = chlorinated dibenzo-*p*-dioxin; DCDD = dichlorodibenzo-*p*-dioxin; HpCDD = heptachlorodibenzo-*p*-dioxin; MCDD = monochlorodibenzo-*p*-dioxin; OCDD = octachlorodibenzo-*p*-dioxin; PnCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin

Source: Van der Berg et al. 1994

3.1.4 Excretion

In humans, the primary route of excretion of absorbed CDDs is the feces (Rohde et al. 1999; Schlummer et al. 1998). Results of a study in two female patients with severe TCDD intoxication show that 2,3,7,8-TCDD undergoes cutaneous elimination (Geusau et al. 2001a). The TCDD exposure source for these patients is unknown (Geusau et al. 2001b). Cutaneous elimination was approximately 1–2% of the total daily TCDD elimination, when adjusted for skin surface area.

A median half-life of 7.1 years was estimated for 2,3,7,8-TCDD in a group of 36 Vietnam veterans (CDC 1987; Pirkle et al. 1989). The calculation was based on the decrease of 2,3,7,8-TCDD serum levels that were measured in these individuals in 1982 and again in 1987. The individual half-life values varied from 2.9 to 26.9 years. In an expanded half-life study of 343 Vietnam veterans participating in Operation Ranch Hand, which included the subjects of the Pirkle et al. (1989) study, a half-life estimate of 8.7 years (95% CI: 8.0–9.5 years) was calculated (Michalek et al. 1996). The half-life estimate was calculated using 2,3,7,8-TCDD levels in blood samples collected in 1982, 1987, and 1992. An earlier study of these subjects (Wolfe et al. 1994), which used data from two blood collection periods (1982 and 1987), estimated a half-life of 11.3 years (95% CI=10–14.1 years). This half-life of 11.3 years was considered too high because it was based on restricted analysis of veterans with 2,3,7,8-TCDD levels >10 ppt. By conditioning the data to lie above a line with slope equal to the negative of the decay rate, the analysis yielded a revised half-life of 8.7 years. In a 15-year follow-up of 97 Operation Range Hand veterans, Michalek and Tripathi (1999) estimated a half-life of 7.6 years (95% CI: 7.0–8.2 years). Michalek et al. (2002) conducted a combined analysis of Seveso adults and Operation Ranch Hand veterans. In the Seveso cohort, a period of fast elimination (half-life: 0.34 years) during the first 0.27 years after exposure was followed by a period of slower elimination (half-life: 6.9 years) from 3 to 16.35 years. In the Ranch Hand cohort, the half-life from 9 to 33 years (7.5 years) was similar to that of the Seveso population. The study authors noted that results in the Seveso cohort are consistent with a two-compartment model, with a distribution phase with rapid elimination, followed by a slower elimination phase.

Several other studies have calculated 2,3,7,8-TCDD half-lives. A mean half-life of 5.8 years was estimated from repeated samples from 29 BASF AG facility workers with initial 2,3,7,8-TCDD serum lipid concentrations of 29–553 ppt (Ott and Zober 1996). In a study of 48 German workers at a pesticide facility who were exposed to a mixture of CDDs/CDFs, a median half-life of 7.2 years was estimated for 2,3,7,8-TCDD (Flesch-Janys et al. 1996). Needham et al. (1994) estimated a half-life of 8.2 years in 27 Seveso residents with initial serum 2,3,7,8-TCDD levels of 130–3,830 ppt. A study of Seveso women

found the half-life to vary with the age at time of exposure (Warner et al. 2014). The half-lives were 7.1 years in women who were exposed at >10 years of age, 5.2 years in women who were exposed at 6–10 years of age, and 4.3 years in women who were <5 years of age at the time of exposure. Using data from a human subject ingesting a single dose of 1.14 ng/kg 2,3,7,8-TCDD, Poiger and Schlatter (1986) calculated a half-life of 2,120 days (5.8 years). Geyer et al. (1986) noted that they calculated a half-life of 3.5–6.9 years, but did not describe the basis of this estimation. Overall, there is good agreement between the 2,3,7,8-TCDD half-lives estimated in four different populations (Vietnam veterans, BASF AG cohort, German pesticide workers, and Seveso residents); the half-lives were 5.8–8.7 years (Aylward et al. 2013; Flesch-Janys et al. 1996; Michalek et al. 1996; Needham et al. 1994; Ott and Zober 1996; Yamamoto et al. 2015b). Several studies have found correlations between percentage of body fat and 2,3,7,8-TCDD elimination half-times (Flesch-Janys et al. 1996; Michalek et al. 1996; Ott and Zober 1996; Wolfe et al. 1994). Ott and Zober (1996) estimated half-lives of 5.1 and 8.9 years in subjects with 20 and 30% body fat, respectively. Age and body burden also appear to influence 2,3,7,8-TCDD half-life (Kerger et al. 2006). Among Seveso children (<18 years of age at the time of the accident), half-lives of 2.4 and 1.6 years were estimated for children with 2,3,7,8-TCDD levels <700 ppt (average concentration of 219 ppt) and >700 ppt (average concentration of 1,400 ppt), respectively; the half-lives were significantly different. Similarly, the half-life in children <18 years of age at the final sampling was 1.6 years, which was significantly lower than the half-life of 3.2 years in children ≥18 years of age at the final sampling.

There are limited data available on the elimination of other CDD congeners in humans. In the Flesch-Janys et al. (1996) study of 48 workers at a German pesticide facility, elimination half-times were estimated for several CDD congeners. The estimated half-lives were 15.7 years for 1,2,3,7,8-PeCDD, 8.4 years for 1,2,3,4,7,8-HxCDD, 13.1 years for 1,2,3,6,7,8-HxCDD, 4.9 years for 1,2,3,7,8,9-HxCDD, 3.7 years for 1,2,3,4,6,7,8-HpCDD, and 6.7 years for OCDD. In a study of six German workers with high CDD/CDF body burdens, elimination half-lives corrected for alterations in body weight ranged from 3.5 years for 1,2,3,4,6,7,8-HpCDF to 7.9 years for 2,3,7,8-TCDD and 15 years for 1,2,3,4,7,8-HxCDD (Rohde et al. 1997). In the same study, half-lives for elimination due only to fecal excretion ranged from 10 years for OCDD to 22 years for 2,3,7,8-TCDD to 27 years for 1,2,3,7,8-PeCDD. The half-lives for 2,3,4,7,8-PeCDF in humans exposed to contaminated rice oil in the Yusho incident ranged from 2 to 30 years, and were inversely dependent on adipose tissue concentrations above approximately 10 ng/kg body weight (i.e., the higher the body burden, the faster the elimination) (Ryan et al. 1993a). Aylward et al. (2013) estimated elimination half-lives for CDD congeners and TEQ in former workers (n=56) at a chlorophenol plant. Median intrinsic half-lives (body burden half-life adjusted for continued exposure) were as follows: 10.7 years for PeCDD (specific congener not reported), 7.0 years for

1,2,3,4,7,8-HxCDD, 9.0 years for 1,2,3,6,7,8-HxCDD; 6.3 years for 1,2,3,7,8,9-HxCDD, 6.7 years for 1,2,3,4,7,8,9-HpCDD, 7.3 years for OCDD, and 8.7 years for total TEQ (CDDs, CDFs, and dioxin-like PCBs. Yamamoto et al. (2015b) estimated the following elimination half-lives for CDD congeners in former workers (n=16) at an incineration plant measured over a 7-year period beginning 3 years after the plant was shut down. Mean half-lives were as follows: 13.8 years for 1,2,3,7,8-PeCDD, 10.0 years for 1,2,3,4,7,8-HxCDD, 12.5 years for 1,2,3,6,7,8-HxCDD, 4.8 years for 1,2,3,7,8,9-HxCDD, 6.7 years for 1,2,3,4,7,8,9-HpCDD, and 9.1 years for TEQ (CDDs, CDFs, and dioxin-like PCBs).

Inhalation Exposure. In male Fischer-344 rats administered a single intratracheal dose of 0.32 μg labeled 2,3,7,8-TCDD/kg, fecal elimination was the major route of elimination over a 3-day period after dosing (Diliberto et al. 1996). The cumulative fecal excretion of 26.3% of the administered dose was observed over 3 days following exposure. Approximately 4% of the dose was excreted in the feces on day 3. The cumulative urinary excretion was only 1.3% of the administered dose.

Oral Exposure. Elimination across the gastrointestinal tract is an important elimination pathway for absorbed CDDs in humans. Results of a mass balance study in six men with high body burdens of CDDs showed that fecal elimination of 2,3,7,8-TCDD and OCDD was 37 and 90%, respectively, of total elimination (Rohde et al. 1999). Fecal elimination of CDDs exceeded dietary intake, indicating gastrointestinal excretion of CDDs from diet or body stores. Similar results were reported in a mass balance study in 14 volunteers (7 males and 7 females), with fecal excretion exceeding dietary intake by approximately 2-fold (Schrey et al. 1998). Fecal excretion was the main route of elimination also in a patient poisoned with a high level of TCDD (Sorg et al. 2009). During the 3-year period of follow-up testing, the patient eliminated in feces and urine the total amount of the two major metabolites equivalent to about 95 μg of TCDD (i.e., 38% of total TCDD eliminated by all means). The half-life of TCDD in this patient was 15.4 months. The elimination pattern fits into a model predicting that expected half-life of TCDD ranges from <3 years in people exposed to high levels (>10,000 pg/g serum lipids of internal dose) to >10 years in those exposed to lower levels (<50 pg/g serum lipids of internal dose) (Aylward et al. 2005).

The half-life for elimination of a single oral dose of 1.14 ng/kg [^{3}H]-2,3,7,8-TCDD in a volunteer was calculated as 5.8 years (Poiger and Schlatter 1986). The excretion in feces was high during the first few days (up to day 6) probably because of elimination of unabsorbed material. During these first few days, about 12% of the administered dose was excreted. However, during days 7–125, only about 3.5%

of the administered dose was eliminated. Urinary levels of radioactivity did not exceed the background levels.

Studies in animals have shown that 2,3,7,8-TCDD can be excreted in feces and urine. In C57BL/6N and *CYP1A2* knockout mice administered single oral doses of [^{3}H]-2,3,7,8-TCDD (0.1 or 10 μg/kg), 24–31 and <5% of the administered dose were eliminated in feces and urine, respectively, within 4 days; no dose-related differences in excretion were observed (Hakk et al. 2009). Following oral administration of [^{14}C]-2,3,7,8-TCDD (1.25 mg/kg) to male Sprague-Dawley rats, only 0.27% of the administered dose of [^{14}C] was eliminated in urine within 3 days (Hakk et al. 1998). Of the [^{14}C] excreted in urine, approximately 8.8% of the urinary [^{14}C] was bound to albumin and approximately 64.2% was unbound. In bile-duct cannulated rats, 9.6% of [^{14}C] in bile was bound to an unidentified 89kDa protein and 76.6% was unbound. In male Sprague-Dawley rats administered a single dose of [^{14}C]-1,2,7,8-TCDD (8 mg/kg) in peanut oil by gavage, 94.2% of the administered radioactivity was recovered in feces (79.8%) and urine (14.3%).

Biliary excretion was estimated as 32.4%, using biliary-cannulated rats (Hakk et al. 2001). Fecal excretion is also the predominant elimination pathway for 1,4,7,8-TCDD (Huwe et al. 1998). In male Sprague-Dawley rats administered a single dose of [^{14}C]-1,4,7,8-TCDD (2 mg total dose), 88.8 and 3.3% of the administered [^{14}C] was eliminated in feces and urine, respectively, within 3 days; biliary excretion was estimated as >30% of the administered [^{14}C]. Following oral administration of [^{14}C]-1,2,3,7,8-PeCDD (2.9 mg/kg) to male Sprague-Dawley rats, only 0.22% of the administered dose of [^{14}C] was eliminated in urine within 3 days (Hakk et al. 1999). Of the [^{14}C] excreted in urine, approximately 17.9% of the urinary [^{14}C] was bound to albumin and approximately 78.1% was unbound. In bile-duct cannulated rats, 7.2% of [^{14}C] in bile was bound to an unidentified 89kDa protein and 91.1% was unbound.

Studies in animals indicated that elimination of 2,3,7,8-TCDD is a relatively slow process. However, the results showed a great variability among species. The half-life for 2,3,7,8-TCDD elimination was 14.95 days in Syrian hamsters (Olson et al. 1980b), 12 and 14 days in male and female Sprague-Dawley rats, respectively (Fries and Marrow 1975), 17 days in male Sprague-Dawley rats in another study (Piper et al. 1973), and 94 days in guinea pigs, the most sensitive species to the acute toxicity of 2,3,7,8-TCDD (Olson 1986). In contrast, the elimination half-life was 391 days in monkeys chronically exposed to low doses of 2,3,7,8-TCDD in the feed (Bowman et al. 1989b). A similar half-life of about 1 year was observed in monkeys after a single-dose exposure (McNulty et al. 1982). In addition, studies of

2,3,7,8-TCDD half-life in highly exposed rats (Abraham et al. 1988), Rhesus monkeys (McNulty et al. 1982), and marmoset monkeys showed that rates of excretion decreased with dose. In mice, the blood elimination half-life is affected by obesity. Obesity in C57BL/6J mice resulted in a 2- and 10-fold increase in the blood elimination half-life following an oral dose of [^{3}H]-labeled 2,3,7,8-TCDD (5 or 0.1 μg/kg dose, respectively) (Emond et al. 2018). The clearance of radioactivity after oral exposure to labeled 2,3,7,8-TCDD followed first-order kinetics in most studies. Fecal elimination was the major route, although excretion in urine, expired air, and milk was also reported.

When Sprague-Dawley rats were given radioactively labeled 2,3,7,8-TCDD, a total of 53% of the administered radioactivity was excreted by feces in the first 21 days (Piper et al. 1973). Elimination of 2,3,7,8-TCDD-derived radioactivity in urine and expired air was 13 and 3% of the administered dose, respectively. Over a 3-day period after dosing, 32.2% of a single gavage dose of 0.32 μg of 2,3,7,8-TCDD/kg was eliminated in the feces of male Fischer-344 rats (Diliberto et al. 1996). Only 1.4% of the administered dose was excreted in the urine over the same period. About 20–30% of the total oral 2,3,7,8-TCDD dose was eliminated in the bile of cholecystectomized and cannulated dogs (Poiger et al. 1982). In addition, excretion of unchanged 2,3,7,8-TCDD in milk was demonstrated in NMRI mice (Nau et al. 1986) and monkeys (Bowman et al. 1989b) after oral exposure.

Of the other congeners, several have been studied. An elimination half-life of 29.5 days was estimated for 1,2,3,7,8-PeCDD in Sprague-Dawley rats following a single oral exposure (Wacker et al. 1986). OCDD was more persistent in Fischer-344 rats, with an estimated elimination half-life of 3–5 months following 10 daily oral doses (Birnbaum and Couture 1988). These congeners were excreted primarily in the feces following biliary elimination as metabolites (1,2,3,7,8-PeCDD, at least three phenolic metabolites) or parent compound. A 13-week dosing study in which Sprague-Dawley rats were administered various mixtures of CDDs estimated liver half-lives of 14.5, 29.3, 45.6, and 100 days for 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, and 1,2,3,4,6,7,8-HpCDD, respectively (Viluksela et al. 1998a).

Dermal Exposure. Within 120 hours after dermal administration of 0.32 μg/kg 2,3,7,8-TCDD to the clipped back skin of male Fischer-344 rats, 4% of the administered dose was excreted in the feces and <1% was excreted in the urine (Banks and Birnbaum 1991). The rate of 2,3,7,8-TCDD elimination significantly increased over time.

Transfer of CDDs Through the Placenta and Human Milk. CDDs are lipophilic compounds that can concentrate in maternal milk. Therefore, lactation provides an efficient mechanism for decreasing the body burden of these compounds (Schecter and Gasiewicz 1987a). Analysis of data obtained through NHANES provides support that human milk levels of CDDs generally reflect blood lipid levels of CDDs, although these ratios may vary considerably between individuals and over time (Aylward et al. 2003). In a study of 21 Japanese women, statistically significant correlations have been reported between CDD concentrations (expressed as TEQs) in maternal blood and milk ($r=0.695$; $p=0.0007$), maternal adipose tissue ($r=0.913$; $p<0.0001$), and cord blood ($r=0.759$; $p<0.0001$) (Nakano et al. 2005). In a study of primiparous women in Japan, the ratio of milk CDDs to blood CDDs were 0.57 for 2,3,7,8-TCDD, 0.64 for 1,2,3,7,8-PeCDD, 0.55 for 1,2,3,6,7,8-HxCDD, 0.23 for1,2,3,4,6,7,8-HpCDD, 0.08 for OCDD, and 0.11 for total CDDs (Todaka et al. 2008). Analysis of tissue CDDs obtained from 20 maternal-fetal pairs showed the highest levels of CDDs in perinatal venous serum, followed by placenta, cord serum, and human milk (Wang et al. 2004). Transfer of CDDs from mothers to fetuses and infants was assessed by measuring CDDs in maternal blood, cord blood, placenta, maternal adipose tissue, and milk in 22 Japanese women (Suzuki et al. 2005). Results show that CDD congeners with high TEQs accumulate in the placenta relative to maternal blood and that CDD levels in milk are influenced, in part, by maternal adipose levels.

CDD levels in human milk samples have been measured in many studies. The results from some of the surveys of samples taken from 2000 to 2024 are reported in Table 3-1. In general, the levels in milk decreased with decreasing degree of chlorination from octa- to tetra-CDD. Milk samples from industrial countries tended to have higher CDD levels than those from less developed countries.

Fürst et al. (1989) also found that the levels of CDDs found in the milk of mothers breastfeeding their second child were about 20–30% lower than in those breastfeeding their first child. It was further noted that the highest excretion of CDDs was during the first few weeks after delivery. The sharpest decline was observed with OCDD; its excretion was reduced by half between the first and fifth week of lactation. In contrast, there was no significant decline in total HxCDDs in milk during the first year of lactation. The concentration of 1,2,3,4,6,7,8-HpCDD in milk fat showed a steady decline over the 1-year period, but its levels stayed relatively high. 2,3,7,8-TCDD represented the smallest portion of the total CDDs, and its levels in milk continuously declined over the year of lactation. Levels of 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD were measured in a mother of twins prior to nursing and after 2 years of nursing (Schecter et al. 1996a). There was a 49.5% decrease in the total amount of CDDs in the lipid fraction of the human milk. 2,3,7,8-TCDD had

Table 3-1. Mean Levels of CDDs in Human Milk (ng/kg Milk Fat)

	2,3,7,8-TCDD	1,2,3,7,8-PeCDD	1,2,3,4,7,8-HxCDD	1,2,3,6,7,8-HxCDD	1,2,3,7,8,9-HxCDD	1,2,3,4,7,8,9-HpCDD	OCDD
Canada (n=298) Rawn et al. 2017	0.45	1.7	1.2	8.1	1.3	8.4	35
France (n=244) Focant et al. 2013	1.09	4.36	1.81	16.15	2.32	16.17	74.97
Hungary[a] (n=22) Vigh et al. 2013	0.28–0.34	0.56–0.74	0.66–0.96	2.17–3.32	0.85–1.12	2.57-–3.71	34.51–48.92
Ireland n=16 Houlihan et al. 2021	0.36	1.1	0.43	2.1	0.52	2.5	20
Ireland (n=11[b]) Pratt et al. 2012	0.61	1.85	0.87	4.76	0.88	8.07	49.8
Italy (n=95) Giovannini et al. 2014	0.70 (median)	2.57 (median)	0.98 (median)	5.55 (median)	0.96 (median)	5.12 (median)	32.34 (median)
Italy (n=39) Abballe et al. 2008	1.11–1.79	2.67-–4.17	1.67–2.55	7.08–12.2	1.64–3.26	11.4–16.5	52.1–68.4
Italy (n= 38) Ulaszewska et al. 2011	0.11–0.13	1.54–1.81	0.71–0.72	3.90–4.57	0.51–0.72	3.08–4.23	25.99–28.29
Germany (n=42) Raab et al. 2008	0.86	2.84	1.68	7.95	1.44	8.62	39.95
Latvia (n=15) Bake et al. 2007	1.335	1.556	0.632	2.626	0.518	3.926	30.128
Slovakia (n=32) Chovancová et al. 2011	0.5–0.7	1.3–2.3	0.5–1.6	2.8–4.3	0.7–1.1	4.2–7.8	20.2–41.9
New Zealand (n=39) Mannetje et al. 2013	0.75	1.57		2.87		5.44	30.53
China (n=158) Sun et al. 2010	0.37–0.76	1.23–1.56	0.23–0.70	1.02–2.06	0.10–0.38	1.20–2.98	15.94–22.53

Table 3-1. Mean Levels of CDDs in Human Milk (ng/kg Milk Fat)

	2,3,7,8-TCDD	1,2,3,7,8-PeCDD	1,2,3,4,7,8-HxCDD	1,2,3,6,7,8-HxCDD	1,2,3,7,8,9-HxCDD	1,2,3,4,7,8,9-HpCDD	OCDD
China (n=74) Shen et al. 2012	0.14-0.19	0.43-0.44	1.05-2.74	0.97-1.99	0.77-2.07	2.30-6.58	16.5-28.5
Japan (n=60) Todaka et al. 2008	0.7	3.2		9.8		5.9	40
Taiwan (n=25) Chen et al. 2018	0.457	1.031	0.493	1.798	0.676	2.76	38.8
Africa[c] (number of samples not reported) UNEP 2023	0.10–1.04	0.30–2.05	0.12–1.14	0.39–7.29	0.28–56.01	1.23–61.97	2.91–323.36
Asia and Pacific Islands[d] (number of samples not reported) UNEP 2023	0.19–1.18	0.43–4.98	0.19–2.81	0.80–12.53	0.32–5.24	1.29–43.98	12.29–250.25
Latin America and Caribbean[e] (number of samples not reported) UNEP 2023	0.23–0.61	0.77–1.75	0.30–0.84	1.17–6.04	0.41–1.62	2.19–17.46	6.32–102.83

[a]Human milk samples collected on days 5, 12, and 84 postpartum.
[b]11 pooled samples from 109 women.
[c]Democratic Republic of the Congo, Egypt, Ethiopia, Ghana, Kenya, Mali, Mauritius, Morocco, Nigeria, Senegal, United Republic of Tanzania, Togo, Tunisia, Uganda, Zambia.
[d]Cambodia, Indonesia, Lao, Mongolia, Philippines, Thailand, Viet Nam, Fiji, Kiribati, Marshall Islands, Niue, Palu, Samoa, Solomon Islands, Tuvalu, Vanuatu.
[e]Antigua and Barbuda, Argentina, Barbados, Brazil, Chile, Colombia, Ecuador, Jamaica, Mexico, Peru, Uruguay.

CDD = chlorinated dibenzo-*p*-dioxin; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; OCDD = octachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin

the largest percent decline in CDD levels, a decrease of 83.9%. A 52.4% decrease in maternal serum lipid levels of total CDD was also observed; the largest percent decline was an 86.8% decline in 1,2,3,7,8-PeCDD levels. In a study of 22 breastfeeding mothers, Vigh et al. (2013) found that human milk concentrations of TEQ (CDDs, CDFs) declined during lactation when concentrations were measured on days 5, 12, and 84 of lactation. The total decrease was from 3.17 to 2.41 pg TEQ/g lipid. In this same study, mean daily intakes of TEQ (CDDs, CDFs plus dioxin-like PCBs) by breastfeeding infants were estimated to be 11.71, 16.54, and 11.59 pg TEQ/kg body weight on days 5, 12, and 84 of lactation, respectively.

Several studies have shown that CDDs in human milk are readily absorbed by nursing infants. In a 19-week-old nursing infant, absorption was estimated as the difference between ingestion and the amount of CDDs found in the feces over a period of 12 days (McLachlan 1993). The mother was 32 years old and nursing for the first time. Several CDD congeners were determined in the milk: 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, three hexachloro-substituted congeners, 1,2,3,4,6,7,8-HpCDD, and OCDD. The percentage of dose absorbed was 90–95%, except for the hepta-substituted congeners and OCDD, which exhibited absorption rates of 61 and 23%, respectively. The percentage of the dose absorbed increased slightly if corrections were made for background levels in the diapers. Similar results were reported by Pluim et al. (1993b) who measured the amount of CDDs consumed via human milk and excreted in the feces in three infants at the ages of 4, 8, and 12 weeks. Because of the high content of CDDs of the diapers relative to the feces, the percentage of dose absorbed was not determined. However, the results showed that, with the exception of OCDD, the bioavailability from human milk was >95%. At 4 weeks of age, the average cumulative intake of CDDs from human milk was 132.1 pg TEQ per kg body weight; 37.4 pg TEQ 2,3,7,8-TCDD, 46.2 pg TEQ 1,2,3,7,8-PeCDD, and 24.4 pg TEQ 1,2,3,6,7,8-HxCDD. With the inclusion of CDFs, the total TEQ at 4 weeks was approximately 257 pg/kg body weight. Exposure to CDDs and CDFs from lactation decreased at 8 and 12 weeks mainly due to a decrease in their concentration in whole human milk, which resulted from a reduced fat content of the milk (the depletion of body burden of the mother while nursing may have also contributed). Abraham et al. (1994, 1996) and Dahl et al. (1995) also reported almost complete absorption of lower chlorinated CDDs and CDFs in breastfed infants during the first year of life. It was also noticed that intake of CDDs and CDFs was up to 50 times higher in breastfed infants compared with a formula-fed infant (Abraham et al. 1996). The latter study further showed that despite much lower intake of CDDs and CDFs after weaning, the concentration of these compounds in stool fat did not decrease substantially, suggesting that concentration in fecal fat more or less reflect that in body fat. Also, at 11 months of age, TEQ concentrations in blood from

formula-fed infants were <25% of maternal values and about 10 times lower than in infants breastfed for 6–7 months (Abraham et al. 1996).

Transplacental transfer of CDDs and CDFs has been demonstrated in humans and animal models. Total TEQ (CDDs plus CDFs) concentrations in maternal and cord plasma (measured using a chemical activated luciferase expression bioassay, CALUX) were similar and correlated when measured just prior to delivery (Pedersen et al. 2010). Schecter et al. (1996b) presented data on the levels of CDDs and CDFs in human fetal tissues (8–14 weeks gestational age with placenta removed) and in placentas from women from the general population who had normal deliveries. On a lipid basis, the total TEQ (CDDs plus CDFs) in a pool of 14 placentas was 10.1 ng/kg; half of this amount (5.3 ng/kg) was measured in a pool of fetal tissues from 10 fetuses. In an analysis of 43 samples of human milk, Schecter et al. (1996b) found that the total concentration of CDDs and CDFs was 16.7 ng/kg (expressed as TEQ). The study authors also calculated that the TEQ body burden for the pooled fetal tissue was 0.034 ng/kg body weight; for pooled placentas, they calculated a total TEQ of 0.086 ng/kg wet weight. These results suggest that the transfer of CDDs to the fetus may be somewhat limited. *In vitro* vascular perfusion of human placental tissue with 2,3,7,8-TCDD resulted in accumulation of 2,3,7,8-TCDD in the placental tissue (Pedersen et al. 2010).

The influence of maternal transfer (placental and via human milk) of CDDs/CDFs on the body burden of newborns and infants was further investigated by Kreuzer et al. (1997). These investigators also developed a pharmacokinetic model for 2,3,7,8-TCDD that allowed them to simulate body and tissue burden for the entire human lifetime as a function of 2,3,7,8-TCDD uptake from contaminated nutrition. On a lipid basis, the concentrations of 2,3,7,8-TCDD in adipose tissue and liver of breastfed infants who died of sudden infant death syndrome were 0.4–4 and 0.5–4 ppt, respectively. The corresponding values in non-breastfed infants were 0.2–0.8 and 0.3–0.7 ppt. Similar values were detected in adipose tissue and livers of three stillborn babies, confirming the placental transfer of these chemicals to the fetus. The model developed by Kreuzer et al. (1997) reflected sex- and age-dependent changes in body weight, volumes of liver, adipose and muscle tissue, food consumption, and excretion of feces and was used to predict the half-life of elimination of 2,3,7,8-TCDD and its concentrations in adipose tissue, blood, liver, and feces at different ages. Also, the influence of breastfeeding on the 2,3,7,8-TCDD burden of the mother, her milk, and her child was simulated. The study authors used their own data, as well as those from others, to validate the model. For non-breastfed infants, the model predicted a decrease in the concentration of 2,3,7,8-TCDD in lipids during the first year, and this was supported by the empirical data. For infants exclusively breastfed, the model predicted an increase in 2,3,7,8-TCDD burden

followed by a decrease after weaning, and this was also confirmed by the measured data. Model validation of 2,3,7,8-TCDD concentrations in liver for the 20 infants investigated and in adipose tissue, blood, and feces for data in infants published by others showed good agreement between the simulated and experimental values. Since one of the model's assumptions was that the concentration of 2,3,7,8-TCDD in fecal lipids reflected the concentration in lipids of the organism, the good correlation between predicted and empirical data validated the assumption. Under the assumption that the 2,3,7,8-TCDD concentration in lipids of human milk equals the concentration in the maternal organism, the model predicted a value of 2.23 ng 2,3,7,8-TCDD/kg lipid for the beginning of the nursing period. The model further predicted that the concentration of 2,3,7,8-TCDD in milk decreases with duration of breastfeeding, such that after 6 months of daily nursing, the concentration in milk and maternal body lipids would be approximately 70% of the value at the time of delivery. These predictions were in good agreement with published values. Lastly, the investigators modeled the concentration of 2,3,7,8-TCDD in lipids or blood of a male subject for a time span of 60 years and compared it with literature values for German subjects. One of two curves constructed was computed assuming breastfeeding for the first 6 months of life followed by formula up to 1 year and the other considering feeding only formula for the same period of time. In both cases, further nutrition was simulated to consist of the common diet. The predicted curves differed considerably during the first years of life. For the non-breastfed case, 2,3,7,8-TCDD concentrations decreased during the first year and subsequently increased, reaching a maximum at 16 years. For the breastfed case, the simulation yielded a rapid rise of 2,3,7,8-TCDD in lipids followed by a 3-year decrease after weaning and merging at about 7 years with the concentrations of non-breastfed individuals. Subsequently, 2,3,7,8-TCDD concentrations leveled at between 2 and 3 ng 2,3,7,8-TCDD/kg body lipids until the end of life. The latter value agreed with average background levels for the German population. The half-life of nonmetabolic elimination (unchanged 2,3,7,8-TCDD) was calculated to be 0.42 years in newborns and 9.5 years in 40-year-old adults. The half-life of the fraction metabolized by the liver ranged from 1.5 years for newborns to approximately 10 years for a 40-year-old individual. The 3 times greater elimination half-life for the metabolized fraction relative to the nonmetabolized fraction in infants suggests that metabolic elimination does not play a major role in the elimination of 2,3,7,8-TCDD in infants. A key finding from the Kreuzer et al. (1997) study is the model prediction that the increased 2,3,7,8-TCDD burden observed as a result of breastfeeding does not lead to a raised lifetime value.

Maternal-fetal transfer has been evaluated in numerous studies in several animal models; results show that placental-fetal transfer is much lower than fetal transfer through lactation. However, maternal-fetal transfer during sensitive periods of organogenesis is biologically important as evidenced by effects on

fetuses or offspring exposed *in utero*. One day following an oral dose of [^{14}C]-labeled 2,3,7,8-TCDD 10 μg/kg administered late in pregnancy, radiolabel recovered in fetuses was 0.02% of the administered dose (Ishida et al. 2010). In this same study, the highest concentration of radiolabel was found in fetal liver while fetal brain contained approximately 20–25% of the concentration in liver. Following a single dose of [^{3}H]-labeled 2,3,7,8-TCDD administered to Long-Evans rats late in pregnancy, the highest concentrations of radioactivity in offspring were found in liver and adipose on PNDs 49, 69, and 70 (Yonemoto et al. 2005). Following administration of single oral doses of several CDDs to Long-Evans rats on GD 15, only 0.5–3% of the administered dose was transferred to the fetus, compared to postnatal transfer of 7–28% through milk (Chen et al. 2001). Following oral administration of a single dose of [^{3}H]-2,3,7,8-TCDD (1.15 μg/kg in corn oil) to pregnant Long-Evans rats on GD 8, the amount of TCDD transferred to the fetus increased from 0.12 to 0.21% of the administered dose from GD 9 to 16 (Hurst et al. 1998a). Similar fetal tissue TCDD levels were observed on GD 21 following exposure of pregnant Long-Evans rats to [^{3}H]-2,3,7,8-TCDD on GD 8 or 15 (Hurst et al. 1998b). Following administration of single oral doses of [^{3}H]-2,3,7,8-TCDD (1, 10, or 30 mg/kg in corn oil) to pregnant Long-Evan rats (1 μg/kg in corn oil) on GD 15, fetal tissues concentration of TCDD were significantly and highly correlated with TCDD concentrations in maternal blood ($r=0.932$; $p<0.0001$) (Hurst et al. 2000a). Fetal tissue concentrations of pups born to female Long-Evans rats administered [^{3}H]-2,3,7,8-TCDD (1, 10, or 30 mg/kg in corn oil) 5 days/week for 13 weeks prior to mating and throughout gestation were similar to those observed following administration of single doses of [^{3}H]-2,3,7,8-TCDD (1, 10, or 30 mg/kg in corn oil) on GD 8 or 15 (Hurst et al. 2000b). Levels of CDDs in placenta exhibit a dose-dependent decrease, possibly due to increased maternal sequestration in the liver due to induction of CYP1A2 (Chen et al. 2000). In fetal liver, a dose-dependent increase in liver:fat TCDD levels, consistent with a similar hepatic sequestration CYP1A2 mechanism, may exist (Yonemoto et al. 2005).

Excretion into milk represents a major pathway for maternal elimination of CDDs and, therefore, for exposure to offspring. In C57BL/6N mice administered a single oral dose of 30 μg [^{14}C]-2,3,7,8-TCDD/kg on GD 11, the levels of 2,3,7,8-TCDD-derived radioactivity in the embryos on GD 12, 13, or 14 were <0.5% of the total 2,3,7,8-TCDD dose (Weber and Birnbaum 1985). In the dams, the highest concentration of radioactivity was in the liver (50–67% of total dose), whereas embryos had a relatively higher concentration of radioactivity in the heads than in the rest of the body. Approximately 0.03% of the administered dose was delivered to each embryo. In a different study in NMRI mice, pregnant females were administered a single dose of 25 μg [^{14}C]-2,3,7,8-TCDD (oral, intraperitoneal, or subcutaneous) on GD 16 and the distribution of radioactivity was examined in the pups on PNDs 7–36

(Nau et al. 1986). At all times, the highest concentration of radioactivity in the pups (per gram of tissue) was found in the liver; extrahepatic tissues such as intestines and skin had a concentration of radioactivity that was approximately one order of magnitude lower than the liver. During the first postnatal week, 2,3,7,8-TCDD concentrations increased considerably in the pups. It was also found that during the first 2 weeks, the pups received doses of 2,3,7,8-TCDD through milk that were, on a body weight basis, similar to those which had been administered to their mothers prior to birth. In pups raised by untreated foster mothers, 2,3,7,8-TCDD tissue concentrations decreased rapidly due to organ growth with concomitant dilution of 2,3,7,8-TCDD. Abbott et al. (1996) examined the distribution of 2,3,7,8-TCDD in embryonic tissues of mice at times earlier than previous studies. Pregnant mice were treated with 2,3,7,8-TCDD on GD 12 and embryonic tissues were examined at various times from 0.5 to 24 hours after dosing. The rate of accumulation of 2,3,7,8-TCDD reached a maximum in placental tissue in about 3 hours and, following a slight decline, remained relatively constant between 8 and 24 hours. After 24 hours, 0.27% of the maternal dose was detected in the placenta. In embryonic liver, 2,3,7,8-TCDD peaked approximately 8 hours after dosing and decreased thereafter, as opposed to maternal liver, where it remained constant after achieving an apparent maximum. The relative decrease in the rate of concentration in the embryonic liver was attributed to a rapid growth of the tissue during that time period. Distribution of 2,3,7,8-TCDD to embryonic palates followed a pattern similar to that in embryonic liver. Twenty-four hours after dosing, the secondary palates had 0.0045% of the administered maternal dose.

Van den Berg et al. (1987b) examined the transfer of CDDs and CDFs through the placenta and via the milk in Wistar rats. Prenatal exposure of the fetus was studied by administering a diet containing a fly ash extract from a municipal incinerator to rats from day 8 until 17 of pregnancy, after which time the rats were sacrificed. Postnatal transfer was assessed in rats fed the same diet during the first 10 days after delivery while nursing their offspring. Of the 49 tetra- to octa-CDDs, only 7 CDD congeners were detected and all had a 2,3,7,8-chlorine-substitution pattern. In the fetus, 2,3,7,8-TCDD had the highest retention (0.13% of total dose, 0.0092% of the dose/g). Retention decreased with the number of chlorine atoms; HpCDDs and OCDD were not detected. In the liver of offspring, 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, and the three 2,3,7,8-substituted HxCDDs had the highest retention (5.3–8.1% of total dose, 0.74–1.13% of dose/g). The 2,3,7,8-penta- and hexa-substituted congeners had the highest retention in the livers of pregnant and lactating rats (53.9–80.2% of total dose, 2.9–5.2% of dose/g). No significant differences were found in liver retention of tetra- to octa-chlorinated congeners between pregnant and lactating rats, but lactating females stored less CDDs in their adipose tissue. Similar results were reported by Li et al. (1995c) in Sprague-Dawley rats. The study authors administered a single intravenous dose of 5.6 μg [^{14}C]-2,3,7,8-TCDD/kg to pregnant rats on GD 18. Sacrifices were conducted on GDs 19 and 20,

and PNDs 1 and 5. Groups of neonates were also cross-fostered between treated and nontreated dams to differentially assess transfer of 2,3,7,8-TCDD through the placenta and through nursing. Only about 0.01% of the dose administered to the dams was found in whole livers of fetuses 1 and 2 days after dosing (0.04 and 0.07% of dose/g fetal liver), indicating limited placental transfer. In contrast, the concentration of 2,3,7,8-TCDD in the liver of neonates after 1 day of lactation was 0.65% of the administered dose/g liver, and this increased to 2.88% after 4 days of nursing. Four days after nursing, the liver concentration of 2,3,7,8-TCDD in neonates from dams dosed 1 day after parturition was 4.1% of the administered dose/g of liver, and this was higher than in the dam's liver (3.32%). As in earlier studies, the results from the cross-fostering experiments confirmed that nursing is a major pathway for transfer of 2,3,7,8-TCDD to the offspring.

The transfer of CDDs and CDFs via placenta and through milk was also investigated in a marmoset monkey administered a defined mixture of CDDs and CDFs subcutaneously 11 weeks prior to delivery (Hagenmaier et al. 1990). Concentrations of CDDs and CDFs were measured in a newborn 1 day after birth and in an infant of the same litter after a period of 33 days of lactation. The highest deposition in newborn liver was observed for 2,3,7,8-TCDD and 1,2,3,7,8-PeCDD (54 and 51 pg/g wet weight, respectively) and corresponded to about 0.15% of the administered dose/g tissue. The concentration of all other congeners was <10% of the corresponding concentrations in adults. In contrast to liver, the concentrations of 2,3,7,8-substituted CDDs in newborn adipose tissue were at least one-third the levels in adults, and for OCDD, the concentration in adipose tissue was 3 times higher than in adult adipose tissue. Transfer of CDDs through milk was considerable, though selective. The concentration of 2,3,7,8-TCDD and 1,2,3,7,8-PeCDD in the infant's liver was 395 and 611 pg/g wet tissue, respectively; the corresponding concentrations in the mother's liver were 107 and 326 pg/g. However, the concentration of OCDD in infant's liver was <10% that of the mother's liver. Bowman et al. (1989b) examined the transfer of 2,3,7,8-TCDD from mother to offspring in rhesus monkeys. Female monkeys had been exposed to 2,3,7,8-TCDD for about 4 years to a diet (5 or 25 ppt) that provided an estimated 0.0001–0.0006 μg 2,3,7,8-TCDD/kg/day before breeding. Breeding started 10 months after exposure ceased. At weaning (4 months), the offspring had a concentration of 2,3,7,8-TCDD in mesenteric fat 4.3 times higher than in subcutaneous fat from their respective mothers. Bowman et al. (1989b) estimated that the mothers excreted between 17 and 44% of their 2,3,7,8-TCDD burden by lactation. Based on measurements of 2,3,7,8-TCDD in fat at 4, 12, and 24 months of age, it was found that in the young monkeys, the decline in 2,3,7,8-TCDD in fat followed first-order, single-compartment kinetics, with a half-life of approximately 181 days (Bowman et al. 1990). For the purpose of comparison, the mean half-life in seven adult female Rhesus monkeys was 391 days with standard error of 88 days (Bowman et al. 1989b).

In summary, CDDs can be transferred to the fetus across the placenta and, although the amounts may be relatively small, the transfer may have great biological significance if it occurs during critical periods of organogenesis. Due to their lipophilicity, CDDs can concentrate in human milk and can be transferred to infants through nursing. In general, the amount of individual congeners in human milk decreases as chlorination decreases. Excretion via milk is highest during the first weeks after delivery. Also, the concentration of CDDs in milk is higher in mothers breastfeeding their first child than in those breastfeeding their second child. CDDs transferred to infants through nursing are readily absorbed by the infants. A pharmacokinetic model predicted that the increased body burden in infants that results from breastfeeding does not translate into raised lifetime body burden. Studies in animals have also shown transfer of CDDs across the placenta and via mother's milk.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

PBPK models for 2,3,7,8-TCDD are discussed below. The pharmacokinetic behavior of 2,3,7,8-TCDD, especially distribution, has been shown to be dose-dependent and involves protein binding and enzyme induction in hepatic tissue. Thus, terms describing these interactions have been included in the animal models described below. Furthermore, since induction of these dioxin-binding proteins is a process mediated by the interaction of a dioxin-receptor (the AhR) complex with specific binding sites on DNA,

additional terms were included in the models. For a detailed explanation regarding the AhR and its involvement in the mechanism of action of 2,3,7,8-TCDD and structurally related halogenated aromatic hydrocarbons, see Section 2.21.

Summary of PBPK Models. Numerous models of 2,3,7,8-TCDD kinetics have been developed that include humans, mice, rats, and pigs. Models have been developed to simulate maternal-fetal and lactational transfer kinetics. Several of these models simulate AhR-mediated induction of CYP1A2 and protein binding of 2,3,7,8-TCDD, which provide more realistic predictions of the effects of these processing on 2,3,7,8-TCDD distribution and elimination. PBPK models of 2,3,7,8-TCDD have been applied in various ways to support risk assessment, including dosimetry extrapolation in derivation of toxicity values, dose reconstruction of past exposures, and prediction of elimination half-lives.

The Kissel and Robarge Model

Description of the Model. The elimination of 2,3,7,8-TCDD from humans was described with a fugacity-based model using physiologically based parameters (Kissel and Robarge 1988). In this model, transport of 2,3,7,8-TCDD was assumed to be perfusion-limited (flow-limited), 2,3,7,8-TCDD was assumed to be uniformly distributed within each tissue group or fluid phase, and tissue levels were considered to be in equilibrium with exiting fluids (blood, urine, bile). Because 2,3,7,8-TCDD appears to be poorly metabolized in humans, the model did not include terms for metabolites. Transport between gut lumen and gut tissue was described as a diffusive process. Included in the differential equations used to solve the system were data for several diets. Body compartment sizes and densities used in the simulations of background exposure and of elimination from individuals with body burdens similar to those of Ranch Hand veterans were based on reference-man data. Tissue perfusion rates and partition coefficients were obtained from the literature. The diet used in all simulations was adapted from the literature and also included a typical intake of added fats and oils. The fugacity capacity of the various diet components, gastric secretions, and fecal materials were either calculated or obtained from the literature. The model was used to predict tissue levels resulting from background exposures, elimination of 2,3,7,8-TCDD from Ranch Hand veterans, and elimination of 2,3,7,8-TCDD from a volunteer.

Validation and Discussion. The steady-state adipose tissue concentrations predicted by the model, assuming no metabolism and a daily background exposure of 50 pg/day in North America, was 7.7 ppt. This value was similar to the lipid-based blood tissue levels reported in the general population with no known unusual exposure. The body burden projected for an intake of 100 pg/day fell outside the typical

range associated with background sources. In simulating the elimination of 2,3,7,8-TCDD from Ranch Hand veterans, the model assumed a background exposure of 50 pg/day and no metabolism. Under these conditions, apparent half-lives of 4.4, 5.2, 5.9, 7.2, 9.1, and 20 years were estimated for individuals with 2,3,7,8-TCDD adipose tissue concentrations of 100, 50, 30, 20, 15, and 10 ppt, respectively. This was in good agreement with a half-life of 7.1 years determined by analysis of blood lipids of veterans with adipose burdens >10 ppt (Pirkle et al. 1989). The results showed that the apparent half-lives increased greatly as tissue concentrations approached the steady-state level associated with background exposure. The model also approximated the uptake efficiency and elimination of 2,3,7,8-TCDD from a volunteer as reported by Poiger and Schlatter (1986). The fact that the predicted uptake efficiency was similar to that found experimentally indicated that the estimated gut-lumen/gut-tissue mass transfer coefficient used was in the appropriate range. The reported half-life was 5.8 years and the model estimated a value of 6.7 years. Overall, the result suggested that a fugacity-based model can provide a viable method for describing overall elimination of 2,3,7,8-TCDD from humans, but it does not provide much insight regarding why elimination occurs in a particular manner.

The Leung et al. Model in Mice

Description of the Model. The model described by Leung et al. (1988) in mice provides quantitative descriptions of the time-course of elimination and levels of 2,3,7,8-TCDD in various organs of C57BL/6J mice and DBA/2J mice, a less-responsive strain with higher body fat content. The model contains five compartments: blood, liver, fat, richly perfused tissues, and slowly perfused tissues. To account for the 2,3,7,8-TCDD binding to receptors in the liver, the model contained two hepatic binding sites: one corresponding to the high-affinity/low-capacity cytosolic AhR and the other to the inducible, low-affinity/high-capacity microsomal protein (CYP1A2). To simulate the intraperitoneal dose route used by Gasiewicz et al. (1983), 2,3,7,8-TCDD was assumed to be absorbed into the liver compartment by a first-order uptake process. Bioavailability was assumed to be 100%. Partition coefficients, physiological parameters, and biochemical constants were obtained or calculated from the literature for each mouse strain. The kidney was assumed to be representative of the richly perfused tissue, whereas the slowly perfused tissue consisted mainly of muscle and skin. The binding capacity of the Ah-less responsive DBA/2J mice was set to equal that of the Ah-responsive mice even though the binding affinity is extremely low. Blood binding was described as a linear process with an effective equilibrium between bound and free 2,3,7,8-TCDD given by a constant. In blood, only one form of 2,3,7,8-TCDD is exchangeable in the tissues, which gives rise to kinetic behavior observed for diffusion-limited uptake into tissues.

Validation and Discussion. The simulation of the time-course of 2,3,7,8-TCDD concentration in the liver and fat of C57BL/6J mice after a single 10 μg/kg intraperitoneal injection generated by the model was in good agreement with the empirical data of Gasiewicz et al. (1983). In trying to simulate the 3-times-higher liver/fat ratio of 2,3,7,8-TCDD in the C57BL/6L mice than in the DBA/2J mice, Leung et al. (1988) varied the fat content parameter in the C57BL/6J mice from 3 to 12% of body weight. The rationale was that the difference in hepatic concentration may have been due to greater capacity of the DBA/2J mouse to sequester the highly lipophilic 2,3,7,8-TCDD in adipose tissue. However, the results showed that the 2,3,7,8-TCDD concentration in the liver was relatively insensitive to body fat content, indicating that this was not an important factor influencing the disposition of 2,3,7,8-TCDD in the liver between the two strains of mice. The study authors also found that the distribution of 2,3,7,8-TCDD was strongly influenced by the binding characteristics of the microsomal binding protein, especially the binding constant. The model gave good simulations of 2,3,7,8-TCDD excretion in both strains of mice. The simulation of the time-course of 2,3,7,8-TCDD concentration in the liver and fat of DBA/2J mice after a single 10 μg/kg intraperitoneal injection was not as good as that for the C57BL/6J mouse if the input was set to be consistent with the uptake and elimination. As with the C57BL/6J mouse, disposition of 2,3,7,8-TCDD in the liver of DBA/2J mice was greatly influenced by the microsomal protein binding constant and rather insensitive to changes in body fat content. The best fit of the empirical data was obtained with a binding constant of 75 nM (20 nM for the C57BL/6J mice), indicating that the 2,3,7,8-binding affinity to the hepatic microsomal protein in the DBA/2J mice was at least 3.5 times lower than that of the C57BL/6J mice.

The Leung et al. Model in Rats

Description of the Model. This model in the Sprague-Dawley rat (Leung et al. 1990b) is an extension of the mouse model previously described and contains the same five compartments and two types of binding proteins: one corresponding to the high-affinity, low-capacity cytosolic 2,3,7,8-TCDD (Ah) receptor, and the other to the inducible, lower-affinity, high-capacity microsomal protein (CYP1A2). In the rat model, both types of binding proteins are defined with their own binding capacities and dissociation constants. The model was used to analyze experimental data for the single-dose studies of McConnell et al. (1984) and Rose et al. (1976), the 7-week Rose et al. (1976) study, the 13-week multiple-dose study of Kociba et al. (1976), and the 2-year feeding study of Kociba et al. (1978). In simulating the single-dose gavage study, 2,3,7,8-TCDD was assumed to be absorbed from the gastrointestinal tract by a first-order uptake process with a rate constant of 0.2/hour. In simulating the multidosing studies, bioavailability was

assumed to be 100%. Physiological parameters, partition coefficients, and biochemical constants were calculated or obtained from the literature. Since there was no literature value for the binding capacity of the microsomal 2,3,7,8-TCDD-binding site in the rat, the value used was approximated by assuming it to be 10 times that of the mouse. The total microsomal binding capacity was apportioned between a basal level and an induced level. Also, AHH activity was taken to be the sum of a basal and induced level. A first-order metabolic rate constant for 2,3,7,8-TCDD metabolism in the liver was adjusted to provide a biological half-life of about 25–30 days.

Validation and Discussion. When the simulation of the McConnell et al. (1984) data for AHH induction included a term for induction of microsomal binding protein, there was good agreement between the simulation and the empirical data. This had not been the case in an initial fitting, which included a constant concentration of microsomal binding protein. Rose et al. (1976) examined the accumulation of 2,3,7,8-TCDD in adipose and liver tissues in rats administered 0.01, 0.1, and 1 μg 2,3,7,8-TCDD/kg/day 5 days/week for 7 weeks; sampling was done at weeks 1, 3, and 7. Model predictions of 2,3,7,8-TCDD concentrations were in good agreement with the experimental data except for concentration in fat at the 0.01 μg/kg/day dose level, in which case the model overpredicted the tissue concentration. Model formulations that had constant microsomal binding capacity overpredicted liver 2,3,7,8-TCDD concentrations at the lower-dose rates. Also, model formulations that contained final amounts of microsomal binding protein (CYP1A2) very different (much higher or lower) from the basal 200 nmol/liver could not simulate 2,3,7,8-TCDD concentration in liver at the highest-dose rate. Similar to the findings in mice, the liver/fat concentration ratio in rats was extremely sensitive to the dissociation constant of the microsomal binding protein. The model simulated well the data from the 7- and 13-week studies (Kociba et al. 1976; Rose et al. 1976), but not as well for data from the 2-year feeding study (Kociba et al. 1978). There was underprediction of 2,3,7,8-TCDD concentration in fat and liver at the low-dose level (0.001 μg/kg/day) and overprediction of the liver concentration at the high-dose level (0.1 μg/kg/day). However, the ratios of the concentrations were consistent with those observed experimentally (1/1 at low doses, much higher in liver at high doses). According to Leung et al. (1990b), the underprediction at the low dose may reflect the fact that the low-dose fat concentration in the 2-year study was close to the limit of detection and thus, subject to more error. At the high dose, physiological parameters such as tissue volume, metabolic constants, and amounts of binding proteins may have been altered by weight loss and changes in body composition, known effects of chronic-duration exposure to 2,3,7,8-TCDD. Leung et al. (1990b) indicated that the overprediction at the high dose could have been due to a loss of microsomal 2,3,7,8-TCDD-binding sites in the chronically exposed rats. The affinity of 2,3,7,8-TCDD for the microsomal binding protein appeared to be greater in the Sprague-Dawley rats than

in C57BL/6J mice, which could account for the higher liver/fat concentration ratio in rats than in mice, assuming that the partitioning between tissues is approximately the same in the two species.

Wang et al. (1997) extended the work of Leung et al. (1988, 1990b) and Andersen et al. (1993) and developed an improved model to describe the disposition of 2,3,7,8-TCDD in multiple tissues from female Sprague-Dawley rats. The model of Wang et al. (1997) improved previous modeling attempts in some specific areas such as: (1) providing information on distribution of 2,3,7,8-TCDD at early time points (important for determining unique parameters related to mass transfer such as permeability); (2) better handling of mass balance when considering 2,3,7,8-TCDD binding to plasma proteins; and (3) improved estimation of physical and biochemical parameters. The Wang et al. (1997) model accurately described the time course distribution of 2,3,7,8-TCDD following a single oral dose, as well as the concentration of 2,3,7,8-TCDD in eight target tissues on day 3 after six different doses. The model described by Wang et al. (1997) was coupled to a biologically based pharmacodynamic (BBPD) model to quantitatively describe the relationship between disposition and response in multiple tissues (Santostefano et al. 1998). This later model incorporated both pharmacokinetic and pharmacodynamic events to account for the ability of 2,3,7,8-TCDD to induce CYP1A1 and the fact that CYP1A2 is responsible for maintaining high concentrations of 2,3,7,8-TCDD in the liver. The results showed that the BBPD model accurately described the time course of CYP1A1 protein expression and EROD activity in the liver, skin, and kidneys. It also confirmed that EROD activity can be an appropriate marker for CYP1A1 protein expression, and the shape of the induction curves supported the hypothesis that similar time-dependent mechanism of 2,3,7,8-TCDD-induced CYP1A1 protein expression and associated EROD activity occurs in multiple tissues. This, in turn, suggested that parameter estimation in the study accurately described the AhR-mediated mechanism on protein expression and enzymatic activities in multiple tissues.

Emond et al. Model

Description of the Model. Emond et al. (2004), simplifying the Wang et al. (1997) model, developed a model with four compartments (liver, fat, placenta, and rest of the body) for the dam and one compartment for the fetus. The maternal compartments were described as diffusion limited and the model assumes simple diffusion of 2,3,7,8-TCDD between the placental and fetal compartments (no blood flow to the fetal compartment is assumed). Additionally, the model includes 2,3,7,8-TCDD induction of CYP1A2 and binding in the liver. All parameters for the nonpregnant animal (only fat, liver, and rest of the body compartments were activated) were adapted from Wang et al. (1997) and parameters for growth

of the placental, blood, and fetal compartments and blood flow rates were based on data from O'Flaherty (1994) and Buelke-Sam et al. (1982a, 1982b).

Validation and Discussion. The Emond et al. (2004) model was validated by comparisons of simulations to the Wang et al. (1997) model and using experimental data for four scenarios: acute-duration 2,3,7,8-TCDD exposure in nonpregnant rats, intermediate-duration 2,3,7,8-TCDD exposure in nonpregnant rats, single exposure to 2,3,7,8-TCDD on GD 15, and intermediate-duration 2,3,7,8-TCDD exposure prior to mating and continuing throughout gestation. Reasonable agreements were found in these comparisons (typically within 20–30% of the experimental data). The investigators noted that limited data are available to develop and validate the developmental model and that extrapolation to humans should be done with caution. The model was subsequently modified to include inducible hepatic elimination, which describes the elimination rate as a function of CYP1A2 induction (Emond et al. 2006). The Emond et al. (2004) model has also been extrapolated to humans (Emond et al. 2005). This model was optimized using serum 2,3,7,8-TCDD levels from 20 Ranch Hand veterans and data from a subject ingesting a single dose of 2,3,7,8-TCDD and followed for 40 days, and the model was validated using an additional 10 Ranch Hand veterans and data from 2 Austrian women. A good correlation between predicted blood concentrations and measured blood concentrations was found for both groups of subjects. EPA (2012a) reported parameter values for human, rats, and mice and used the models for dosimetry extrapolation in deriving toxicity values for 2,3,7,8-TCDD (EPA 2012a).

Emond et al. (2018) applied the mouse model (EPA 2012a) to simulate effects of obesity on 2,3,7,8-TCDD kinetics. Feeding a high fat diet to C57BL/6J mice resulted in obesity and an increase in the terminal blood elimination half-life for radiolabeled 2,3,7,8-TCDD following a single oral dose of [^{3}H]-labeled 2,3,7,8-TCDD. The PBPK model did not predict the increase in half-life even when the model was adjusted to account for the increase in body mass and fat content of the mice, suggesting that other factors were responsible for the increase in the half-life.

Emond et al. Maternal Model

Description of the Model. The Emond et al. (2005, 2006) human model was expanded to simulate transplacental transfer of 2,3,7,8-TCDD to the developing fetus and transfer from human milk to the nursing child (Emond et al. 2016, 2017). Parameter values and sources for the values are reported in Table 1 of Emond et al. (2016). The maternal-fetal model includes compartments representing the mammary gland, placenta, and fetus. Transfer of 2,3,7,8-TCDD from blood to placenta is simulated as a

diffusion-limited process governed by a placental diffusion permeability coefficient. Exchanges between the placenta and fetus are simulated as diffusion-limited processes governed by the concentrations in the placenta and fetus and a clearance coefficient (mg/hour). Maternal-fetal transfer is assumed to begin at 8 weeks of pregnancy. Transfer of 2,3,7,8-TCDD to the nursing infant is simulated as a balance between transfer to human milk from maternal blood and transfer out of milk from nursing. The model simulates flow-limited transfer between maternal blood and mammary tissue blood and first order (day^{-1}) transfer from mammary blood to milk. Kinetics parameters governing lactational transfers were optimized to achieve a maternal blood/milk concentration ratio reported by Schecter et al. (1995, 1996a). Transfers to the nursing infant assumed 150 mL of human milk consumed in each feeding. The model is configured to be able to simulate multiple pregnancies. A sensitivity analysis of the Emond et al. (2016) model showed that the predicted area under the curve for maternal blood levels was most sensitive to parameters governing the induction of CYP1A2, absorption from the gastrointestinal tract, and the adipose/blood partition coefficient.

Validation and Discussion. Emond et al. (2016) applied the model to simulate that time profile for blood 2,3,7,8-TCDD in two cohorts of women exposed during the Seveso accident. Women in cohort A were 4–39 years of age at the time of the accident (n=23). Women in cohort B were 3–17 years of age at the time of the accident (n=18). Oral exposure was adjusted to achieve the best fit to the observed blood levels in individual women (all exposure was attributed to oral). A linear model applied to the observed and predicted maternal blood concentrations showed that the PBPK model explained approximately 85% of the variance in the observed blood levels of cohort A (r^2 0.8457) and tended to underpredict the observations by approximately 23% (regression slope 0.774 with observed as the independent variable). The PBPK model explained 100% of the observed variance in cohort B (r^2 0.9976, regression slope 0.995).

Emond et al. (2017) applied the model to simulate blood serum 2,3,7,8-TCDD (TEQ) levels reported for various exposure cohorts. Oral exposure was adjusted to achieve the best fit to observed blood levels. The model predicted the age-dependent increase in serum TEQ observed in the Calcasieu Parish Louisiana cohort (Wong et al. 2008; see Figure 1 of Emond et al. 2017). The model also predicted the observed declines in serum 2,3,7,8-TCDD levels in a subset of the Operation Ranch Hand cohort, Seveso women cohort, and a cohort exposed from operations of a hazardous waste incinerator in Spain (Michalek et al. 1996, 1997; Schuhmacher et al. 2014; Wong et al. 2008; see Figures 4, 5 and 6 of Emond et al. 2016).

Joffin et al. Model

Description of the Model. Joffin et al. (2018) extended the Emond et al. (2004; EPA 2012a) mouse model to include a skin compartment. The model was applied to simulate disposition of 2,3,7,8-TCDD in C57BL/6J mice that received subcutaneous skin xenografts of adipose tissue collected from mice dosed with 2,3,7,8-TCDD. The model simulated first order ($hour^{-1}$) release of 2,3,7,8-TCDD from the adipose graft to the skin compartment. Transfer of 2,3,7,8-TCDD from skin to blood was simulated as a diffusion-limited process governed by a skin permeability coefficient. Blood flow to the graft (from skin) was assumed to begin 4 weeks after the graft. Parameter values and bases for the values are reported in Table 1 of Joffin et al. (2018). Values for the first-order rate coefficient for transfer of 2,3,7,8-TCDD from graft to skin, skin permeability coefficient, and graft permeability fraction were optimized against observations of graft 2,3,7,8-TCDD concentrations in preliminary experiments.

Validation and Discussion. The model predicted the observed liver and adipose concentrations in donor mice that received an intraperitoneal dose of 2,3,7,8-TCDD (10 μg/kg). The model also simulated the time course for the decrease in 2,3,7,8-TCDD concentration in the graft and buildup of concentration in the host adipose tissue and liver.

The Andersen et al. Model

Description of the Model. This model (Andersen et al. 1993) is an extension of the earlier PBPK models developed by Leung et al. (1988, 1990b) for 2,3,7,8-TCDD. Like the earlier models, this model consists of five compartments. Each of the four tissue compartments has a specified blood flow, tissue compartment volume, and tissue blood volume. Movement of chemical from blood to tissue was modeled to be proportional to the product of a permeation coefficient times surface area for the tissue. When this product is lower that the specified blood flow for the tissue, tissue uptake is diffusion-limited. Because of the diffusion-limited tissue compartments, the model did not require blood binding to match the time-course of tissue uptake. It was assumed that in the liver both the AhR and the inducible binding protein act to sequester 2,3,7,8-TCDD through a capacity-limited binding process, and the binding protein was assumed to be CYP1A2. Binding interactions with CYP1A2 and CYP1A1 were described by reversible equilibrium relationships, which is valid as long as the rate constants for association/dissociation are large. It was also assumed that the DNA sites to which the Ah-2,3,7,8-TCDD complex binds are present at much lower concentrations than the Ah-ligand complex. For both CYP1A1 and CYP1A2 induction, it was assumed that the Ah-ligand complex formation was equivalent, but that

the Hill term, *n* (a measure of interaction for multiple Ah-ligand complex binding sites), and the Hill binding constant were different for the two responses. The model also allowed for autoinduction of metabolism following 2,3,7,8-TCDD treatment. Data from Abraham et al. (1988) and Krowke et al. (1989) were analyzed. The former study provided dose-response characterization of concentrations of 2,3,7,8-TCDD in liver and of liver CYP1A1 activity and time-course characterization of 2,3,7,8-TCDD concentration in tissues and enzyme activities in female Wistar rats. Krowke et al. (1989) examined liver and fat concentrations in male Wistar rats dosed weekly for up to 6 months. In addition, Andersen et al. (1993) examined the potential correlation between several measures of dose estimated by the model and the promotional efficacy and carcinogenicity of 2,3,7,8-TCDD in Sprague-Dawley rats. Cancer data from Kociba et al. (1978) and Pitot et al. (1980) were analyzed.

Validation and Discussion. Abraham et al. (1988) found that the disposition of 2,3,7,8-TCDD in liver and fat from rats administered a single subcutaneous dose (0.001–10 μg/kg) of the chemical was highly dose-dependent. The disproportionately higher concentration in the liver at higher doses appeared to be due to induction of a dioxin-binding protein, presumably CYP1A2. The model developed by Andersen et al. (1993) successfully simulated the experimental data. The affinity of the binding protein was estimated to be 6.5 nmol, while a value of 1 for *n* suggested little interaction among 2,3,7,8-TCDD-responsive DNA-binding sites involved in the expression of CYP1A2. For describing induction of CYP1A1, an *n* of 2.3 was required, which suggested possible interactions among DNA-binding sites for the Ah-ligand complex with this gene. The simulation of the time-course of elimination from liver and of induction of CYP1A1 was in good agreement with the empirical data but required the inclusion of time-dependent growth parameters over the 100 days of the experiment. The model also successfully simulated the data from the repeated-dosing study by Krowke et al. (1989) after small adjustments were made to fat and slowly perfused tissue parameters. The measures of dose that were used for comparison with the promotional and carcinogenic properties of 2,3,7,8-TCDD were integrated total liver concentration during the treatment period, or integrated free liver 2,3,7,8-TCDD concentration. Also, measures of tissue dose related to enhanced expression of CYP1A1 and hepatic binding proteins were calculated and examined for correlation with promotional activity. Results of the analysis revealed that under the exposure conditions, the tumor promotional response of 2,3,7,8-TCDD in the rat liver most closely correlated with integrated expression of the CYP1A1 gene. However, Andersen et al. (1993) indicated that since there is no expectation of causality between tumor responses and induction of CYP1A1 (or CYP1A2), the correlation should be regarded cautiously. Consistent with the findings of Leung et al. (1988, 1990b), the results from the Andersen et al. (1993) study showed that over a certain dose range (e.g., at doses several fold above background), protein (CYP1A2) induction greatly alters 2,3,7,8-TCDD disposition.

Andersen and co-workers developed a model of hepatic enzyme zonation that was combined with the PBPK model of protein induction (Andersen et al. 1993) to create a multicompartmental representation of the liver architecture that can be used to predict the degree of induction in both the whole liver and in specific regions (Andersen et al. 1997a, 1997b). A geometric representation was used to divide functional units (based on enzyme distribution) within the liver into five zones. The primary objective was to compare model predictions for regional induction with regional protein induction as visualized by immuno-histochemistry. The data set modeled included analysis of tissue distribution of 2,3,7,8-TCDD in the first days or weeks after a single dose, time course studies for about 100 days after a single dose, and initiation-promotion studies in rats dosed for up to 6 months. The results showed that the five-compartment model was more successful than conventional homogeneous one-compartment liver models not only in simulating low-dose behavior for mRNA in whole liver, but also in representing immunohistochemical observations. Five or more compartments were required to give a sharp boundary between induced and noninduced regions of the liver. When the five-compartment liver model was used to account for CYP1A1 and CYP1A2 induction and regional distribution of induced enzymes, the low-dose behavior appeared to be nonlinear and was better described, with a large *n* value (Hill coefficient) and a range of affinities in the liver covering about 81-fold differences between centrilobular and periportal regions.

The Kohn et al. (National Institute of Environmental Health Sciences [NIEHS]) Model

Description of the Model. Kohn et al. (1993) constructed a mathematical model (the NIEHS model) to describe 2,3,7,8-TCDD tissue distribution and 2,3,7,8-TCDD-mediated alterations in hepatic proteins in the rat. The model assumed that 2,3,7,8-TCDD mediates increases in liver concentration of transforming growth factor-α (TGF-α) by a mechanism which requires the AhR. TGF-α subsequently binds to the EGF receptor, a process that is known to cause internalization of the receptor in hepatocytes. This is thought to be an early event in the generation of a mitogenic signal. The model included equations for the AhR-dependent induction of CYP1A1 and CYP1A2 activity and of the AhR itself. Because it was also assumed that estrogen action is required for 2,3,7,8-TCDD-mediated induction of TGF-α, production of the estrogen receptor, CYP1A2-catalyzed formation of catechol estrogens, and deactivation of estrogens by glucuronidation were included in the model. The model predictions were compared to the two-stage initiation-promotion data of Tritscher et al. (1992) and Sewall et al. (1993). Gavage doses equivalent to 3.5–125 ng 2,3,7,8-TCDD/kg/day for 30 weeks were used in these studies. Data from Abraham et al. (1988) were also analyzed. Model parameters were obtained from the literature or calculated from

experimental data and adjusted to make the model reproduce the observations of Tritscher et al. (1992) and Sewall et al. (1993).

Validation and Discussion. The model prediction for the percentage of absorption (>90%) from ingestion of 2,3,7,8-TCDD was in good agreement with experimental data of Rose et al. (1976). The model also predicted that 92.2% of the metabolite appears in the feces and 7.8% in the urine at a dose of 125 ng/kg/day. The dose of 2,3,7,8-TCDD did not have a significant effect on these predictions. From the fit to the data of Abraham et al. (1988), the model predicted an initial and overall half-time clearance from liver of 11.8 and 13.5 days, respectively, which is very close to the experimentally obtained 11.5 and 13.6 days. Similar good agreement was obtained for half-time elimination from fat (22.3 days versus 24.5 days). The model predicted a linear relationship between administered dose and the concentration of 2,3,7,8-TCDD in the liver at doses between 3.5 and 125 ng/kg/day, which was in good agreement with the data of Tritscher et al. (1992). The relationship between 2,3,7,8-TCDD dose and induction of both CYP1A1 and CY1A2 was best fit by a hyperbolic curve suggesting lack of cooperative interactions among binding sites. The hyperbolic curve was consistent with the experimental data for induction of these proteins from Tritscher et al. (1992). The model also predicted that the fractional occupancy of the AhR by 2,3,7,8-TCDD rises from 13.4% at a dose of 3.5 ng/kg/day to 69.3% at 125 ng/kg/day. The model prediction of the degree of internalization of the EGF receptor as a function of the concentration of TGF-α was also hyperbolic in shape and successfully reproduced the experimental data of Sewall et al. (1993). Kohn et al. (1993) indicated that as this response may be involved in the mechanism of tumorigenesis in 2,3,7,8-TCDD-treated rats, it would be expected that it would correlate with tumor incidence better than does tissue dose. If so, extrapolation of effects at high dose to low doses may underestimate low-dose effects. However, extrapolation from low dose to extremely low dose would still be valid. The model predicted that 10 days after administration of a single dose of 1 μg 2,3,7,8-TCDD/kg, there should be a greater decrease in plasma membrane EGF receptor in female rat liver than in male rat liver, which is consistent with the observed lower sensitivity of the male. Consistent with the experimental data, the model reproduced the decrease in hepatic estrogen receptor (ER) level resulting from exposure to 2,3,7,8-TCDD, and the relationship between concentration of 2,3,7,8-TCDD and amount of receptor was also hyperbolic. Overall, the model's success in reproducing the observed responses to 2,3,7,8-TCDD for the various proteins included in the model supports the proposed mechanism that internalization of the EGF receptor in response to induction of TGF-α may be the origin of the mitogenic signal important for carcinogenesis.

Kohn et al. (2001) updated the Kohn rat PBPK model (described in ATSDR 1998) to include multiple TCDD-liganded AhR binding sites for CYP1A1 and CYP1B1 genes, a lag of 0.2 days for production of mRNA and induced proteins, and stabilization of mRNA by a poly(A) tail. The model was validated using observed liver TCDD levels from the literature. In general, there was good agreement between the predicted and measured tissue TCDD concentrations and the dose-response curves for CYP1A1, CYP1A2, and CYP1B1.

The Carrier et al. Model

Description of the Model. The first part of this model provides a quantitative description of the distribution of 2,3,7,8-substituted CDDs (and CDD-like compounds) between liver and adipose tissues as a function of overall body concentration at any given time (Carrier et al. 1995a). In a second step, differential equations were used to describe the disposition of CDDs in liver, adipose tissues, and whole body as a function of time (Carrier et al. 1995b). The first step of the model was based on several hypotheses: (1) changes in overall CDD concentration are slow relative to inter-tissue diffusion exchanges, protein induction, and binding of CDDs in the liver; (2) CDDs are mainly in adipose tissue and in the liver, but exchanges between these two sites are mediated via the blood; (3) the liver synthesizes proteins that bind free CDDs according to standard mass action association-dissociation mechanisms; (4) synthesis of binding proteins in the liver is linked to binding of free CDDs to the AhR; (5) CDDs in fat deposits within the liver contribute to the overall liver burden and is taken into account; and (6) small amounts of CDDs are contained in organs other than the liver and adipose tissues, and this fraction is assumed to be constant. In the second step, CDDs were assumed to be eliminated mainly by hepatic clearance; elimination by lactation or transplacental distribution was not considered. Model simulations of various experimental data sets, as specified below, were conducted. When not readily available, anatomical and physicochemical parameters were obtained from laboratory or clinical data.

Validation and Discussion. The model successfully simulated data from Abraham et al. (1988), who provided dose-response characterization of concentrations of 2,3,7,8-TCDD in the liver of rats after a single dose of the compound. Analysis of the data showed that the higher the body burden, the higher the proportion of the burden contained in the liver. However, the model predicted that a plateau is reached when body burden is >1 mg 2,3,7,8-TCDD/kg body weight. The model predictions were also in good agreement with experimental data from Van den Berg et al. (1986a), who administered a single dose of a mixture of CDDs and CDFs to rats and hamsters and with data in monkeys administered a single oral dose of 2,3,7,8-TCDD (McNulty et al. 1982). Results from simulations conducted on data from chronic-

duration studies in rats (Kociba et al. 1978; Rose et al. 1976) and on human data from Yusho patients also showed that increasing the body burden results in an increase in the fraction of the body burden present in the liver and in an increase in the liver/adipose concentration ratio. These changes in fractional distributions were attributed to the affinity of specific liver proteins for binding of free hepatic CDDs and the saturable capacity of the binding proteins at high concentration of free CDDs. Model simulations of elimination data in rats after single (Abraham et al. 1988) or repeated doses (Kociba et al. 1978; Rose et al. 1976) of 2,3,7,8-TCDD, as well as data from a Yu-Cheng patient agreed well with the empirical data and showed that disposition kinetics of 2,3,7,8-substituted CDDs are nonlinear (i.e., as body burden decreases with time, liver and adipose tissue half-lives increase). According to the model, an additional factor that can influence the disposition kinetics of 2,3,7,8-CDDs is a rapid change in body weight and/or adipose tissue mass. A rapid loss of adipose tissue whether by dieting or in patients experiencing anorexia, would result in a higher concentration of the chemical in the remaining adipose tissue, particularly if the loss of tissue is much faster than whole body elimination via the liver.

Aylward et al. (2005) modified the concentration- and age-dependent model of elimination developed by Carrier et al. (1995a, 1995b) to include the amount of 2,3,7,8-TCDD eliminated through partitioning from circulating lipids across the lumen of the large intestine into the fecal content. The modified model was fit to serial serum 2,3,7,8-TCDD sampling data from two Austrian subjects with a mean follow-up of 2.7–3 years and 36 subjects (19 males and 17 females) from Seveso with a mean follow-up of 16 years. The modified model allows for a better prediction of peak historical exposures using current serum 2,3,7,8-TCDD levels. Aylward et al. (2005) compared the estimated peak serum 2,3,7,8-TCDD levels for the NIOSH cohort back-extrapolated assuming first-order kinetics with a fixed half-life of 7–9 years to peak levels predicted by the modified model and found that assuming first-order kinetics resulted in an underestimation of maximum concentrations by several fold to an order of magnitude.

Maruyama et al. Model

Description of the Model. The Maruyama et al. (2002) PBPK model, which is a modification of the Lawrence and Gobas (1997) fugacity model, consists of six compartments: blood, liver, kidney, fat, muscle, and richly perfused tissue (brain, lung, and spleen). Exposure was assumed to be through diet only. Tissue:blood partition coefficients were determined using autopsy data from eight Japanese men and women exposed to background levels of CDDs and CDFs. For most congeners, the measured values were within the simulated ranges in liver, kidney, and blood; the model underestimated 1,2,3,6,7,8-HxCDD concentrations in the kidney, fat, blood, and muscle.

Validation and Discussion. Predicted mean concentrations of CDD and CDF congeners were compared to measured values from autopsy data for 30 different Japanese persons. Overall, there was good agreement between the estimated and measured values, although the model tended to underestimate CDD levels and overestimate CDF levels. Maruyama et al. (2001) also developed a PBPK model that would allow for the estimation of dioxin concentrations in Japanese breastfed infants. This model was composed of six compartments (liver, kidney, fat, blood, muscle, and richly perfused tissues) and the source of exposure was presumed to be human milk exclusively.

Savvateeva et al. Model of Pigs

Description of the Model. Savvateeva et al. (2020) developed a model to simulate the kinetics of ingested 2,3,7,8-TCDD in growing pigs. The model includes three compartments representing the blood, adipose, and liver. The adipose and liver compartments are subdivided into tissue and extracellular compartments. Ingested 2,3,7,8-TCDD enters the blood compartment with the rate governed by a dose-dependent absorption fraction and is distributed to the extracellular compartments of adipose and liver. Transfer to adipose and liver tissue is assumed to be diffusion-limited governed by permeability coefficients. Elimination is simulated as first-order excretion from blood and inducible first-order metabolism in liver. Induction of metabolism (CYP1A2) is simulated as an AhR-mediated response (Emond et al. 2005; Wang et al. 1997). Growth of the body and adipose weights were simulated with a logistic equation fit to observations on pig growth (Savvateeva et al. 2020). Blood and liver weights were assigned values of 6 and 3% of body weight, respectively (Savvateeva et al. 2020). Partition coefficients were predicted based on physical-chemical properties and predicted values compared to measured tissue and blood concentrations observed in pigs dosed with 2,3,7,8-TCDD.

All other chemical parameters were optimized to observations made on pigs following 13 weeks of daily oral dosing with capsules containing a mixture of CDD and CDF congeners. The daily doses increased with body weight. Ranges for the three dose groups were: low, 0.128–0.364 ng; middle, 1.874–5.353 ng; and high, 17.005–48.584 ng. At 13 weeks, the per kg doses for 70 kg pigs were approximately 0.005, 0.076, and 0.69 ng/kg/day, for the low-, middle-, and high-dose groups, respectively. Optimization relied on observations of 2,3,7,8-TCDD concentration in blood, liver, and adipose following exposure in the three dosing groups.

Validation and Discussion. The optimized model predicted the time course for the decline in adipose 2,3,7,8-TCDD concentration following dosing (measured from fat biopsies collected at three time points). The model also predicted blood and liver concentrations measured 60 days following dosing. The model was applied to predicting elimination half-lives of 2,3,7,8-TCDD in blood, adipose, liver, and whole body. These values were 19–25 days in the low-dose group, 19–24 days in the middle-dose group and 14–21 days in the high-dose group. The model was used to predict adipose TEQ concentrations following a period in which pigs had been accidentally exposed to contaminated feed in Belgium (Covaci et al. 2007).

Risk Assessment. In early efforts to model the disposition of persistent PAHs, disposition was described by simple partitioning between the blood and the various tissues with first-order metabolism in the liver. In those studies, the role that extensive tissue binding to particular cellular proteins might play in determining the overall disposition of the chemical was not accounted for. In contrast, the descriptions of Leung et al. (1988, 1990b) and Carrier et al. (1995a, 1995b) attempted to provide a biochemical basis for the observed tissue distribution. The use of this type of model may help explain interspecies differences in 2,3,7,8-TCDD sensitivity and carcinogenicity. The rodent PBPK model for 2,3,7,8-TCDD revealed very consistent behavior between species, and some of the predictions of high dose-low dose behavior were verified.

One advantage of a description that explicitly includes protein binding is the ultimate ability to develop pharmacodynamic models for 2,3,7,8-TCDD (and related chemicals) toxicity based on AhR occupancy or Ah-TCDD complex concentration *in vivo* and to realistically couple it with the biologically based cancer models (or with models for other 2,3,7,8-TCDD responses). This was attempted by Andersen et al. (1993) and Kohn et al. (1993), who included estimates of binding constants between the AhR and 2,3,7,8-TCDD and between the AhR-dioxin complex and sites on DNA. Santostefano et al. (1998) extended previous modeling attempts by determining parameter values based on time course of CYP1A1 and CYP1A2 responses in multiple tissues using a simultaneous PBPK and PBPD models. However, as noted by Andersen et al. (1993), in order to develop a complete biologically motivated risk-assessment model, these dosimetry models need to be combined with quantitative descriptions of cell and tissue responses. Kohn et al. (1993) used the NIEHS model to successfully predict tissue concentrations of 2,3,7,8-TCDD and of various induced proteins involved in the carcinogenic response to 2,3,7,8-TCDD and suggested that such a model might permit extrapolation of responses beyond the range obtained from experimental data and lead to scientifically sound approaches for estimating risks of adverse health effects of exposure to 2,3,7,8-TCDD. The importance of the results of Kohn et al. (1993) can be illustrated by

the finding that the dose-response curves for various proteins were hyperbolic rather than sigmoid. A sigmoid dose-response relationship in the response requires a higher concentration to produce a given response at a low dose than a hyperbolic response having the same concentration for half-maximal effect. This implies that the response is approximately linear at very low doses. Expansion of previous models to include maternal-fetal and maternal-infant transfer of 2,3,7,8-TCDD provided a basis for dosimetry extrapolation to support derivation of toxicity values for developmental endpoints (Emond et al. 2005, 2006; EPA 2012a).

3.1.6 Animal-to-Human Extrapolations

As discussed in Section 2.1, there are a number of limitations in the human database; for most health effects, the data are inadequate to assess the potential for humans having a particular effect. Because the human data are incomplete, hazard and risk must be extrapolated across species. A large number of adverse effects have been observed in animals, and most have been observed in every experimental animal species tested, if the appropriate dose is administered. This is illustrated in Table 3-2 for eight major effects associated with CDD toxicity (acute lethality, hepatotoxicity, wasting syndrome, chloracne, immunotoxicity, reproductive toxicity, developmental toxicity, and cancer). With the exception of acute lethality in humans, positive responses have been observed in each tested species, when a response has been investigated. Despite the similarities in hazard response between different species, large species differences in sensitivity have been observed. Comparisons of species sensitivity demonstrate that no species is consistently sensitive or refractory for all effects and, for some effects, there is a small range of species sensitivity. As presented in Table 3-3, the range of LD_{50} values for six commonly tested animal species spans several orders of magnitude. Guinea pigs have the lowest LD_{50} value (0.6 μg/kg) and hamsters have the largest (1,157 μg/kg). However, if these outliers are removed, the range of LD_{50} values for mice, monkeys, rabbits, and rats is less than an order of magnitude (22–115 μg/kg). The range of LOAELs for developmental effects (increases in mortality and hydronephrosis) were typically within an order of magnitude. In contrast, the range of ED_{50} values for thymic atrophy spans more than 2 orders of magnitude, with guinea pigs (0.8 μg/kg) being the most sensitive and mice the least sensitive (280 μg/kg). These data suggest that even though some effects have wide ranges of sensitivity, for most of the effects, the LOAELs for the majority of species cluster within an order of magnitude (Table 3-3).

Table 3-2. Comparison of Health Effects Among Species Exposed to CDDs

Effect	Human	Monkey	Rat	Mouse	Hamster	Dog	Rabbit	Guinea pig	Mink
Acute lethality	–	+	+	+	+	+	+	+	+
Hepatotoxicity	+	+	+	+	ND	ND	ND	+	+
Wasting syndrome	**	+	+	+	+	ND	ND	+	+
Chloracne	+	+	ND	+	ND	ND	+	ND	ND
Immunotoxicity (thymic atrophy)	ND	+	+	+	+	ND	ND	+	ND
Reproductive toxicity (loss of pregnancy)	**	+	+	+	ND	ND	+	+	ND
Developmental toxicity (fetal toxicity and/or mortality)	**	+	+	+	+	ND	+	+	ND
Cancer	+	ND	+	+	+	ND	ND	ND	ND

+ = observed; – = not observed; ** = some effects have been observed but data limitations preclude drawing conclusions; CDD = chlorinated dibenzo-*p*-dioxin; ND = no data

Table 3-3. Comparison of LOAELs Among Animal Species Following a Single Oral Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	LOAEL (µg/kg)			
	Death	Immunological effects	Developmental effects	
Species	LD_{50}	Thymic atrophy (ED_{50})	Fetal/pup mortality	Hydronephrosis
Guinea pig	0.6 (Schwetz et al. 1973)	0.8 (Hanberg et al. 1989)	1.5 (Olson and McGarrigle 1992)	ND
Hamster	1,157 (Olson et al. 1980a)	48 (Hanberg et al. 1989)	18 (Olson and McGarrigle 1992)	1.5 (Olson and McGarrigle 1992)
Mouse	100 (Weber et al. 1995)	280 (Hanberg et al. 1989)	10 (Mustafa et al. 2008)	0.5 (Silkworth et al. 1989b)
Monkey	70 (1/3 died) (McConnell et al. 1978a)	ND	1 (McNulty 1984)	ND
Rabbit	115 (Schwetz et al. 1973)	ND	ND	ND

Table 3-3. Comparison of LOAELs Among Animal Species Following a Single Oral Dose of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD)

	LOAEL (µg/kg)			
	Death	Immunological effects	Developmental effects	
Species	LD_{50}	Thymic atrophy (ED_{50})	Fetal/pup mortality	Hydronephrosis
Rat	22 (Schwetz et al. 1973)	26 (Hanberg et al. 1989)	0.7 (Bjerke and Peterson 1994; Bjerke et al. 1994a; Ishimura et al. 2002; Kransler et al. 2009; Tomasini et al. 2012)	1 (Nishimura et al. 2006)

ED_{50} = median effective dose; LD_{50} = median lethal dose; ND = no data

It is generally accepted that the AhR plays a role in mediating many toxic responses attributed to exposure to CDDs (for additional information on the mechanisms of toxicity, see Section 2.21). For some responses, receptor binding appears necessary but may not be sufficient to result in downstream biological effects. AhRs have been found in most species, including humans, monkeys, rats, mice, hamsters, rabbits, and guinea pigs (Denison et al. 1986; Landers and Bunce 1991). A simple way to explain sensitivity differences among species to 2,3,7,8-TCDD and related compounds, at least for AhR-mediated responses, would be to assume that they are related to differences in receptor levels in target tissues and/or to differences in the affinity of binding of the specific CDD congeners. However, experimental data indicate that differences in such parameters cannot explain marked differences in CDD toxicity across species. For example, single-dose LD_{50} values range from 0.6 µg/kg in guinea pigs to 1,157 µg/kg in hamsters, but the affinity with which 2,3,7,8-TCDD binds to the AhR from guinea pigs is not significantly different from the affinity with which 2,3,7,8-TCDD binds to the hamster AhR (Denison et al. 1986). In addition, there are no significant differences in the level of the hepatic AhR between the two species, suggesting that in addition to species differences in receptor levels and in their affinities for the ligand, differences in species sensitivity to 2,3,7,8-TCDD may be determined by some event or events occurring after the initial binding of 2,3,7,8-TCDD to the AhR. These late events may involve a complicated interplay between genetic and environmental factors, which may be key determinants of 2,3,7,8-TCDD biological potency and toxicity. Factors unrelated to the AhR, such as toxicokinetic differences, may also account for some of the observed species differences (for additional information, see Section 2.21). The AhR has been identified in many human tissues and human cell lines (Okey et al. 1994). However, considerable individual differences in the expression levels of both AhR and ARNT mRNAs have been found in human tissues (Hayashi et al. 1994). Furthermore, based on findings in

inbred mice, polymorphism in the AhR probably exists in humans, so that a concentration of TCDD that produces a response in one individual may not do the same in another (Whitlock 1993). This could explain why there was a wide range of serum 2,3,7,8-TCDD levels among Seveso residents where the occurrence of chloracne was sporadic over a generally wide range of doses (Mocarelli et al. 1991).

The weight of evidence from animal species comparisons and mechanistic data indicates that caution should be exercised when extrapolating from animals to humans. Some theoretical models indicate a basis for extrapolating from animals to humans, but such models have not been validated; there is wide variation in the results of different models and a great deal of uncertainty remains regarding whether valid, predictive extrapolations can be made. It is reasonable to assume that humans will not be the most sensitive responder or be refractory to all effects, and that they will have a wider range of response due to increased heterogeneity. Levels of exposure to CDDs that produce toxicity in experimental animals cannot be directly compared to levels associated with adverse health effects in humans because most epidemiologic studies do not provide adequate data to estimate CDD exposures in the studied populations.

Several factors need to be considered when understanding species differences in CDD toxicity, in particular 2,3,7,8-TCDD toxicity. One of the primary factors is binding affinity, and quantitative measures of binding affinity can serve as a preliminary indicator of species susceptibility to 2,3,7,8-TCDD. Events in the AhR signaling pathway, such as binding of cofactors (e.g., ARNT) or chaperone proteins, translocation to the nucleus, and interaction with transcriptional control elements on DNA, and transcriptional cofactors could also affect 2,3,7,8-TCDD responsiveness. However, the limited available data on species differences in these downstream AhR signaling events have not found marked differences, and none of the available data suggest that a species with a low binding affinity would have a high responsiveness to 2,3,7,8-TCDD (Connor and Aylward 2006). The binding affinities (expressed as the dissociation constant, K_d) from several species are presented in Table 3-4 (note that the dissociation constant is inversely proportional to the binding affinity). The dissociation constant in humans is approximately 10-fold higher than most laboratory species, indicating approximately one-tenth of the binding capacity. Molecular genetic studies have compared the human AhR to the AhRs in C57BL/6 mice (2,3,7,8-TCDD-responsive strain) and DBA/2 mice (2,3,7,8-TCDD-nonresponsive strain). Two single nucleotide changes are believed to be responsible for the differences in the binding affinity and function between the AhR in C57BL/6 mice and DBA/2 mice (Connor and Aylward 2006; Harper et al. 2002). In DBA/2 mice, the single nucleotide change in the ligand binding domain of the receptor causes valine to be substituted for alanine, resulting in decreased binding affinity (Harper et al. 2002). The

second nucleotide change (leucine to proline) in the DBA/2 mouse converts a stop codon into an arginine, resulting in a longer transcript and extending the C-terminal portion of the AhR protein (Harper et al. 2002). Humans have both "DBA-type" mutations, whereas Sprague-Dawley rats, Golden Syrian hamsters, and domestic guinea pigs have the leucine and proline mutations (Connor and Aylward 2006).

Table 3-4. AhR-TCDD Equilibrium Dissociation Constants (K_d) in various Laboratory Species and Human Tissues

Species/strain	Dissociation constant[a] (K_d, nM)
Hartley guinea pig	0.06, 0.16
Gerbil	0.20
Syrian hamster	0.22, 0.33
Sprague-Dawley rat	0.12, 0.22, 2.4
C56BL/6 (N or 1) mouse	0.29, 0.27, 0.52, 0.5–1.6, 1.1, 1.8
B6D2F1 mouse	0.42
Long-Evans rat	3.4
Han/Wistar (Kuopio) rat	3.9
Wistar rat	5.4
Cynomolgus monkey	0.26, 16.5
Swine	17.5
Beagle dog	17.1
DBA/2 mouse	16
Human liver	18.6
Human lymphoblastoid cells	4.6
Human tonsils	17.6
Human placenta	9.6

[a]For some species, values were taken from multiple studies.

AhR = aryl hydrocarbon receptor; TCDD = tetrachlorodibenzo-*p*-dioxin

Source: Connor and Aylward (2006)

Using *in vitro* and *in vivo* data, Connor and Aylward (2006) compared the biological responses of humans and laboratory animals to assess whether differences in binding affinity and molecular structure of the AhR translate to differences in biological responsiveness (as assessed by induction of CYP1A1 and CYP1A2). The ratios of human EC_{50} to rat EC_{50} values for EROD activity, measured *in vitro*, were 8–34, suggesting that approximately 10-fold or higher 2,3,7,8-TCDD levels were needed in human cells to elicit the same response as rat cells, which is consistent with the comparison of ligand binding affinities. Comparisons were also made using *in vivo* data by measuring gene expression of *CYP1A1* (as mRNA) in Seveso residents and German herbicide manufacturing workers. No detectable increases in gene

expression of CYP1A1 were found at body burdens of ≤250 ng TEQ/kg; at body burdens of ≥750 ng TEQ/kg, increases in gene expression were observed (no studies examined body burdens between 250 and 750 ng TEQ/kg). In contrast, longer-term studies in B6C3F1 mice and Sprague-Dawley rats have found ≥4-fold increases in EROD activity at ≥100 ng TEQ/kg. These findings suggest that humans do not respond with detectable induction of enzyme activity at the same dioxin body burden as laboratory rodents (Connor and Aylward 2006).

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to CDDs are discussed in Section 5.7, Populations with Potentially High Exposures.

There is a limited amount of information available on the toxicity of CDDs in children. Most of the available data come from a series of studies on children living in Seveso during the accidental release of airborne trichlorophenol contaminated with 2,3,7,8-TCDD. Shortly after the accident, early irritative dermal lesions (this effect may not have been related to 2,3,7,8-TCDD exposure) and chloracne were observed in a number of children. Erythema and edema, the main clinical features of the early irritative lesions, were only observed in children and young adults (<20 years old) (Caputo et al. 1988). Chloracne was observed in 187 individuals; 88% of them were children aged 0–14 years (Bisanti et al. 1980). Based on serum 2,3,7,8-TCDD levels measured in 30 Seveso residents with and without chloracne, Mocarelli et al. (1991) suggested that children may develop chloracne at lower 2,3,7,8-TCDD body burdens than adults following acute-duration exposure to 2,3,7,8-TCDD. Other effects observed in the exposed

children include a significant increase in the number of children with chloracne having clinical and electrophysiological signs of peripheral nervous system involvement (assessed 6 years after the accident) (Barbieri et al. 1988) and slight transient increases in serum GGT and ALT levels in boys aged 6–10 years (Mocarelli et al. 1986). Although the serum enzyme levels were higher than in non-exposed children, the values were within the normal range and were elevated 1, 2, and 3 years after the accident, but not after 4 or 5 years. Increased risks of Hodgkin's lymphoma, myeloid leukemia, and thyroid cancer were also reported among children who were 0–19 years old at the time of the Seveso accident (Pesatori et al. 1993). However, the differences in relative risks for these cancer types between the Seveso residents and the control population did not reach statistical significance. Similar results were found in a 15-year follow-up study of this cohort (Bertazzi et al. 1997).

A wide variety of effects have been observed in adults exposed to 2,3,7,8-TCDD at work or following an accidental release of 2,3,7,8-TCDD into the environment. The primary targets appear to be the skin, liver, body weight, and endocrine, reproductive, and immune systems; an increased cancer risk has also been observed. In the absence of data to the contrary, it is likely that these organs/systems will also be sensitive targets in children.

A number of human studies have investigated the potential of 2,3,7,8-TCDD to induce developmental effects. Although some studies have found associations between maternal and/or paternal CDD exposure and developmental effects, particularly for impaired development of the reproductive system, there is no consistent evidence of adverse birth outcomes, thyroid hormone levels, immune effects, or neurodevelopment (see Section 2.17 for additional information).

The toxicity of 2,3,7,8-TCDD has been extensively examined in animal oral toxicity studies, and effects have been observed in most organs/systems (see Section 2.17 for additional information). The animal studies clearly demonstrate that the developing organism is very sensitive to the toxicity of 2,3,7,8-TCDD. The types of effects observed in the offspring of animals exposed to 2,3,7,8-TCDD include fetal/newborn mortality, decreased growth, structural malformations, decreases in birth weight and growth, immunotoxicity, thymic atrophy, impaired development of the reproductive system, and neurodevelopmental effects. The most sensitive developmental effects are impaired development of the reproductive system and neurobehavioral effects.

There is a limited amount of data on the toxicokinetic properties of CDDs in children or immature animals. A toxicokinetic model was constructed that accurately predicted the lifetime concentrations of

2,3,7,8-TCDD in adipose tissue, blood, liver, and feces at different ages (Kreuzer et al. 1997). In formula-fed infants, the model predicted that 2,3,7,8-TCDD lipid levels would decrease during the first year and subsequently increase, reaching a maximum at 16 years of age. In contrast, the model predicted an initial increase in 2,3,7,8-TCDD lipid levels in exclusively breastfed infants followed by a 3-year decrease after weaning and merging at about 7 years with concentrations in formula-fed individuals. The half-life of nonmetabolic elimination (unchanged 2,3,7,8-TCDD) was calculated to be 0.42 years in newborns and 9.5 years in 40-year-old adults. The half-life of the fraction metabolized by the liver ranged from 1.5 years for newborns to approximately 10 years for a 40-year-old individual. The 3 times greater elimination half-life for the metabolized fraction relative to the nonmetabolized fraction in infants suggests that metabolic elimination does not play a major role in the elimination of 2,3,7,8-TCDD in infants. 2,3,7,8-TCDD accumulates preferentially in liver and adipose tissue. Accumulation in the liver is due to sequestration by the microsomal binding protein, CYP1A2. To the extent that this protein is developmentally regulated (Leeder and Kearns 1997), infants (<4 months old) might accumulate relatively less 2,3,7,8-TCDD in their livers than adults. Little is known about the metabolism of 2,3,7,8-TCDD in humans and it is unknown whether the metabolism of 2,3,7,8-TCDD or other CDDs differs between adults and children. In animals, phase II enzymes play an important role in the biotransformation and elimination of 2,3,7,8-TCDD. If this were the case in humans, it would be expected that very young infants would metabolize and eliminate 2,3,7,8-TCDD slower than adults since glucuronosyltransferase activity achieves adult levels by 6–18 months of age (Leeder and Kearns 1997).

CDDs are transferred from mother to offspring through the placenta and human milk. Although there are human data indicating placental transfer of 2,3,7,8-TCDD (Kreuzer et al. 1997; Schecter et al. 1996b), quantitative data are not available. A study in mice administered a single dose of 2,3,7,8-TCDD on GD 12 showed that the rate of accumulation of 2,3,7,8-TCDD in placental tissue reached a maximum in about 3 hours (Abbott et al. 1996); after 24 hours, 0.27% of the maternal dose was detected in the placenta. The transfer of CDDs through the placenta and human milk is discussed in more detail in Section 3.1.4.

CDDs are lipophilic compounds that can concentrate in maternal milk and be transferred to the nursing infant. Numerous studies have examined the transfer of 2,3,7,8-TCDD and related chemicals to infants via human milk and for the most part, the results showed that infants may absorb up to 95% of the administered dose (Abraham et al. 1994, 1996; Dahl et al. 1995; McLachlan 1993; Pluim et al. 1993b). This percentage is similar to the percent of 2,3,7,8-TCDD absorbed (>87%) by an adult volunteer after ingestion of a single oral dose of 2,3,7,8-TCDD (Poiger and Schlatter 1986). As stated previously, it has

also been shown that breastfed infants have a larger 2,3,7,8-TCDD burden during the first year of life compared to formula-fed infants (Kreuzer et al. 1997). However, this initial higher burden does not translate into a higher lifetime burden. A number of human studies have examined breastfed infants of mothers with high background levels of CDDs. These studies have found alterations in some markers of liver, thyroid, and immune function and in neurodevelopment (neurological optimality score) (Huisman et al. 1995a; Koopman-Esseboom et al. 1994; Pluim et al. 1993b, 1994a; Weisglas-Kuperus et al. 1995); however, all of the markers were within the normal range. The impaired neurological optimality score that was observed in newborns was not significantly altered in children aged 6, 18, or 31 months (Ilsen et al. 1996; Huisman et al. 1995b; Pluim et al. 1996).

Subsequent sections of this chapter (Sections 3.3 and 3.4) discuss the available information on biomarkers and interactions. Most of the available information is from adults and mature animals; no child-specific information was identified, with the possible exception of biomarker data. However, there are some data to suggest that interactions with PCBs and CDFs may influence the developmental toxicity of 2,3,7,8-TCDD. Data from children living in Seveso suggest that serum 2,3,7,8-TCDD levels are reflective of exposure levels and are a sensitive indicator of past exposure. Likewise, it is likely that the available information in adults on interactions and methods for reducing toxic effects will also be applicable to children.

As discussed previously, children appear to be unusually susceptible to the dermal toxicity of 2,3,7,8-TCDD. The data are inadequate to assess whether they will also be more sensitive to other CDD effects. Additionally, the available animal data suggest that the developing fetus is very sensitive to 2,3,7,8-TCDD-induced toxicity. 2,3,7,8-TCDD appears to interfere with the development of the reproductive, immune, and nervous systems; the mechanisms of action for these toxic effects have not been elucidated.

Children are primarily exposed to CDDs in the same manner as adults in the general population (i.e., via consumption of foods contaminated with small amounts of CDDs, particularly meat, milk and other dairy products, and fish). Children who are at additional risk of exposure primarily through dietary habits, include: infants and young children who are breastfed; children of recreational and subsistence fishers, who typically consume larger amounts of locally caught fish and shellfish than the general population; children of subsistence hunters, particularly those in the high latitudes, who typically consume large amounts of locally caught game especially marine mammals; and children of subsistence farmers living in

areas contaminated with CDDs (either by waste incinerators or the use of CDD-contaminated sewage on their land) who exclusively consume their own farm-raised beef and dairy products (see Section 5.7).

The human fetus is exposed to CDDs/CDFs through transplacental transfer from the mother. Schecter et al. (1990a) reported 2,3,7,8-TCDD concentrations in liver tissue of three stillborn infants of 0.03–0.18 ppt (whole weight basis) and 1.3–4.3 ppt (lipid weight basis). Schecter et al. (1990a) also reported CDD/CDF concentrations in liver tissue of three stillborn infants of 2.1–4.92 ppt (whole weight basis) and 98–104 ppt (lipid weight basis). The TEQ for CDDs/CDFs combined were 0.14–0.49 ppt (whole weight basis) and 6.4–12 ppt (lipid weight basis). In another study, Schecter et al. (1996c) reported TEQs for CDDs/CDFs in placental material of 8.4–17.6 ppt (lipid basis). In a pooled sample of fetal tissue (8–14 weeks), the TEQ was 5.3 ppt (lipid basis). Concentrations of 2,3,7,8-TCDD in adipose tissue and liver were also reported by Kreuzer et al. (1997) for stillborn babies at levels of 0.2–0.8 and 0.3–0.7 ppt, respectively. Kreuzer et al. (1997) developed a pharmacokinetic model for 2,3,7,8-TCDD that predicted a decrease in body burdens during the first year for non-breastfed infants and this was supported by empirical data (see Section 3.1.4).

In addition to transplacental transfer, CDDs and CDFs have been found in human milk (Fürst et al. 1992; Ryan et al. 1993a; Schecter and Gasiewicz 1987b; Schecter et al. 1986a, 1989b, 1989d, 1989e, 1991a); human milk is thus a potential source of CDDs for nursing infants and children (see Section 5.6). In Binghamton, New York, and Los Angeles, California, human milk was found to contain almost identical levels of detectable CDDs on a lipid basis probably because food consumption and sources are similar across the United States (Schecter et al. 1989e). Mean values of two pooled samples (n=42) from both cities showed that OCDD was the most abundant congener present (233 ppt), followed in decreasing order by total HxCDD (42.65 ppt), 1,2,3,4,6,7,8-HpCDD (42 ppt), 1,2,3,6,7,8-HxCDD (30.5 ppt), 1,2,3,7,8-PeCDD (6.7 ppt), 1,2,3,7,8,9-HxCDD (6.2 ppt), 1,2,3,4,7,8-HxCDD (4.95 ppt), and 2,3,7,8-TCDD (3.3 ppt). The total CDDs value was reported as 327 ppt. The TEQ for CDDs/CDFs, but not PCBs, in human milk in the United States was 17 ppt (Schecter et al. 1989e). Between 1986 and 1987, concentrations of CDDs found in human milk sampled from Canadian women ranged from 2.2 ng/kg (ppt) (lipid basis) for TCDDs to 173 ppt for OCDD. In addition, the combined CDD/CDF mean TEQ of 15.6 ppt (lipid basis) declined from a TEQ of 24.7 ppt measured in 1981–1982 (Ryan et al. 1993a).

CDD/CDF concentrations also have been measured in human milk in several foreign studies. The levels of CDDs were 5.3–139.5 ng TEQs/kg milk fat in studies of women in the Netherlands, Canada, Germany,

Siberia, United Kingdom, South Vietnam, and Cambodia (Dewailly et al. 1991; Duarte-Davidson et al. 1992; Fürst et al. 1994; Pluim et al. 1994a). Transplacental transfer of CDDs has also been demonstrated in humans (Kreuzer et al. 1997; Pedersen et al. 2010). OCDD was a major component in human milk (50.2–494.0 ng/kg milk fat) and the concentrations tended to decrease with the degree of chlorination. CDD concentrations in human milk can be directly correlated with the age of the mother and the amount of animal (but not vegetable) fat and protein consumed, suggesting that meat, milk and other dairy products, and fish are the major sources of CDD intake (Pluim et al. 1993a). The fact the CDD concentrations in milk fat were significantly related to age is in agreement with the results of Stanley et al. (1986) and Orban et al. (1994) who reported a strong correlation between age group and CDD levels in adipose tissue in the general U.S. population. The positive correlation can be expected because of the long half-life of CDDs in humans (7–11.3 years) (Pirkle et al. 1989; Wolfe et al. 1994).

Estimated daily intakes of CDD/CDF TEQs by nursing infants in the United States have been reported by Schecter and Gasiewicz (1987a). The daily intake by nursing infants in the United States was estimated to be 83.1 pg TEQs/kg body weight/day. To determine this daily intake, various assumptions were made regarding infant body weight (10 kg), duration of nursing, average amount of milk consumed, and gastrointestinal absorption. It was also assumed that human milk was the only source of CDDs while the infant was nursing during the first year of life. From results of earlier studies that determined the concentrations of CDDs/CDFs in human milk in the United States (Schecter et al. 1989e) and in cow's milk and soybean-derived infant formula sold in the United States (Schecter et al. 1989c) (see Section 5.5.4), Schecter et al. (1994a) estimated intakes of 35–53 pg TEQ/kg of body weight/day for infants (7.3 kg) who were breastfed within the first year of life as compared to 0.07–0.16 pg TEQ/kg of body weight for infants who were fed soy formula.

Exposure of infants and young children to CDDs may be very high because of their relatively high consumption of milk, including human milk (ECETOC 1992). Schecter et al. (1994a) evaluated the intake of CDDs/CDFs from human milk and estimated that high levels reported for human milk in the United States (≈17 ppt TEQ on a lipid basis) contribute 35–53 pg TEQ/kg of body weight per day to the nursing infant in its first year of life (Schecter et al. 1989e). The CDD concentrations in cow's milk and soy-based formula were much lower than the 327 ppt concentration in human milk (Schecter et al. 1991a). The following concentrations for CDDs (on a lipid basis) were reported: cow's milk (25.1 ppt), 2% cow's milk (32.3 ppt), Similac™ infant formula (39 ppt), Isomil™ infant formula (23.3 ppt), and Prosobee™ infant formula (42.7 ppt) (Schecter et al. 1989c). The TEQ values for cow's milk and soy-based infant formula were also much lower than for human milk (≈17 ppt). The corresponding TEQ

values for CDDs/CDFs (on a lipid basis) were reported: cow's milk (2.1 ppt), 2% lowfat cow's milk (0.79 ppt), Similac™ infant formula (0.08 ppt), Isomil™ infant formula (0.05 ppt), and Prosobee™ infant formula (0.127 ppt) (Schecter et al. 1989c). Schecter and Gasiewicz (1987a, 1987b) calculated TEQ values for CDDs/CDFs in human milk in two populations in Vietnam and in the general population in the United States. The study authors reported mean values during the 1980s of 1.04 pg TEQ/g (whole milk basis) for the United States (maximum 4.72 pg TEQ/g), a mean of 1.11 pg TEQ/g for South Vietnamese (maximum value 4.38 pg TEQ/g) exposed to Agent Orange sprayed between 1962 and 1970, and a mean of 0.065 pg TEQ/g (maximum value 0.18 pg TEQ/g) for a North Vietnamese population that was not exposed to Agent Orange. The study authors concluded that some infants in the United States (whose mothers had CDD milk concentrations in the upper range of measured values) were being exposed to mean concentrations comparable to levels observed in the South Vietnamese population exposed to Agent Orange (Schecter and Gasiewicz 1987a, 1987b).

The highest exposure to CDD-contaminated human milk reported was associated with the widespread use of Agent Orange as a defoliant during the Vietnam War. Human milk specimens from Ho Chi Minh City and Song Be Province in South Vietnam had lower 2,3,7,8-TCDD values in the late 1980s (7.1 and 17 ppt lipid basis, TEQ values of 18.5 and 31.7 ppt, respectively) than they did in the 1970s when Agent Orange spraying occurred (Schecter et al. 1989e). A 1970 mean value for 2,3,7,8-TCDD in human milk in South Vietnam was reported to be 484.9 ppt (range, not detectable to 1,450 ppt) (Baughman and Meselson 1973; Schecter et al. 1986a). These values serve as reference values for the highest levels of 2,3,7,8-TCDD documented in human milk (Schecter et al. 1989e). Estimated daily intakes of TEQs by nursing infants from Vietnam have been reported (Schecter and Gasiewicz 1987a). The estimated daily intake by nursing infants in southern Vietnam in 1970 was 908 pg TEQs/kg body weight/day, whereas the daily intakes in southern and northern Vietnam in 1984 were 88.7 and 5.1 pg TEQs/kg body weight/day, respectively. Analysis of nine milk samples from individuals living in northern Vietnam showed no detectable concentrations of 2,3,7,8-TCDD (detection limit 2 ppt) (Schecter and Gasiewicz 1987a). To determine these daily intakes, various assumptions were made regarding infant weight, duration of nursing, average amount of milk consumed, and gastrointestinal absorption. It was also assumed that human milk was the only lifetime source of exposure to CDDs during the first year of life. In another study, Tarkowski and Yrjanheikki (1989) evaluated the health risks associated with human milk. The study authors concluded that levels of CDDs/CDFs in human milk did not present a health risk to infants or children and that there was no justification for limiting breastfeeding. However, the study authors believed that there was a need for primary prevention of CDD/CDF exposure in humans. Because of the relatively short period of intake and the accepted benefits of breastfeeding, WHO (1991) did not

recommend limitations on breastfeeding at the levels of background exposures to CDDs and CDFs. Pohl and Hibbs (1996) reviewed studies indicative of a possible link between development of subtle health effects in children and their exposure to CDDs and CDFs from maternal milk. It is the ATSDR position that for background exposures, the benefits of breastfeeding outweigh any potential risk associated with exposure. For higher CDDs levels in human milk, the safety of breastfeeding may be of concern in some cases.

Two studies have looked at ways to reduce CDD exposure in breastfed infants. Koppe (1995) reported that exposure before and after birth to CDDs and PCBs has given rise to subtle abnormalities (disturbed cognitive development and delayed motor development) in approximately 10% of newborns in the Netherlands. The study author examined possibilities of reducing this exposure by influencing the diet of the lactating mother. Mobilization of fatty acids from adipose tissue will cause release of stored CDDs, which will then be secreted in human milk. Two maternal diets were tested for their ability to reduce concentrations of CDDs in human milk. One diet was a low-fat/high-carbohydrate/low-CDD diet, while the second was a high-fat/low-carbohydrate/low-CDD diet. Despite significant changes in fatty acid profiles of the milk, no significant changes in CDD concentrations in human milk were observed. The study author concluded that short-term dietary measures will not reduce CDDs in human milk. A lowering of CDD intake must occur years before the woman becomes pregnant. An important food source for the women is cow's milk and other dairy products and these are responsible for about half of the daily exposure CDDs and PCBs in women in the Netherlands, so levels of the compounds in dairy foods must be lowered. In addition, the study author believed that a lowering of CDD concentrations in fish is also necessary. Based on the results of his dietary study, Koppe (1995) reported that daily dietary intake of CDDs during lactation represents only 14% of the daily secretion of CDD in human milk, while 86% was derived from CDDs stored in adipose tissue. Thus, reducing dietary intake of CDDs during lactation would only reduce CDDs in milk by 14%. Schlaud et al. (1995) also reported that to reduce organochlorine residue levels, including CDDs in human milk in the short-term, nursing mothers should be advised not to try to reduce their body weight until after lactation. The study authors reported statistically significant positive associations between human milk contamination and average dietary fat intake per week ($p=0.001$) and proximity of residence to hazardous waste sites ($p<0.05$) for CDDs. The study authors believe that public promotion of a lower dietary fat intake may reduce the lifetime accumulation of CDDs in human fatty tissues and in the long-term, resulting in lower concentrations in human milk as well.

In addition to exposure to CDDs through consumption of human milk, cow's milk, and soy-based infant formula, older children can be exposed through dietary practices similar to those of adults in the general population (see Section 5.5.4). One study looked at the exposure that might occur in a 6-year-old child who consumes "fast foods." In 1995, Schecter and Li (1997) conducted a congener-specific analysis of CDDs, CDFs, and dioxin-like PCBs in U.S. fast foods. The study authors reported CDD/CDF TEQ values, depending on the treatment of not detected congeners, of 0.03–0.28 pg/g wet weight for one McDonald's Big Mac, 0.03–0.29 pg/g for one Pizza Hut personal pan pizza supreme with all toppings, 0.01–0.49 pg/g for one Kentucky Fried Chicken three-piece original recipe meal, and 0.3–0.31 pg/g for one Häagen-Daz chocolate-chocolate chip ice cream. The daily intake from one serving of each of the fast foods tested, assuming a 20-kg child (6 years old), ranged between 0.15 and 5.05 pg TEQ/kg body weight. The study authors calculated that, on average, a child (6 years old) consumes 3 times more TEQs on a per kg/body weight basis than an adult eating any one of the fast foods tested.

As a result of the transfer of CDDs through the placenta to the fetus, by human milk to infants and young children, and by lifelong dietary intakes from the consumption of meat, milk and dairy products, and fish, CDDs are found to be widespread in the adipose tissue of members of the general population (Orban et al. 1994). Human adipose samples from the 1987 National Human Adipose Tissue Survey (NHATS) provide a representative sample of CDD body burden in the general U.S. population (see Section 5.6). The average concentration of 2,3,7,8-TCDD in the U.S. population was estimated to be 5.38 pg/g (±6%). The 1987 survey data clearly show, however, that nearly all the CDD/CDF congeners in adipose tissue increased with the age of the donor (i.e., the highest concentrations occurred in the ≥45-year-old age group and the lowest concentrations occurred in children in the 0–14-year-old age group). The average concentration of 2,3,7,8-TCDD in the 1987 survey increased from 1.98 pg/g in the 0–14-year-old group, to 4.37 pg/g in the 15–44-year-old group, to 9.4 pg/g in the ≥45-year-old group.

Children may be exposed to CDDs through a variety of lifestyle practices of their parents or of their own. For example, CDD/CDF concentrations have been reported in cigarette smoke (Lofroth and Zebuhr 1992; Muto and Takizawa 1989) (see Section 5.5.4). Young children and infants may be exposure to CDDs indirectly by inhalation of room air contaminated from cigarette smoking of their parents. In addition, older children and teenagers may be directly exposed if they become smokers themselves. Malisch (1994) reported that some colored candle wax produced with certain dye pigments contained CDDs/CDFs. By burning these candles, CDDs could be released into room air and be an additional source of inhalation exposure for children.

Children may also be exposed to CDDs by dermal contact with some new, unwashed clothing, particularly those manufactured in some developing countries or from fabric shipped from developing countries where PCP is used for preserving cotton fabrics during sea transport (Horstmann and McLachlan 1994). Exposures can be reduced by washing new clothes prior to wearing.

Children could potentially be exposed to CDDs at home from a variety of incineration sources. For example, if their parents routinely burn domestic garbage containing scrap wood treated with PCP (Chiu et al. 1983) or untreated wood (Clement et al. 1985), have old pesticide containers that may have contained 2,4,5 T or 2,4-D or Silvex (Arthur and Frea 1989), have PVC pipes or other plastics items (Lustenhouwer et al. 1980), or extensively use a wood stove (Clement et al. 1985), children may be exposed to higher levels of CDDs in outdoor and/or indoor air. Time spent in a garage where cars or trucks are being repaired and the engines are running exposes children and teenagers to exhaust products and engine soot that may also contain CDDs (Bingham et al. 1989; Cirnies-Ross et al. 1996).

Although there are many studies on the effects of CDDs on adults who receive occupational exposures (Fingerhut et al. 1989; Hesso et al. 1992; Patterson et al. 1989a; Schecter et al. 1985a, 1994b; Tepper et al. 1997), no information was located on the potential for workers in the United States to bring CDDs home on their clothing or shoes, thus contaminating other family members, including children. It is conceivable, however, that because CDDs are present in a variety of diverse occupational settings (see Section 5.6), poor occupational hygiene could result in CDDs being brought home and contaminating domestic dwellings.

Children in populations with potentially high exposure living in the vicinity of former or current production sites where CDDs are released as byproducts (e.g., incinerators, other waste disposal facilities, and hazardous waste sites) may be exposed to CDDs by several pathways (see Section 5.7). Children may be exposed to CDDs in CDD-contaminated soils. Dermal absorption from contaminated soil, however, is likely to be inefficient (Poiger and Schlatter 1980; Shu et al. 1988; Weber et al. 1991b). Young children are potentially exposed to CDDs because of their tendency, through hand-to-mouth activity, to ingest soils (pica) that may be contaminated with CDDs (see Section 5.7 for further details) (Fries and Paustenbach 1990; Kimbrough et al. 1984; Paustenbach et al. 1992; Pohl et al. 1995). LaGoy (1987) estimated the following average soil ingestion rates for children: 0–1 year old, 50 mg/day (maximum 250 mg/day); 1–6 years old, 100 mg/day (maximum 500 mg/day); 6–11 years old, 50 mg/day (maximum 250 mg/day); and >11 years old, 50 mg/day (maximum 100 mg/day). If children ingest

between 50 and 100 mg of soil per day (LaGoy 1987) and the soil that they ingest contains 1 pg/g (1 ppt) of CDDs, a child may be exposed to 0.05–0.1 pg CDDs/day by this pathway alone (see Section 5.7).

Children in high-risk populations include children of recreational or subsistence fishers, children of subsistence hunters particularly those who consume tissues of marine mammals, and children of subsistence farmers who consume meat, milk, and/or dairy products from their own farm-raised animals (see Section 5.7 for further details). For example, Native American and other subsistence fishing communities may be at greater health risks from CDDs in fish, and children in these population often consume larger amounts of fish than adult members of the general population (CRITFC 1994; Mott 1995). Children of recreational and subsistence fishers who routinely consume locally caught fish from CDD-contaminated waterbodies can be exposed to higher CDD concentrations than children who consume similar or larger amounts of commercially marketed fish from a variety of sources (Ebert et al. 1996; EPA 1995; Mott 1995). The exposure to CDDs will also be highest among children who regularly eat fish as compared to those who only occasionally eat fish or never eat fish. Several studies have documented the higher fish consumption rates among subsistence fishers, some of which are Native American populations (CRITFC 1994; Nobmann et al. 1992; Wolfe and Walker 1987). A study of fish consumption patterns among the Umatilla, Nez Perce, Yakama, and Warm Springs tribes of the Columbia River Basin in Washington and Oregon (CRITFC 1994) found that the consumption rate for these Native American children (≤5 years) from these four tribes was 19.6 g/day (a consumption rate over 3 times higher than that for adults in the general population [6.5 g/day]).

This increased exposure has been demonstrated by serum CDD levels that are found to be several times higher in people who regularly eat fish as compared to those who occasionally eat fish or never eat fish (Anderson et al. 1998; Svensson et al. 1991) (see Sections 5.7). In addition, this same situation also applies for consumption of wildlife, specifically marine mammals (Ayotte et al. 1997; Dewailly et al. 1992). Similar dietary situations exist for children of subsistence hunters who tend to consume tissues of marine mammals and children of subsistence farmers who consume beef, milk, and other dairy products from their own farm-raised animals. In the case of subsistence fishers, subsistence hunters, and subsistence farmers, all three populations share one problem, that the sources of their fish, meat, and/or milk and other dairy products are typically restricted to a localized area, and if these food sources are contaminated with CDDs, adults and children in these populations will be exposed to higher levels of CDDs than members of the general population (see Section 5.7 for additional details on these populations at risk).

In order to reduce exposure from consumption of CDD-contaminated fish and wildlife, consumption advisories are issued by states recommending that individuals restrict their consumption of specific fish, shellfish, and wildlife species from certain waterbodies where CDD concentrations in tissues of these species exceed the human health level of concern (EPA 1995) (see Section 5.7 for additional information). Recreational and subsistence fishers typically consume larger quantities of fish and shellfish than the general population and frequently fish the same waterbodies routinely. Because of this, children living in these populations are at greater risk of exposure to CDDs and other chemical contaminants if the waters they fish are contaminated. EPA (1998b) reported that 66 advisories have been issued by 21 states restricting the consumption of CDD-contaminated fish and shellfish, and one state Arkansas also issued a consumption advisory for wood ducks, a species of migratory waterfowl. Three states (New Jersey, New York, and Maine) also had statewide advisories for CDDs in their marine waters (EPA 1998a).

As reviewed by Connor and Aylward (2006), a number of AhR polymorphisms (defined as an allelic frequency of >1% in a given population) have been identified. However, correlations between the observed human AhR genotype and CYP1A/B inducibility have not been established. Connor and Aylward (2006) noted that because the AhR has been shown to have a critical role in development and homeostasis, there is little tolerance for genetic variations, other than those that are inconsequential to AhR function. Human polymorphisms frequently occur in exon 10, a region that encodes a major portion of the transactivation domain of the AhR that is responsible for regulating the expression of other genes (e.g., CYP1A1) (Harper et al. 2002). Variation that is confined to the transactivation domain may permit finely tuned modulation in gene regulation without abolishing the critical roles of AhR in development and homeostasis (Harper et al. 2002). Most of the ‘defective’ phenotypes that have been identified in human cells or tissues are in the direction of non-responsiveness or low inducibility. Only one pair of human polymorphisms, those at codons 517 and 570, has been shown to have a clear-cut and strong effect on the phenotype of an AhR-mediated response.

A wide range of AhR binding capacities has been measured in humans, and a number of investigators have interpreted this range of dissociation constants as indicating a heterogeneous human AhR with functionally important polymorphisms (Connor and Aylward 2006). However, some of the observed variation may be due to experimental factors (differences in composition/cellular makeup of the samples) and environmental and dietary influences. Studies on human placental tissues have found at least a 10-fold range of AhR binding affinities for 2,3,7,8-TCDD. However, sequencing the AhR complimentary DNA (cDNA) from a few individuals with the highest and lowest affinities did not reveal

any polymorphisms that would explain the variation in ligand binding (Harper et al. 2002). Although polymorphisms on the AhR that would influence normal receptor function are unlikely, genetic variations might exist in non-AhR components such as ARNT, AhR repressor (AhRR), co-activators, or co-repressors, which may affect AhR-mediated events. However, the possible variations have not been fully explored (Harper et al. 2002).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 2006).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for CDDs from this report are discussed in Section 5.6, General Population Exposure.

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 2006). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to CDDs are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for CDDs from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 2006). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly

adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by CDDs are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

CDDs are ubiquitous environmental contaminants that have been measured in biological fluids and tissues of the general population. Adipose tissue and the liver are the primary storage sites for CDDs. It was demonstrated that the relative (lipid-based) levels of 2,3,7,8-TCDD are similar in hepatic and adipose tissues (Leung et al. 1990a) and between adipose tissue and serum (Patterson et al. 1988; Schecter et al. 1990b) from the same patients. Thus, measurement of 2,3,7,8-TCDD levels in serum lipids is considered an accurate and practical measure of body burden. However, this was not the case for more highly chlorinated dioxins; for example, for OCDD, there is a 2:1 ratio between serum and adipose tissue lipid fractions (Schecter et al. 1990b) and a 12:1 ratio between liver and adipose tissue levels (Thoma et al. 1990). The important TEQ variable was close to a 1:1 ratio. CDDs have also been detected in human milk of women exposed to high levels of CDDs and in women presumably exposed to background levels. How human milk levels relate to CDD exposure or body burden has not been established; both parity and the length of time the woman has been lactating influence the CDD concentration in human milk.

The half-lives of CDDs have been estimated from blood samples of highly exposed individuals (workers, Operation Ranch Hand veterans, and the Seveso cohort). The half-lives of 2,3,7,8-TCDD range from 5.8 to 8.7 years (Aylward et al. 2013; Flesch-Janys et al. 1996; Michalek et al. 1996; Needham et al. 1994; Ott and Zober 1996; Yamamoto et al. 2015b). Less information is available of other CDD congers; estimated half-lives of 13.8–15.7 years for 1,2,3,7,8-PeCDD, 8.4–10.7 years for 1,2,3,4,7,8-HxCDD, 9.0–13.1 years for 1,2,3,6,7,8-HxCDD, 4.8–6.3 years for 1,2,3,7,8,9-HxCDD, 6.7–3.7 years for 1,2,3,4,6,7,8-HpCDD, and 6.7–7.3 years for OCDD have been reported (Aylward et al. 2013; Flesch-Janys et al. 1996; Yamamoto et al. 2015b). Aylward et al. (2013) and Yamato et al. (2015b) also estimated half-lives of 8.7–9.1 years for total TEQ (CDDs, CDFs, and dioxin-like PCBs). Information on the levels of CDDs in biological tissues is presented in Sections 5.6 and 5.7.

3.3.2 Biomarkers of Effect

Chloracne is one effect that is clearly associated with exposure to high levels of CDDs and other halogenated organic chemicals and has been observed in some individuals who were exposed occupationally or in the environment to increased levels of 2,3,7,8-TCDD or chemicals contaminated with 2,3,7,8-TCDD. However, while the presence of chloracne indicates exposure to CDDs or other halogenated organic compounds, its absence does not preclude such exposure. For example, in a cohort from the Seveso incident, no chloracne was observed below an initial serum lipid 2,3,7,8-TCDD level of 800 ppt (body burden of 2.5 μg/kg, assuming 22% body fat and 70 kg body weight); above 12,000 ppt (body burden of 38 μg/kg), chloracne was always observed; and between 800 and 12,000 ppt, the occurrence of chloracne was sporadic (Mocarelli et al. 1991). In the Yu-Cheng population, chloracne was associated with a body burden in 2,3,7,8-TCDD equivalents of 2–3 μg/kg body weight, or about 140–210 μg for a 70-kg adult (Ryan et al. 1990).

Biochemical changes (raised serum hepatic enzyme levels, disorders of lipid and carbohydrate metabolism, unbalanced porphyrin metabolism) and/or an enlarged liver can indicate effects induced by 2,3,7,8-TCDD exposure, but these effects are not specific for this or other compounds. Light and electron microscope changes in the liver (e.g., lipid droplets in parenchymal cells, increased endoplasmic reticulum, enlarged and pleomorphic mitochondria) are also sensitive but nonspecific biomarkers for exposure to CDDs (Schecter et al. 1985b). When biochemical changes in the placenta of women exposed in the Yu-Cheng incident were evaluated for use as possible biomarkers, the EGF receptor autophosphorylation effect was found to be associated with decreased birth weight in the neonates (Lucier et al. 1986). The study authors suggested using this response as a biomarker of effect for all toxic chlorinated aromatic compounds.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Several studies were located regarding interactions that affect the toxicity of CDDs. Probably the most important interactions that have an impact on human health are those involving CDDs, CDFs, and PCBs. It has been recognized that chloroaromatics cause a complex of similar effects that vary in severity depending on the number of chlorine atoms, positional substitution, and species susceptibility. Sufficient information is available for assessment of risk associated with exposure to 2,3,7,8-TCDD. However, exposure to a mixture of chloroaromatics is common in the general environment. The assessment of

health risk resulting from exposure to chemical mixtures of chloroaromatics was enabled by the development of TEFs (2,3,7,8-TCDD equivalence factors) that relate the relative toxic potency for CDDs and CDFs to that of 2,3,7,8-TCDD (EPA 1989). It was assumed based on previous literature data (Eadon et al. 1986) and in animal dosing studies (Van den Berg et al. 1989), that CDDs and CDFs have an additive effect in the organism when weighted for relative toxicity compared to 2,3,7,8-TCDD (for further information see Sections 2.1). The assumption of additivity was later supported by experimental data. The concept of TEFs was used, for example, to assess the potential toxicity of background levels of CDFs and CDDs in general populations based on body burdens of indicator CDDs that were associated with chloracne and other effects in the Yusho and Yu-Cheng rice oil poisoning incidents (Ryan et al. 1990).

However, some studies further investigated the interactions of various chloroaromatics and indicated that the interactions may be more complicated. *In vitro* studies compared relative toxicity of various chloroaromatics in human cell lines monitoring enzyme induction and binding to the AhR that mediates the induced responses (Nagayama et al. 1985; Safe 1987). *In vivo* studies concentrated on monitoring enzyme induction, inhibition of body weight gain, and immunotoxic and teratogenic effects. Coexposure of Long-Evans rats to 6-methyl-1,3,8-trichlorodibenzofuran (MCDF) and 2,3,7,8-TCDD induced a partial inhibition of the monooxygenase enzyme-induction response caused by 2,3,7,8-TCDD treatment alone (Harris et al. 1989). Although MCDF did not decrease the levels of occupied nuclear 2,3,7,8-TCDD AhRs, it inhibited the effects of 2,3,7,8-TCDD on the cytosolic AhR (Harris et al. 1989).

Other studies further indicated that PCBs may antagonize AhR-mediated responses to 2,3,7,8-TCDD. In a review, Van den Berg et al. (1994) suggested that toxicokinetic factors contribute to the observed nonadditive toxicological and biological effects. Co-treatment of C57BL/6 mice with various commercial Aroclors (PCB mixtures) and 2,3,7,8-TCDD resulted in antagonizing the 2,3,7,8-TCDD-mediated inhibition of the splenic plaque-forming cell response (Bannister et al. 1987; Davis and Safe 1989). Similarly, significant antagonism of 2,3,7,8-TCDD and Aroclor 1254 was observed in the induction of CYP-dependent monooxygenases in C57BL/6J mice (Bannister et al. 1987). The effects were dependent on the dose of both 2,3,7,8-TCDD and Aroclor 1254 and on their respective ratios. The ratios of Aroclor 1254/2,3,7,8-TCDD that induced antagonist reactions were comparable to the ratios of PCBs/CDDs found in human tissues and environmental samples. The study authors speculated that less-toxic chlorinated compounds may have a protective effect against the more-toxic compounds in the environment. However, by comparing the immune sensitivities of both Ah-responsive and Ah-less-responsive mouse strains, it was demonstrated that a complex mixture of contaminants taken from the Love Canal site was immunosuppressive and that this effect was primarily due to the 2,3,7,8-TCDD component of the

mixture, although 2,3,7,8-TCDD was a very minor component and there was little interaction with the other hydrocarbon components of the mixture (Silkworth et al. 1989a).

Experimental studies have shown that interactions of 2,3,7,8-TCDD and CDFs or PCBs resulted in fetotoxic and teratogenic effects in the offspring of exposed animals. Exposure of pregnant mice to 2,3,7,8-TCDF resulted in cleft palates and hydronephrosis in the offspring (Hassoun et al. 1984). The results obtained in different strains of mice indicated an association with the Ah locus. Comparable results were obtained previously in mice exposed to 2,3,7,8-TCDD (Abbott and Birnbaum 1989a; Abbott et al. 1987a, 1987b; Courtney 1976). When C57BL/6N mice were treated orally with 2,3,7,8-TCDD and 2,3,7,8-TCDF on GD 10, hydronephrosis and cleft palates were observed in the offspring (Weber et al. 1985). The effects of both chemicals were additive. Similarly, an increased incidence (10-fold) of cleft palates was observed in offspring of C57BL/6N mice after a combined treatment with 2,3,7,8-TCDD and 2,3,4,5,3',4'-hexachlorobiphenyl during gestation, as compared with those treated with 2,3,7,8-TCDD alone (cleft palate was not observed when 2,3,4,5,3',4'-hexachlorobiphenyl was administered alone) (Birnbaum et al. 1985). In contrast, no potentiation of CDD-mediated effect was found with 2,4,5,2',4',5'-hexachlorobiphenyl. Furthermore, co-treatment of pregnant C57BL/6J mice with Aroclor 1254 and 2,3,7,8-TCDD resulted in a sharp decrease in the incidence of cleft palate per litter (8.2%) compared with those treated with 2,3,7,8-TCDD alone (62%) (Haake et al. 1987).

Similarly, 2,3,7,8-TCDD-induced fetotoxicity and teratogenicity were altered by co-exposure to other chemicals. A synergistic effect on the induction of cleft palates was observed in offspring of C57BL/6N mice treated orally with 2,3,7,8-TCDD and retinoic acid on GD 10 or 12 (Abbott and Birnbaum 1989b; Birnbaum et al. 1989b). However, the co-administration of retinoic acid did not influence the incidence of 2,3,7,8-TCDD-induced hydronephrosis, nor did 2,3,7,8-TCDD affect the incidence or severity of limb-bud defects induced by retinoic acid (Birnbaum et al. 1989b). A synergistic effect was observed when 2,3,7,8-TCDD (orally) and hydrocortisone (subcutaneously) were administered to C57BL/6N mice on GDs 10–13 (Birnbaum et al. 1986). The incidence of cleft palate in the offspring increased to 100% following the combined treatment. Pretreatment of pregnant NMRI mice with benzo(*a*)pyrene subcutaneously 5 hours prior to an intraperitoneal injection of 2,3,7,8-TCDD caused an increase in CDD-induced lethality but did not alter the rate of cleft palate formation (Hassoun 1987). Offspring of male mice, treated with chlorinated phenoxy acids and 2,3,7,8-TCDD in their feed for 8 weeks before the mating, did not differ in their development or survival from offspring in the control group (Lamb and Moore 1981).

Results in B6C3F1 mice indicated that α-naphthoflavone antagonizes 2,3,7,8-TCDD in induction of splenocyte EROD activity (Blank et al. 1987). It was further suggested that α-naphthoflavone impedes 2,3,7,8-TCDD suppression of B lymphocyte differentiation by competing for binding to the AhR. The mechanism of interaction of these chemicals was studied *in vitro* using rat hepatic cytosol or mouse hepatoma cells (Gasiewicz and Rucci 1991). The results indicated that α-naphthoflavone acts as a 2,3,7,8-TCDD antagonist by binding to the AhR and forcing on it a conformation that cannot identify the DNA recognition sequence contained in the dioxin-responsive enhancer element of the CYP1A1 gene. In contrast, *in vitro* experiments showed that co-exposure of a thymus organ culture with the weakly toxic β-naphthoflavone and 2,3,7,8-TCDD results in a significant increase in the lymphoid inhibitory effect mediated by 2,3,7,8-TCDD (Hassoun 1987). A developmental toxicity study in mice administered 28 µg/kg 2,3,7,8-TCDD on GD 10 demonstrated that administration of 5 or 5,000 µg/kg α-naphthoflavone significantly reduced the incidence of cleft palate (Yuan et al. 2017). This study also found that administration of 5 mg/kg folic acid also decreased the incidence of cleft palate.

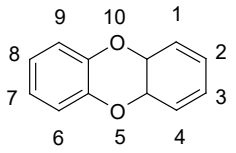
Hexachlorobenzene acted like a weak AhR agonist and caused an up to 40% decrease in specific hepatic cytosol binding of 2,3,7,8-TCDD in rat cells (Hahn et al. 1989). Similarly, 2,3,7,8-TCDD-induced myelotoxicity and enzyme induction were antagonized by 1-amino-3,7,8-trichlorodibenzo-*p*-dioxin in B6C3F1 mice, presumably by competitive binding to the cytosolic AhR (Luster et al. 1986). Comparable effects were observed *in vitro* in murine bone-marrow-cell cultures. Treatment of Fischer-344 rats orally with di(2-ethylhexyl)phthalate (DEHP) before or after oral administration of 2,3,7,8-TCDD reduced the hyperlipidemia induced by the latter compound (Tomaszewski et al. 1988). Furthermore, DEHP pretreatment followed by daily doses of this hypolipidemic substance was partially protective against 2,3,7,8-TCDD-induced mortality, wasting, and liver fatty changes.

The addition of activated charcoal or dehydrocholic acid to the feed, protected animals (C57BL/6J mice, CD-COBS rats, and guinea pigs) from increased mortality caused by a single lethal dose of 2,3,7,8-TCDD (Manara et al. 1984). In the case of the former agent, the effect was probably due to the general high binding ability of superactivated charcoal; since no other antidote is known, its use for therapeutic purposes was recommended. Protective effects of ascorbic acid (administered orally) and butylated hydroxyanisole (BHA) (administered orally) against 2,3,7,8-TCDD given by gavage were investigated in Sprague-Dawley rats (Hassan et al. 1987). BHA administration partially protected rats from losses in organ weights and 2,3,7,8-TCDD-induced lipid peroxidation and inhibition of glutathione peroxidase activity. In contrast, ascorbic acid had no protective effects.

Data regarding interactions affecting the toxicity or toxicokinetics of other chemicals by 2,3,7,8-TCDD were limited. Dermal pretreatment with 2,3,7,8-TCDD inhibited the induction of skin tumors by subsequently applied benzo(*a*)pyrene or dimethylbenz(*a*)anthracene in Sencar mice (Cohen et al. 1979). It was proposed that 2,3,7,8-TCDD caused qualitative alteration of hydrogen binding to DNA. In addition, 2,3,7,8-TCDD may also promote the metabolism of procarcinogens (e.g., 3-methylcholanthrene) to active metabolites by the induction of metabolizing enzymes (Kouri et al. 1974, 1978).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

CDDs are a class of related chlorinated hydrocarbons that are structurally similar. The basic structure is a dibenzo-*p*-dioxin (DD) molecule, which is comprised of two benzene rings joined at their *para* carbons by two oxygen atoms. There are eight homologues of CDDs, monochlorinated through octachlorinated. The class of CDDs contains 75 congeners, consisting of 2 monochlorodibenzo-*p*-dioxins (MCDDs), 10 dichlorodibenzo-*p*-dioxins (DCDDs), 14 trichlorodibenzo-*p*-dioxins (TrCDDs), 22 tetrachlorodibenzo-*p*-dioxins (TCDDs), 14 pentachlorodibenzo-*p*-dioxins (PeCDD), 10 hexachlorodibenzo-*p*-dioxins (HxCDDs), 2 heptachlorodibenzo-*p*-dioxins (HpCDDs), and a single octachlorodibenzo-*p*-dioxin (OCDD) (Ryan et al. 1991). The general structure of the dibenzo-*p*-dioxins is shown below. The numbers indicate the positions for chlorine substitutions, excluding, of course, positions 5 and 10.



Not all congeners have been studied for their chemical and physical properties, but basic properties are known for the CDDs as a chemical family and for the homologous groups. Chlorinated dioxins exist as colorless solids or crystals in the pure state. They have low solubility in water and low volatility. Chlorinated dioxins have an affinity for particulates and readily partition to particles in air, water, and soil. The more toxic compounds appear to be the 2,3,7,8-substituted tetra-, penta-, and hexachloro-compounds (i.e., 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, and 1,2,3,7,8,9-HxCDD). These are also the congeners, along with OCDD, that have the greatest tendency to bioaccumulate. One of the most toxic congeners in mammals is believed to be 2,3,7,8-TCDD; this compound has also been the most studied of the TCDD congeners.

4.1 CHEMICAL IDENTITY

Information regarding the chemical identities of CDDs is presented in Table 4-1.

Table 4-1. Chemical Identity of CDDs[a]

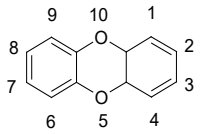
Characteristic	Monochlorodibenzo-*p*-dioxins	Dichlorodibenzo-*p*-dioxins
Chemical name	1-Chlorodibenzo-*p*-dioxin (CAS Registry Number 39227-53-7); 2-Chlorodibenzo-*p*-dioxin (CAS Registry Number 39227-54-8)[b]	2,7-Dichlorobenzo-*p*-dioxin (CAS Registry Number 33857-26-0)[c]
Synonym(s) and registered trade name(s)[d]	1-Chlorodibenzo-*p*-dioxin; 1-Chlorodibenzo-*p*-dioxin; 1-Chlorodibenzo[*b,e*](1,4)dioxin[b]; 2-Chlorodibenzo[*b,e*](1,4)dioxin[b]	1,3- or 1,6- or 2,3- or 2,7- or 2,8-Dichlorodibenzo-*p*-dioxin; 1,3- or 1,6- or 2,3- or 2,7- or 2,8-Dichlorodibenzo[b,e](1,4)dioxin; 1,3- or 1,6- or 2,3- or 2,7- or 2,8-Dichlorodibenzodioxin[b]
Total number of possible isomers	2	10
Chemical formula	$C_{12}H_7ClO_2$[e]	$C_{12}H_6Cl_2O_2$[b]
SMILES	c1(Cl)c2c(ccc1)Oc1c(cccc1)O2	c1(Cl)c(Cl)cc2c(c1)Oc1c(cccc1)O2
Chemical structure[b,f]		See footnote "f"
CAS Registry Number(s)[g]	39227-53-7 (1-)[e] 39227-54-8 (2-)[b]	50585-39-2 (1,3-); 38178-38-0 (1,6-); 29446-15-9 (2,3-)[e]; 33857-26-0 (2,7-)[c]; 38964-22-6 (2,8-)[e]

Table 4-1. Chemical Identity of CDDs[a]

Characteristic	Trichlorodibenzo-*p*-dioxins	Tetrachlorodibenzo-*p*-dioxins
Chemical name	1,2,4-Trichlorodibenzo-*p*-dioxin (CAS Registry Number 39227-58-2); 2,3,7-Trichlorodibenzo-*p*-dioxin (CAS Registry Number 33857-28-2)[b]	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (CAS Registry Number 1746-01-6)[c]
Synonym(s) and registered trade name(s)[d]	1,2,4- or 2,3,7-Trichlorodibenzo-*para*-dioxin; 1,2,4- or 2,3,7-Trichloro-dibenzo[b,e](1,4)dioxin; 1,2,4- or 2,3,7-Trichlorodibenzodioxin[b]	1,2,3,4- or 1,2,3,8- or 1,3,6,8- or 1,3,7,8- or 1,2,7,8- or 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin[h]; 1,2,3,4- or 1,2,3,8- or 1,2,7,8- or 1,3,6,8- or 1,3,7,8- or 2,3,7,8-Tetrachlorodibenzodioxin; 1,2,3,4- or 1,2,3,8- or 1,3,6,8- or 1,3,7,8- or 1,2,7,8- or 2,3,7,8-Tetrachloro-dibenzo[b,e](1,4)dioxin; 1,2,7,8- or 2,3,7,8-Tetrachlorodibenzo-1,4-dioxin; 2,3,6,7-Tetrachloro-dibenzodioxin; 1,2,7,8-Tetrachlorodibenzo-*p*-dioxin; Dioxin; TCDBD; TCDD[b]
Total number of possible isomers	14	22
Chemical formula	$C_{12}H_5Cl_3O_2$[e]	$C_{12}H_4Cl_4O_2$[b]
SMILES	c1(Cl)c(Cl)c(Cl)c2c(c1)Oc1c(cccc1)O2	c1(Cl)c(Cl)c(Cl)c(Cl)c2c1Oc1c(cccc1)O2
Chemical structure[b,f]	See footnote "f"	See footnote "f"
CAS Registry Numbers[g]	39227-58-2 (1,2,4-); 33857-28-2 (2,3,7-)[e]	30746-58-8 (1,2,3,4-); 53555-02-5 (1,2,3,8-); 34816-53-0 (1,2,7,8-); 33423-92-6 (1,3,6,8-); 50585-46-1 (1,3,7,8-)[e] 1746-01-6 (2,3,7,8-)[c]

Table 4-1. Chemical Identity of CDDs[a]

Characteristics	Pentachlorodibenzo-*p*-dioxins	Hexachlorodibenzo-*p*-dioxins
Chemical name	1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin (CAS Registry Number 40321-76-4)[e]	1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin (CAS Registry Number 57653-85-7); 1,2,3,7,8,9- Hexachlorodibenzo-*p*-dioxin (CAS Registry Number 19408-74-3); Hexachlorodibenzo-*p*-dioxin (CAS Registry Number 34465-46-8)[c]
Synonym(s) and registered trade name(s)[d]	1,2,3,4,7- or 1,2,3,7,8- or 1,2,4,7,8-Pentachlorodibenzo-para-dioxin; 1,2,3,4,7- or 1,2,3,7,8- or 1,2,4,7,8-Pentachlorodibenzodioxin; 1,2,3,4,7- or 1,2,3,7,8- or 1,2,4,7,8-Pentachlorodibenzo[b,e] (1,4)dioxin[b]	1,2,3,4,7,8- or 1,2,3,6,7,8- or 1,2,3,6,7,9- or 1,2,3,7,8,9- or 1,2,4,6,7,9-Hexachlorodi-benzo-para-dioxin; 1,2,3,4,7,8- or 1,2,3,6,7,8- or 1,2,3,6,7,9- or 1,2,3,7,8,9- or 1,2,4,6,7,9-Hexachlorodibenzodioxin[b]; Hexachlorodibenzo-4-dioxin[c]
Total number of possible isomers	14	10
Chemical formula	$C_{12}H_3Cl_5O_2$[e]	$C_{12}H_2Cl_6O_2$[b]
SMILES	c1(Cl)c(Cl)c(Cl)c(Cl)c2c1Oc1c(c(Cl)ccc 1)O2	c1(Cl)c(Cl)c(Cl)c(Cl)c2c1Oc1c(c(Cl)c(Cl) cc1)O2
Chemical structure[b,f]	See footnote "f"	See footnote "f"
CAS Registry Numbers[g]	39227-61-7 (1,2,3,4,7-); 40321-76-4 (1,2,3,7,8-); 58802-08-7 (1,2,4,7,8-)[e]	57653-85-7 (1,2,3,6,7,8-)[c]; 64461-98-9 (1,2,3,6,7,9-)[e]; 19408-74-3 (1,2,3,7,8,9-)[c]; 39227-62-8 (1,2,4,6,7,9-)[c]; 34465-46-8[e]

Table 4-1. Chemical Identity of CDDs[a]

Characteristic	Heptachlorodibenzo-*p*-dioxins	Octachlorodibenzo-*p*-dioxin
Chemical name	Heptachlorodibenzo-*p*-dioxin (CAS Registry Number 35822-46-9)[c]	Octachlorodibenzo-*p*-dioxin[c]
Synonym(s) and registered trade name(s)[d]	1,2,3,4,6,7,8- or 1,2,3,4,6,7,9-Heptachlorodibenzo-*p*-dioxin; 1,2,3,4,6,7,8- or 1,2,3,4,6,7,9-Heptachlorodibenzo[b,e](1,4) dioxin; 1,2,3,4,6,7,8- or 1,2,3,4,6,7,9-Heptachlorodibenzodioxin; 1,2,3,4,6,7,8- or 1,2,3,4,6,7,9-Heptachlorodibenzo-*para*-dioxin[e]; Heptachlorodibenzo[b,e](1,4)dioxin[c]	1,2,3,4,6,7,8,9-Octachlorodibenzo-*p*-dioxin; OCDD; Octachlorodibenzodioxin; Octachlorodibenzo[b,e](1,4)dioxin; Octachlorodibenzo-*p*-dioxin; 1,2,3,4,6,7,8,9-Octachlorodibenzodioxin; 1,2,3,4,6,7,8,9-Octachlorodibenzo[b,e](1,4)dioxin; Octachloro-*para*-dibenzodioxin[b]
Total number of possible isomers	2	1
Chemical formula	$C_{12}HCl_7O_2$[e]	$C_{12}Cl_8O_2$[c]
SMILES	c1(Cl)c(Cl)c(Cl)c(Cl)c2c1Oc1c(c(Cl)c(Cl)c(Cl)c1)O2	Clc3c(Cl)c(Cl)c2Oc1c(Cl)c(Cl)c(Cl)c(Cl)c1Oc2c3Cl
Chemical structure[b,f]	See footnote "f"	See footnote "f"
CAS Registry Numbers[g]	35822-46-9 (1,2,3,4,6,7,8-)[i]; 58200-70-7 (1,2,3,4,6,7,9-)[e]; 37871-00-4 (b,e)(1,4)[c]	3268-87-9[c]

[a]In some cases, information regarding chemical identity was not available for all isomers of a homologous class.
[b]IARC 1977.
[c]IARC 1997.
[d]Example, alternative nomenclature shown; not all possible isomers are listed but can be extrapolated from the general structure or from the literature (Ryan et al. 1991).
[e]RTECS 1996.
[f]The structural formula of unsubstituted dibenzo-*p*-dioxin and the numbering of the carbon atoms in the ring are given under monochlorodibenzo-*p*-dioxins. The chlorinated dibenzo-*p*-dioxins contain chlorine atoms at the positions indicated in their names (IARC 1977).
[g]Specific chlorine substitutions are given in parentheses following the identification numbers when multiple identification numbers are given.
[h]1,2,7,8- is the same isomer as 2,3,6,7- in tetrachlorodibenzo-*p*-dioxins.
[i]NLM 2024.

CAS = Chemical Abstracts Services; CDD = chlorinated dibenzo-*p*-dioxin; SMILES = simplified molecular-input line-entry system

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of CDDs is presented in Table 4-2.

Table 4-2. Physical and Chemical Properties of CDDs[a]

Characteristic	Monochlorodibenzo-*p*-dioxins	Dichlorodibenzo-*p*-dioxins	Trichlorodibenzo-*p*-dioxins
Molecular weight	218.6	253.1	287.5
Color	Colorless[b]	Colorless[b]	Colorless (1,2,4-)[b]
Physical state	Crystals (1-); solid (2-)[b]	Needles (1,6-); solid (2,3-, 2,8-); crystals (2,7-)[b]	Solid (1,2,4-)[b]
Melting point	105.5°C (1-); 89.0°C (2-)[c]	114–115°C (1,3-); 184–185°C (1,6-)[b]; 164°C (2,3-); 210°C (2,7-); 151°C (2,8-)[c]	129°C (1,2,4-)[c]; 128–129°C (1,2,4-)[b]; 153–163°C (2,3,7-)[b]
Boiling point	No data	No data	No data
Density at 25°C	No data	No data	No data
Odor	No data	No data	No data
Odor threshold: Water Air	 No data No data	 No data No data	 No data No data
Solubility: Water at 25°C[d]	0.417 mg/L (1-); 0.278–0.318 mg/L (2-)[c]	0.0149 mg/L (2,3-); 0.00375 mg/L (2,7-); 0.0167 mg/L (2,8-)[c]	0.00841 mg/L (1,2,4-)[c]
Organic solvent(s)[e]	No data	No data	No data
Partition coefficients: Log K_{ow} Log K_{oc}	 4.52–5.45 (1-, 2-)[f] No data	 5.86–6.39 (2,7-)[f] No data	 6.86–7.45 (1,2,4-)[f] No data
Vapor pressure at 25°C	9.0×10^{-5} mm Hg (1-); 1.3×10^{-4} mm Hg (2-)[g]	2.9×10^{-6} mm Hg (2,3-); 9.0×10^{-7} mm Hg (2,7-); 1.1×10^{-6} mm Hg (2,8-)[g]	2.7×10^{-7} mm Hg (1,3,7-); 7.5×10^{-7} mm Hg (1,2,4-)[g]
Henry's law constant at 25°C	82.7×10^{-6} to 146.26×10^{-6} atm·m^3/mol[c]	21.02×10^{-6} to 80.04×10^{-6} atm·m^3/mol (2,3-, 2,7-, 2,8-)[c]	37.9×10^{-6} atm·m^3/mol (1,2,4-)[c]
Degradation	Atmospheric lifetime using gas-phase reaction with OH radical=0.5 days[h]	Atmospheric lifetime using gas-phase reaction with OH radical=0.5–0.7 days[h]	Atmospheric lifetime using gas-phase reaction with OH radical=0.7–0.9 days[h]
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors in air at 25°C, 760 mm Hg	1 mg/m^3 = 0.112 ppm; 1 ppm = 8.94 mg/m^3	1 mg/m^3 = 0.0966 ppm; 1 ppm = 10.35 mg/m^3	1 mg/m^3 = 0.0850 ppm; 1 ppm = 11.76 mg/m^3
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of CDDs[a]

Characteristic	Tetrachlorodibenzo-*p*-dioxins[i]	Pentachlorodibenzo-*p*-dioxins	Hexachlorodibenzo-*p*-dioxins
Molecular weight	322	356.4	390.9
Color	White or colorless[b,j] (2,3,7,8-); colorless (1,2,3,4-, 1,3,6,8-)[b]	Colorless (1,2,3,4,7-)[b]	Colorless (1,2,3,4,7,8-, 1,2,4,6,7,9-)[b]
Physical state	Crystalline solid[j] (2,3,7,8-)	Solid (1,2,3,4,7-)[b]	Solid (1,2,3,4,7,8-, 1,2,4,6,7,9-)[b]
Melting point	190°C (1,2,3,4-); 175°C (1,2,3,7-)[c]; 219–219.5°C (1,3,6,8-); 193.5–195°C (1,3,7,8-); 305–306°C (2,3,7,8-)[b]	195–196°C (1,2,3,4,7-); 240–241°C (1,2,3,7,8-); 205–206°C (1,2,4,7,8-)[b]	273°C (1,2,3,4,7,8-)[c]; 275°C (1,2,3,4,7,8-)[b]; 285–286°C (1,2,3,6,7,8-); 243–244°C (1,2,3,7,8,9-); 238–240°C (1,2,4,6,7,9-)[b]
Boiling point	446.5°C[f] (2,3,7,8-)	No data	No data
Density at 25°C	1.827 g/mL[k] (2,3,7,8-)	No data	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water at 25°C[d]	4.7×10^{-4}–6.3×10^{-4} mg/L (1,2,3,4-)[c,l] 4.2×10^{-4} mg/L (20°C) (1,2,3,7-); 3.2×10^{-4} mg/L (20°C) (1,3,6,8-); 1.9×10^{-5} mg/L (2,3,7,8-)[m] 7.9×10^{-6}–3.2×10^{-4} mg/L (2,3,7,8-)[c]	1.18×10^{-4} mg/L (20°C) (1,2,3,4,7-)[c]	4.42×10^{-6} mg/L (20°C) (1,2,3,4,7,8-)[c]
Organic solvent(s)[e]	*o*-Dichlorobenzene, chloro-benzene, benzene, chloroform, n-octanol[b]	No data	No data
Partition coefficients:			
Log K_{ow}	7.02–8.7 (1,2,3,7-)[f,g]; 7.02–8.93 (2,3,7,8-)[c]; 7.39–7.58 (2,3,7,8-)[n]; 6.8 (2,3,7,8-TCDD)[o;] 6.6 (1,2,3,4-TCDD)[o]	5.80–9.65 (1,2,3,4,7-)[c]	9.19–10.4 (1,2,3,4,7,8-)[f]
Log K_{oc}	No data	No data	No data

Table 4-2. Physical and Chemical Properties of CDDs[a]

Vapor pressure at 25°C	$7.5x10^{-9}$ mm Hg (1,2,3,7-)[c]; $4.8x10^{-8}$ mm Hg (1,2,3,4-)[g]; $1.5x10^{-9}$–$3.4x10^{-5}$ mm Hg (2,3,7,8-)[g]; $5.3x10^{-9}$–$4.0x10^{-3}$ mm Hg (1,3,6,8-)[c]; $7.4x10^{-10}$ mm Hg (2,3,7,8-)[p]	$6.6x10^{-10}$ mm Hg (1,2,3,4,7-)[c]	$3.8x10^{-11}$ mm Hg (1,2,3,4,7,8-)[c]
Henry's law constant at 25°C	$16.1x10^{-6}$–$101.7x10^{-6}$ atm·m^3/mol (2,3,7,8-); $7.01x10^{-6}$–$101.7x10^{-6}$ atm·m^3/mol[c]	$2.6x10^{-6}$ atm·m^3/mol (1,2,3,4,7-)[c]	$44.6x10^{-6}$ atm·m^3/mol (1,2,3,4,7,8-)[c]
Degradation	Photodegradation half-life on grass (2,3,7,8-)=44 hours (k_2=0.0156 h^{-1})[o,q]; atmospheric lifetime using gas-phase reaction with OH radical=0.8–2 days[h]	Atmospheric lifetime using gas-phase reaction with OH radical=1.1–2.4 days[h]	Atmospheric lifetime using gas-phase reaction with OH radical=1.5–3.4 days[h]
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors in air at 25°C, 760 mm Hg	1 mg/m^3=0.0759 ppm 1 ppm=13.17 mg/m^3	1 mg/m^3=0.0686 ppm 1 ppm=14.58 mg/m^3	1 mg/m^3=0.0625 ppm 1 ppm=15.99 mg/m^3
Explosive limits	No data	No data	No data

Characteristic	Heptachlorodibenzo-*p*-dioxins	Octachlorodibenzo-*p*-dioxin
Molecular weight	425.3	459.8
Color	No data	No data
Physical state	No data	No data
Melting point	265°C (1,2,3,4,6,7,8-)[c]	332°C[c]; 325–326°C[p]
Boiling point	507.2°C[g]	510°C[g]; 485°C[o]
Density at 25°C	No data	No data
Odor	No data	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water at 25°C[d]	$2.4x10^{-6}$ mg/L at 20°C (1,2,3,4,6,7,8-)[c]	$7.4x10^{-8}$ mg/L[c]
Organic solvent(s)[e]	No data	Acetic acid, anisole, chloroform, *o*-dichlorobenzene, dioxane, diphenyl oxide, pyridine, xylene[b]

Table 4-2. Physical and Chemical Properties of CDDs[a]

Partition coefficients:		
Log K_{ow}	9.69–11.38 (1,2,3,4,6,7,8-)[f]	10.07–12.26[f]; 8.20[p]
Log K_{oc}	No data	No data
Vapor pressure at 25°C	$5.6x10^{-12}$ mm Hg (1,2,3,4,6,7,8-)[g]	$8.25x10^{-13}$ mm Hg[g]; $1.68x10^{-12}$ [o]
Henry's law constant at 25°C	$1.31x10^{-6}$ atm–m^3/mol (1,2,3,4,6,7,8-)[c]	$6.74x10^{-6}$ atm·m^3/mol[c]
Degradation	Atmospheric lifetime using gas-phase reaction with OH radical=4.4 days[h]	Atmospheric lifetime using gas-phase reaction with OH radical=9.6 days[h]
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors in air at 25°C, 760 mm Hg	1 mg/m^3=0.0575 ppm 1 ppm=17.39 mg/m^3	1 mg/m^3=0.0532 ppm 1 ppm=18.81 mg/m^3
Explosive limits	No data	No data

[a]In some cases, information regarding chemical and physical properties was not available for all isomers of a homologous class.
[b]IARC 1977.
[c]Shiu et al. 1988.
[d]Solubility is given for 25°C unless noted otherwise in text.
[e]In most cases, no specific solubilities were found. However, solvation in organic solvents such as toluene, hexane, and methylene chloride is possible given that these solvents are used in extraction and analysis methods.
[f]Webster et al. 1985.
[g]Rordorf 1989.
[h]Atkinson 1991.
[i]Physical and chemical properties of 2,3,7,8-TCDD are shown in bold.
[j]Sax and Lewis 1987.
[k]Schroy et al. 1985.
[l]Doucette and Andren 1988.
[m]Marple et al. 1986.
[n]Des Rosiers 1986.
[o]McCrady and Maggard 1993.
[p]IARC 1997.
[q]k_2 = elimination rate constants.

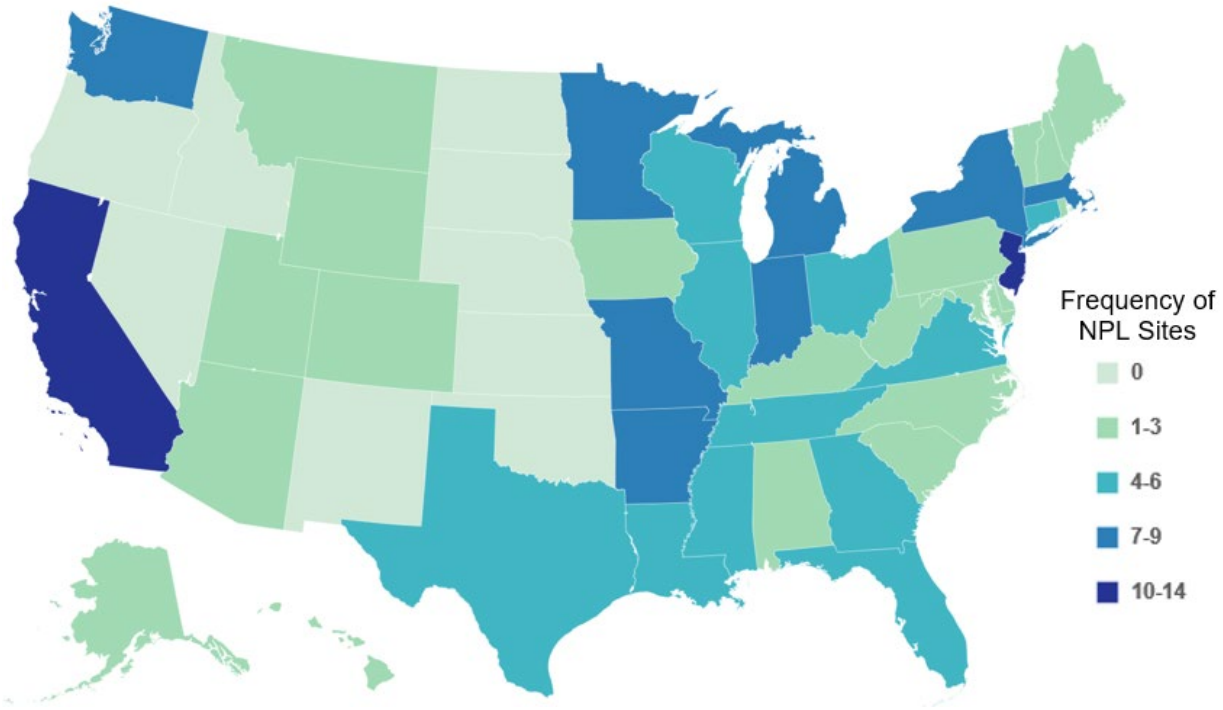
CDD = chlorinated dibenzo-*p*-dioxin

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

CDDs have been identified in at least 179 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022). However, the number of sites in which CDDs have been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 177 are located within the United States, and 2 are located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with Chlorinated Dibenzo-*p*-Dioxin (CDD) Contamination



Source: ATSDR 2022

- Ingestion of food items containing CDDs is the primary exposure pathway for the general population.
- Inhalation of ambient air, as well as ingestion of drinking water, are minor routes of human exposure to CDDs; however, inhalation exposure can be a major source in specific locations, near specific industrial sites. Exposure can also occur from certain consumer products.
- The lower chlorinated CDDs are semi-volatile; however, the tetra-, penta-, hexa-, and octa-congeners are considered nonvolatile.

- The lower chlorinated CDDs degrade in the atmosphere by reaction with atmospheric oxidants in a matter of days; however, the higher chlorinated congeners are more persistent and subject to long-range transport. Dioxins have also a high partitioning ratio to ambient particulate matter and particulates released from emission sources.

- Direct photolysis of CDDs is an important degradation process; however, biodegradation occurs slowly, especially for the higher chlorinated CDDs and they are considered persistent in the environment.

- CDDs have large soil adsorption coefficients and possess low mobility in soil surfaces. CDDs bioconcentrate in aquatic organisms.

CDDs are a family of compounds that includes some extremely toxic and potent congeners. The two most toxic of the CDDs in mammals are 2,3,7,8-TCDD and 1,2,3,7,8-PeCDD (Buser 1987; Poland and Knutson 1982; Safe 1986). In general, the more toxic congeners to mammals appear to be the 2,3,7,8-substituted tetra-, penta-, and hexachloro- compounds, (e.g., 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, and 1,2,3,7,8,9-HxCDD) (Poland and Knutson 1982; Safe 1986). A more detailed discussion of the relative toxicities of the different CDD congeners is provided in Section 2.1.

CDDs in the environment are often measured and studied in conjunction with CDFs, and further information on these substances can be found in the ATSDR Toxicological Profile for CDFs (ATSDR 2023). CDDs and CDFs are highly persistent compounds and have been detected in air, water, soil, sediments, animals, and foods. CDFs include 135 congeners, which are structurally similar to CDDs and elicit a number of similar toxicological and biochemical responses in animals. CDDs and CDFs are released to the environment during combustion processes (e.g., municipal solid waste, medical waste, and industrial hazardous waste incineration, and fossil fuel and wood combustion); during the production, use, and disposal of certain chemicals (e.g., PCBs, chlorinated benzenes, chlorinated pesticides); and during the production and recycling of several metals (Buser et al. 1985; Czuczwa and Hites 1986a, 1986b; Oehme et al. 1987, 1989; Zook and Rappe 1994). EPA has developed procedures for estimating risks associated with exposures to mixtures of CDDs and CDFs in environmental matrices (EPA 1989). This approach is based on the assignment of 2,3,7,8-TCDD TEFs to CDD/CDF congeners or homologues in complex mixtures. The rationale behind the use of TEFs is explained in Section 2.1. Although the focus of this profile is CDDs, it should be recognized that most exposure scenarios involve exposure to CDDs, CDFs, and the non-ortho PCBs that have CDD-like toxicity; many of these exposure scenarios are discussed in this chapter. These exposures are usually reported in TEQs (for more information, see Section 2.1).

Source-specific regulations, improvements in source technology, advancements in pollution control technologies, and voluntary actions of U.S. industries (such as metal smelting) to reduce or prevent dioxin releases have decreased the amount of CDDs and CDFs emitted to the environment over the past several decades (EPA 2006). It is currently estimated that nearly 90% of all U.S. total dioxin emissions arise from landfill fires, forest and brush fires, and backyard burning (Dwyer and Themelis 2015). The 2012 dioxin emissions from 53 U.S. waste-to-energy (WTE) power plants that combusted a total of 27.4 million metric tons emitted 3.4 g TEQ and represented only 0.54% of the controlled industrial dioxin emissions.

CDDs occurred as contaminants in the manufacture of various pesticides and, as a result, have been released to the environment during use of these pesticides. 2,3,7,8-TCDD is a byproduct formed in the manufacture of 2,4,5-TCP (Arthur and Frea 1989). 2,4,5-TCP was used to produce the bactericide, hexachlorophene, and the chlorophenoxy herbicide, 2,4,5-T. Trichlorophenol-based herbicides were used extensively for weed control on crops, rangelands, roadways, rights-of-way, etc. Various formulations of 2,4-D, contaminated mainly with higher chlorinated CDDs/CDFs, and 2,4,5-T, contaminated mainly with 2,3,7,8-TCDD, were used extensively for defoliation and crop destruction by the American military during the Vietnam War. Although six herbicides were used (Orange, Purple, Pink, Green, White, and Blue), herbicide Orange (Agent Orange) was the primary defoliant (Wolfe et al. 1985). Agent Orange was a 1:1 mixture of 2,4-D and 2,4,5-T. Hexachlorophene use has been restricted by the U.S. Food and Drug Administration (FDA) and its disposal is regulated by EPA under the Resource Conservation and Recovery Act (RCRA). In 1983, EPA canceled registration for all chlorophenoxy herbicides used on foods, rice paddies, pastures, and rangelands (IARC 1986b). 2,4,5-T can no longer be used legally in the United States for any purpose (IARC 1986b). Other countries, including Canada, Sweden, the Netherlands, Australia, Italy, and the Federal Republic of Germany, have also canceled registrations for 2,4,5-T (IARC 1986b), but many other countries have not. 2,4,5-T can be produced with lower 2,3,7,8-TCDD concentrations than were previously possible. 2,4,5-TCP production has been discontinued in many countries, including the United States, Canada, the United Kingdom, the Federal Republic of Germany, and Austria (IARC 1986a). HxCDD, HpCDD, and OCDD are known contaminants of PCP, primarily a wood preservative and pesticide, which was used extensively in the 1970s and is still used today (to a lesser extent) in the lumber industry. PCP is currently registered as a restricted-use pesticide in the United States, but its uses are scheduled for cancellation by February 28, 2027 (EPA 2021).

Although little definitive data exist to prove or disprove that CDDs form during natural processes, results from dated sediment cores have shown that there were significant increases in CDDs and CDFs after about 1940 (Czuczwa and Hites 1984, 1986a, 1986b) and lower levels of CDDs are currently found in persons from less industrialized countries (Schecter et al. 1991a). The congener/homologue profile of the sediments was similar to that of atmospheric samples, strongly suggesting that combustion processes were the source of CDDs in the sediments. The historical increase in CDDs/CDFs also was similar to the trends for the production, use, and disposal of chlorinated organics, suggesting that accumulation of these compounds in the environment is a phenomenon related to the production, use, and subsequent incineration of chlorinated organic chemicals (Schecter et al. 1988).

CDDs are ubiquitous in the environment and are found at low background levels (parts per trillion [ppt] or parts per quadrillion [ppq]) in the air, water, and soil. Lower levels are found in biological and environmental samples from less industrialized rural regions than in those from more industrialized urban regions (Czuczwa and Hites 1986a; Des Rosiers 1987; Edgerton et al. 1989; Schecter et al. 1989b, 1989e, 1991a, 1994d; Tiernan et al. 1989). HpCDD and OCDD are the most common CDDs found in environmental samples (Christmann et al. 1989; Clement et al. 1985, 1989; Pereira et al. 1985; Reed et al. 1990; Tashiro et al. 1989a; Tiernan et al. 1989).

The environmental fate and transport of CDDs involve volatilization, long-range transport, wet and dry deposition, photolysis, bioaccumulation, and biodegradation (Kieatiwong et al. 1990). CDDs strongly partition to soils and sediments. Due to their low vapor pressure and low aqueous solubility and their strong sorption to particulates, CDDs are generally immobile in soils and sediments. Although most biological and nonbiological transformation processes are slow, photolysis has been shown to be relatively rapid. Photolysis is probably the most important transformation process in environmental systems into which sunlight can penetrate (Kieatiwong et al. 1990). Estimates of the half-life of 2,3,7,8-TCDD on the soil surface range from 9 to 15 years, whereas the half-life in subsurface soil may range from 25 to 100 years (Paustenbach et al. 1992). CDDs have been shown to bioaccumulate in both aquatic and terrestrial biota. CDDs have a high affinity for lipids and, thus, will bioaccumulate to a greater extent in organisms with a high fat content.

The detection of CDDs in blood, adipose tissue, human milk, and other tissue samples from the general population indicates universal exposure to CDDs from environmental sources (CDC 2024a, 2024b; Fürst et al. 1994; Orban et al. 1994; Patterson et al. 1986a; Ryan et al. 1986, 1993a; Schecter and Gasiewicz 1987a, 1987b; Schecter et al. 1986b, 1989e; Stanley 1986; Stanley et al. 1986). The general population is

exposed to CDDs released from industrial and municipal incineration processes, exhausts from automobiles using leaded gasoline, cigarette smoke, and foods, including human milk (Pohl and Hibbs 1996; Schecter et al. 1994a). The major source (>90%) of exposure for the general population, however, is primarily associated with meat, dairy products, and fish (Beck et al. 1989a; FDA 2006; Schaum et al. 1994; Schecter et al. 1994a, 1994d, 1996a). CDDs are transferred through the placenta to the fetus, by human milk to infants and young children, and by lifelong dietary ingestion. Workers involved with incineration operations or those who have been or may be involved in the production, use, or disposal of trichlorophenol, phenoxy herbicides, hexachlorophene, PCP, and other compounds that contain impurities of CDDs are at a greater risk from exposure to CDDs and TEQs (Päpke et al. 1992; Schecter and Ryan 1988; Schecter et al. 1991b). Individuals in the general population who may be exposed to potentially higher levels of CDDs include recreational and subsistence fishers (including many native Americans) and their families living in CDD-contaminated areas who consume large quantities of fish from contaminated waters (CRITFC 1994; Ebert et al. 1996), subsistence hunters such as the Inuit of Alaska who consume large quantities of wild game (particularly marine mammals) (Dewailly et al. 1993; Hebert et al. 1996; Norstrom et al. 1990), subsistence farmers and their families living in areas contaminated with CDDs who consume their own farm-raised beef and dairy products (EPA 1996b; McLachlan et al. 1994), individuals who live in the vicinity of an industrial or municipal incinerator, or individuals who live in the vicinity of hazardous waste sites where CDDs (and more especially where 2,3,7,8-substituted CDDs) have been detected (Gough 1991; Liem et al. 1991; Pohl et al. 1995; Riss et al. 1990; Wuthe et al. 1993).

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

CDDs are not manufactured commercially in the United States except on a small scale for use in chemical and toxicological research. CDDs are unique among the large number of organochlorine compounds of environmental interest in that they were never intentionally produced as desired commercial end products (Zook and Rappe 1994). Typically, CDDs are unintentionally produced during various uncontrolled chemical reactions involving the use of chlorine (EPA 1990a) and during various combustion and incineration processes (Zook and Rappe 1994). CDDs are also produced as undesired byproducts during the manufacture of chlorinated phenols such as PCP, 2,4,5-TCP, and related chemicals, and during incineration of chlorinated wastes (IARC 1977; NTP 1989; Podoll et al. 1986). By far, the greatest unintentional production of CDDs occurs via various combustion and incineration processes including all forms of waste incineration (municipal, industrial, and medical), many types of metal production (iron,

steel, magnesium, nickel, lead, and aluminum), and fossil fuel and wood combustion (Czuczwa and Hites 1986a, 1986b; Oehme et al. 1987, 1989; Zook and Rappe 1994).

In general, there are two conventional methods for the preparation of CDDs for research purposes: condensation of a polychlorophenol and direct halogenation of the parent dibenzo-*p*-dioxin or a monochloro- derivative. For example, 2,3,7,8-TCDD is generally synthesized by the condensation of two molecules of 2,4,5-TCP in the presence of a base at high temperatures or by chlorination of dibenzo-*p*-dioxin in chloroform in the presence of iodine and ferric chloride (EPA 1987b; IARC 1977). Other methods of 2,3,7,8-TCDD synthesis include the following: pyrolysis of sodium α-(2,4,5-trichloro-phenoxy) propionate at 500 EC for 5 hours; reaction of dichlorocatechol salts with *o*-chlorobenzene by refluxing in alkaline dimethyl sulfoxide; ultraviolet (UV) irradiation of CDDs of high chlorine content; Ullman reaction of chlorinated phenolates at 180–400 EC; pyrolysis of chlorinated phenolates and chlorinated phenols; and heating 1,2,4-trichloro-5-nitrobenzene and 4,5-dichlorocatechol in the presence of a base (EPA 1984; IARC 1977).

1,2,3,4-TCDD has been prepared by refluxing a mixture of catechol, potassium carbonate, pentachloronitrobenzene, and acetone in nitrogen (IARC 1977).

DCDD can be synthesized by two methods. In the first method, 2-bromo-4-chlorophenol and potassium hydroxide are dissolved in methanol and evaporated to dryness. The residue is then mixed with bis(2-ethoxyethyl) ether, ethylene diacetate, and a copper catalyst; and then heated, cooled, and eluted from a chromatographic column with chloroform. This residue is evaporated and then sublimed. DCDD can also be synthesized by heating the potassium salt of 2,4-dichlorophenol in the presence of copper powder in a vacuum sublimation apparatus (IARC 1977).

1,2,4,6,7,9-HxCDD has been made by heating the potassium salt of 2,3,5,6-tetrachlorophenol with powdered copper and potassium carbonate in a vacuum sublimation apparatus (IARC 1977). 1,2,3,4,7,8-HxCDD has been prepared by mixing 1,2,3,4-TCDD, ferric chloride, chloroform, and a crystal of iodine and then adding a solution of chlorine in carbon tetrachloride (IARC 1977).

OCDD has been synthesized by the following methods: irradiation of aqueous solutions of CDD-free sodium PCP with UV light; heating the potassium salt of PCP; heating PCP in the presence of an initiator, such as chlorine, bromine, iodine, or 2,3,4,4,5,6-hexachloro-2,5-cyclohexadienone; and heating

hexachlorocyclohexadienone in an atmosphere of carbon dioxide for 30 minutes (Crosby and Wong 1976; EPA 1984; IARC 1977).

Table 5-1 summarizes information on companies that reported the production, import, or use of dioxin-like substances, including CDDs, and the range of maximum amounts that are stored onsite for the Toxics Release Inventory (TRI) in 2021 (TRI21 2022). This is a special category in the Toxics Release Inventory (TRI) and includes 17 CDDs and CDFs. TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use Dioxin and Dioxin-like Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	5	0	0.99	1, 5
AL	45	0	99,999	1, 5, 8, 12, 13, 14
AR	20	0	99,999	1, 5, 12, 13, 14
AZ	13	0	99	1, 5, 6, 13
CA	27	0	99	1, 2, 5, 11, 12, 13, 14
CO	13	0	9.99	1, 4, 5, 13
CT	1	0	0.10	1, 5
DE	1	0.10	0.99	1, 13, 14
FL	21	0	9.99	1, 5, 12, 13, 14
GA	30	0	99,999	1, 2, 5, 12, 13, 14
GU	1	0.10	0.99	1, 5
HI	4	0	0.10	1, 5
IA	18	0	9,999	1, 5, 13, 14
ID	3	0	9,999	1, 5, 12, 14
IL	19	0	99	1, 5, 12, 13, 14
IN	28	0	99	1, 5, 12, 13
KS	7	0	0.99	1, 5, 12
KY	29	0	9,999	1, 5, 13, 14
LA	46	0	99,999	1, 5, 10, 12, 13, 14
MD	5	0	9.99	1, 5, 14
ME	3	0	0.99	1, 5, 9
MI	18	0	9,999	1, 2, 5, 12, 13, 14
MN	19	0	999,999	1, 5, 12, 13, 14
MO	25	0	9.99	1, 2, 5, 12, 13, 14
MS	19	0	99,999	1, 5, 8, 13, 14
MT	5	0	9.99	1, 5
NC	23	0	99,999	1, 5, 8, 12, 13, 14

Table 5-1. Facilities that Produce, Process, or Use Dioxin and Dioxin-like Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
ND	12	0	0.99	1, 5, 12, 13
NE	12	0	99,999	1, 5, 13, 14
NJ	6	0	9.99	1, 5, 13, 14
NM	3	0	0.10	1, 5, 13
NV	5	0	999,999	1, 5, 13, 14
NY	15	0	9,999	1, 5, 12, 13, 14
OH	31	0	999	1, 3, 5, 13, 14
OK	13	0	99	1, 4, 5, 13, 14
OR	11	0	999,999	1, 5, 14
PA	26	0	9.99	1, 2, 5, 12, 13, 14
PR	1	0	0.10	1, 5
SC	24	0	9.99	1, 5, 12, 13, 14
SD	3	0	99	1, 5
TN	24	0	99	1, 5, 8, 12, 13, 14
TX	66	0	9,999	1, 2, 3, 4, 5, 7, 12, 13, 14
UT	17	0	99,999	1, 3, 4, 5, 9, 12, 13, 14
VA	13	0	9.99	1, 5, 7, 13, 14
VI	2	0	0.10	1, 5
WA	22	0	99,999	1, 2, 5, 6, 13, 14
WI	26	0	99,999	1, 2, 5, 12, 13, 14
WV	15	0	99	1, 5, 12, 13
WY	9	0	9.99	1, 5, 13, 14

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

The specific chemicals of this category are Chemical Abstracts Service (CAS) numbers 67562-39-4 (1,2,3,4,6,7,8-heptachlorodibenzofuran), 55673-89-7 (1,2,3,4,7,8,9-heptachlorodibenzofuran), 70648-26-9 (1,2,3,4,7,8-hexachlorodibenzofuran), 57117-44-9 (1,2,3,6,7,8-hexachlorodibenzofuran), 72918-21-9 (1,2,3,7,8,9-hexachlorodibenzofuran), 60851-34-5 (2,3,4,6,7,8-hexachlorodibenzofuran), 39227-28-6 (1,2,3,4,7,8-hexachlorodibenzo-*p*-dioxin), 57653-85-7 (1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin), 19408-74-3 (1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin), 35822-46-9 (1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin), 39001-02-0 (1,2,3,4,6,7,8,9-octachlorodibenzofuran), 3268-87-9 (1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin), 57117-41-6 (1,2,3,7,8- pentachlorodibenzofuran), 57117-31-4 (2,3,4,7,8-pentachlorodibenzofuran), 40321-76-4 (1,2,3,7,8- pentachlorodibenzo-*p*-dioxin), 51207-31-9 (2,3,7,8-tetrachlorodibenzofuran), and 1746-01-6 (2,3,7,8-tetrachlorodibenzo-*p*-dioxin).

Source: TRI21 2022 (Data are from 2021)

5.2.2 Import/Export

CDDs are not imported into the United States (NTP 1989). There were no data located pertaining to the export of any CDD for research purposes.

5.2.3 Use

The only reported use of CDDs/CDFs is as research chemicals (NTP 1989). A large, diversified group of researchers use various CDDs in studies of toxicology, environmental fate, transformation, and transport, and in residue analysis of a variety of contaminated media. The immunotoxic properties of CDDs have also been used in studies evaluating other nontoxic AhR ligands as possible treatments of autoimmune diseases. CDDs have been tested for use in flame-proofing polymers such as polyesters and against insects and wood-destroying fungi; however, there are no data reporting commercial production or use for these purposes (IARC 1977).

5.2.4 Disposal

The 1986 estimates on the degree of TCDD contamination in the environment indicated that approximately 500,000 tons of soil and sediment in the United States were contaminated with 2,3,7,8-TCDD (U.S. Congress 1991). The development of treatment technologies for CDD-contaminated soils and wastes needed to address unique problems associated with CDDs; for example, they are insoluble in water, only slightly soluble in organic solvents, have a strong affinity for adsorption on organic matter, and are biologically and environmentally stable (U.S. Congress 1991). In order to meet the clean-up standards established for CDDs, the treatment system must be capable of removing the CDDs from the contaminated matrix (U.S. Congress 1991). Several treatment or disposal methods for CDDs and CDD-contaminated materials have been investigated, including land disposal, thermal destruction, and chemical and biological degradation.

Land disposal of CDD-containing wastes is prohibited unless the dioxin-containing waste is contaminated soil and debris resulting from a response action taken under Section 104 or 106 of the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA) or a corrective action taken under Subtitle C of RCRA (EPA 1986b, 1988). The Toxic Substances Control Act (TSCA) regulates the use, disposal, and distribution in commerce of process wastewater treatment sludges

intended for land application from pulp and paper mills employing chlorine or chlorine derivative-based bleaching processes (EPA 1991a, 1991b). Also, under the Marine Protection Research and Sanctuaries Act (MPRSA), ocean dumping of CDD-containing wastes is prohibited except when only trace amounts are present (EPA 1977). EPA is responsible for designating and managing ocean dumping sites under the MPRSA for all types of materials. EPA's published ocean dumping regulations appear at 40 CFR Parts 220–229 (EPA 2024). Brief summaries of amendments to this law are available (Congressional Research Service 2016).

Thermal destruction technologies offer the most straightforward approach to treating or disposing of CDD-contaminated materials because under the appropriate conditions, the breakdown of the CDDs is assured (U.S. Congress 1991; WHO 2023). The thermal treatment technologies that are used to treat waste containing hazardous or toxic constituents and that have demonstrated potential use toward the treatment of CDD-contaminated waste include rotary kiln incineration, liquid injection incineration, fluidized-bed incineration, advanced electric reactor (AER), infrared incineration, plasma arc pyrolysis incineration, supercritical water oxidation, and *in situ* vitrification (U.S. Congress 1991). In addition to kiln incinerators, the technologies that have been field-tested for treating CDD-contaminated media under EPA's Superfund Innovative Technology Evaluation (SITE) program include dechlorination, stabilization, and *in situ* vitrification (U.S. Congress 1991). Kulkarni et al. (2008) discusses disposal and remediation technologies of dioxins.

Incineration, involving the high-temperature oxidation of CDD molecules, is the most extensively tested method for disposal of CDDs. CDDs such as TCDD, PeCDD, and HxCDD are classified by EPA as Principal Organic Hazardous Constituents (POHCs). Destruction of compounds with the potential to form dioxins are required to be incinerated under conditions that achieve a destruction and removal efficiency of 99.9999% (EPA 1990b; Sedman and Esparza 1991). Proper incineration of dioxin-contaminated material is the best available method of preventing and controlling exposure to dioxins (WHO 2023). Incineration can also destroy PCB-based waste oils. The incineration process requires temperatures >850°C. For the destruction of large amounts of contaminated material, temperatures of ≥1,000°C are required (WHO 2023).

Kulkarni et al. (2008) discussed treatment and remediation technologies used for dioxins emitted from flue gases. These technologies include particulate matter collection, scrubbers and electrostatic precipitators, sorbent or flow injection processes, fluidized bed processes, and electron irradiation. Waste incineration plants commonly employ filters equipped with activated charcoal or fixed bed activated

carbon filters to reduce emissions of dioxin-like substances. Selective catalytic reduction for NO_x reduction combined with an oxidation catalyst are an effective technology to destroy dioxins. Various methodologies exist to treat contaminated fly ash such as thermal treatment, chemical reactions, non-thermal plasma technology, UV irradiation, hydrothermal treatment, and supercritical water oxidation.

Since the early 1970s, several chemical methods have been investigated for the degradation of CDDs. Treatment of CDD-contaminated materials with alkali polyethylene glycolate (APEG) reagents at hazardous waste sites has been demonstrated to successfully destroy CDDs in liquid wastes and to be viable even under difficult circumstances. This method involves the reaction of potassium hydroxide with polyethylene glycol to form an alkoxide that reacts with one of the chlorine atoms on the CDD to produce an ether and potassium chloride. Bioassays indicate that the byproducts produced by treating 2,3,7,8-TCDD with APEG reagents do not bioaccumulate or bioconcentrate, do not cause mutagenicity, and are far less toxic than 2,3,7,8-TCDD (Klee 1988). Cleavage of the ether linkages with the formation of halophenols may be achieved by treatment with strong acids or quaternary ammonium salts, but the dibenzodioxin nucleus is resistant to chemical attack. Oku et al. (1995) investigated the dechlorination of polychlorinated CDDs and polychlorinated CDFs using a modified alkali-metal hydroxide method. The destruction reagent, prepared by dissolving either potassium hydroxide or sodium hydroxide in 1,3-dimethyl-2-imidazolidinone (DMI) destroyed all components, regardless of the difference in the number of chlorine atoms or isomers of CDDs and CDFs (Oku et al. 1995). The efficiency of the methods was evaluated under varying conditions; in the presence and absence of water, at 90 and 50 EC, for 0.5 and 5 hours. Although the degree of CDD destruction (99.95–99.80%) was less than that for CDFs (99.99–99.98%), overall, the investigators considered the DMI reagent to be more useful than the polyethylene glycols because of its stability under strongly basic conditions and its efficiency in the presence of water (Oku et al. 1995).

CDDs/CDFs can be destroyed by dechlorination of the compounds by UV light most efficiently in the presence of hydrogen donors. The most commonly used hydrogen donor is isopropyl alcohol (des Rosiers 1983). TCDD-contaminated soil was decontaminated by UV treatment of the soil in the presence of olive oil emulsion as a hydrogen donor. A total reduction in excess of 60% was observed after 48 hours of irradiation. Photocatalytic degradation of dioxins using semi-conductor films like TiO_2, ZnO, CdS, and Fe_2O_3 is possible (Kulkarni et al. 2008).

Dougherty et al. (1993) conducted a theoretical analysis of a proposed *in situ* method for decontaminating soil by photodegradation. Up to 87% of TCDD in the soil can be degraded by this process (McPeters and

Overcash 1993). Because of its extremely low water solubility and volatility, TCDD is a very persistent soil contaminant. With the method, based on the physical properties that facilitate photolysis of TCDD by sunlight, an organic solvent mixture (2:1 w/w) of tetradecane and 1-butanol is applied to the contaminated soil (Dougherty et al. 1993). The controlling factors in TCDD photodegradation are desorption of the compound from the soil, the transport mechanism to the soil surface, and the availability of sunlight. As the solvents remove the tightly bound TCDD from the soil, convective upward movements of the compound are caused by the evaporation of the solvent (Dougherty et al. 1993; Zhong et al. 1993). The effectiveness of the process also depends on a balance between the convective movement and sunlight availability for degradation (Dougherty et al. 1993). Modeling conducted by Zhong et al. (1993) identified and quantified the controlling factors governing the TCDD photodegradation process. Following the concentration variation of TCDD in the top 2 mm of soil through sunlight/night cycles over an exposure period of 15 days, the model showed that during the daytime of the first few days, there is little accumulation of TCDD as the losses due to photodegradation were almost equal to the convective flux in magnitude but with different signs. Although the losses due to photodegradation drop to zero at night, the convective flux effected a build-up of TCDD. The losses due to photodegradation held steady while the convective movements decreased as evaporation slowed down (Zhong et al. 1993). A balance between the build-up of TCDD concentration at night and the drop in concentration during the day did not occur until the 11^{th} day of exposure (Zhong et al. 1993).

Hilarides et al. (1994) investigated degradation of TCDD in the presence of surfactants. Their results indicated that radiolytic destruction of TCDD using γ radiation can be achieved. Greater than 92% of the TCDD was destroyed in soils amended with 100 ppb TCDD, 25% water, and 2% nonionic surfactant using ^{60}Co at high radiation doses (800 kGy or 80 Mrad). The use of ^{60}Co as a source avoids the temperature increases and power requirements of other sources of ionizing radiation such as an electron beam. It is also better suited for soil application because of its greater penetration depths (Hilarides et al. 1994).

Biotreatment systems that use microorganisms for degradation of refractory organopollutants, like CDDs, have also been considered. *Phanerochaete chrysosporium*, a white rot fungus, has shown the ability to slowly degrade 2,3,7,8-TCDD in the laboratory (Bumpus et al. 1985; Des Rosiers 1986). The ability of this fungus to metabolize 2,3,7,8-TCDD is thought to be related to its extracellular lignin degrading enzyme system (Bumpus et al. 1985; Des Rosiers 1986).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2022). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2022).

CDDs have been measured in all environmental media including ambient air, surface water, groundwater, soil, and sediment. While the manufacture and use of chlorinated compounds, such as chlorophenols and chlorinated phenoxy herbicides, were important sources of CDDs to the environment in the past, the restricted manufacture of many of these compounds has substantially reduced their current contribution to environmental releases. Incineration/combustion processes are the most important sources of CDDs to the environment (EPA 2006; Zook and Rappe 1994). Important incineration/combustion sources include medical waste, municipal solid waste, hazardous waste, and sewage sludge incineration; industrial coal, oil, and wood burning; secondary metal smelting, cement kilns, diesel fuel combustion; and residential oil and wood burning (Clement et al. 1985; EPA 2006; Thoma 1988; Zook and Rappe 1994).

5.3.1 Air

Estimated releases of 1,067 g (~2.35 pounds [<1 metric ton]) of dioxin compounds, including CDDs, to the atmosphere from 799 domestic manufacturing and processing facilities in 2021 accounted for about <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2022). These releases are summarized in Table 5-2.

For reporting purposes in the TRI, dioxin-like substances releases are reported in grams per year.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Dioxin and Dioxin-like Compounds[a]

	Reported amounts released in grams per year[b]								
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	45	22	110	0	5,186	0	5,280	38	5,319
AK	5	2	0	0	0	0	2	0	2
AZ	13	24	0	0	55	0	24	55	79
AR	20	15	14	0	22	2	47	6	53
CA	27	4	4	0	70	0	26	52	78
CO	13	14	0	0	0	0	14	0	14
CT	1	0	0	0	0	0	0	0	0
DE	1	0	0	0	0	0	0	0	0
FL	21	12	5	0	9	0	24	3	27
GA	30	17	24	0	20	0	61	1	61
HI	4	0	0	0	1	0	0	1	1
ID	3	26	0	0	1,920	0	1,947	0	1,947
IL	19	11	0	0	11	0	11	11	22
IN	28	43	0	0	344	0	124	263	387
IA	18	20	0	0	41	0	20	41	61
KS	7	5	0	0	0	0	5	0	5
KY	29	61	90	0	14,605	3	170	14,589	14,758
LA	46	41	74	0	331	215	256	404	661
ME	3	3	0	0	2	0	3	2	5
MD	5	2	0	0	0	0	2	0	2
MI	16	15	3	0	819	0	730	107	838
MN	19	80	1	0	81	0	81	81	162
MS	19	11	20	0	1,368	0	1,399	0	1,399
MO	25	25	0	0	0	0	25	0	25
MT	5	7	0	0	2	0	7	2	8
NE	12	4	1	0	0	0	5	0	5
NV	5	3	0	0	2	0	3	2	5
NJ	6	1	0	0	25	0	1	25	27
NM	3	3	0	0	0	0	3	0	3
NY	15	8	1	0	3	10	10	12	22
NC	23	85	8	0	8	0	100	0	101
ND	11	14	0	0	0	0	14	0	14
OH	31	26	1	0	755	0	752	31	782
OK	13	6	0	0	50	0	14	42	56
OR	11	2	0	0	7	0	4	5	9
PA	26	12	0	0	0	0	12	0	12
SC	24	12	5	0	0	0	17	0	17

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Dioxin and Dioxin-like Compounds[a]

	Reported amounts released in grams per year[b]								
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
SD	3	11	0	0	0	0	11	0	11
TN	24	27	5	0	1,986	0	1,994	23	2,017
TX	65	281	917	209	36,247	0	8,310	29,345	37,655
UT	17	33	0	0	7,508	0	7,537	4	7,541
VA	13	6	2	0	16	0	10	14	24
WA	22	8	7	0	103	0	15	103	118
WV	15	13	3	0	30	0	16	30	46
WI	25	30	0	0	464	0	30	464	494
WY	9	17	0	0	0	0	17	0	17
GU	1	1	0	0	0	0	1	0	1
PR	1	2	0	0	0	0	2	0	2
VI	2	0	0	0	0	0	0	0	0
Total	799	1,067	1,295	209	72,093	230	29,136	45,756	74,893

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility; due to TRI reporting guidelines, amounts released for dioxin and dioxin-like compounds are reported in grams.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI21 2022 (Data are from 2021)

The key sources of CDD releases to air are from anthropogenic combustion processes and the production and use of chemicals contaminated with CDDs. In 2006, EPA published a report summarizing dioxin-like compound releases in the United States for 1987, 1995, and 2000 (EPA 2006). Quantitative results of the inventory are expressed in terms of grams TEQ. The annual releases to the U.S. environment over the 3 reference years were reported as 13,965 g TEQ in 1987, 3,444 g TEQ in 1995, and 1,422 g TEQ in 2000. This indicates that between 1987 and 2000, there was approximately a 90% reduction in the

releases of dioxin-like compounds to the environment of the United States from all known combined sources. For years 1987 and 1995, the leading source of emissions to the U.S. environment was municipal waste combustion; however, because of technology improvements, it dropped to the fourth ranked source by 2000. Burning of domestic refuse in backyard burn barrels remained fairly constant over the years, but in 2000, it emerged as the largest source of dioxin emissions to the U.S. environment (EPA 2006). In the 1980s, bleached chlorine pulp and paper mills were a significant source of emissions but were relatively minor by 2000 due to changes in bleaching practices. The top five sources of dioxin-like compound releases to the atmosphere in 2000 were reported as backyard barrel burning of refuse (498.5 g TEQ), medical waste incineration (378 g TEQ), municipal wastewater treatment sludge applied to land and incinerated (89.7 g TEQ), municipal waste combustion (83.8 g TEQ), and coal fired utility boilers for electric generating plants (69.5 g TEQ). The report concluded that reductions observed over this temporal period were attributed to source-specific regulations, improvements in source technology, advancements in the pollution control technologies specific to controlling dioxin discharges and releases, and the voluntary actions of U.S. industries to reduce or prevent dioxin releases. Dwyer and Themelis (2015) performed a similar analysis of emissions to the atmosphere for 2012 and concluded that nearly 90% of all U.S. total dioxin emissions arise from landfill fires, forest and brush fires, and backyard burning. It is likely that the train derailment and subsequent fire that occurred in February 2023 in East Palestine, Ohio, released CDDs and CDFs to the nearby atmosphere (EPA 2023); however, no studies are available that report atmospheric emissions of dioxins, and most early air sampling tests focused on levels of volatile organic compounds not CDDs. Full reports of EPA ordered testing are available at: https://www.epa.gov/east-palestine-oh-train-derailment/data-validation-reports.

CDDs are known trace contaminants of certain chlorinated industrial chemicals like chlorophenols (Buser 1987). CDDs can inadvertently form as byproducts during the manufacture of chlorophenols.

PCP was developed primarily for use as a wood preservative but has also been used as an herbicide on pineapple and sugarcane plantations. It has also been employed as a molluscicide against schistosomiasis, a severe human parasitic disease prevalent in much of tropical Asia, Africa, and South America (Hutzinger et al. 1985); the disease is caused by the larval form of the *Schistosoma* parasite is released by freshwater snails. A major contaminant of commercial PCP was identified as OCDD, which was shown to be present at concentrations between 500 and 1,500 mg/kg (ppm) (Dobbs and Grant 1979; Miller et al. 1989a). PCP is currently registered as a restricted-use pesticide for use as a wood preservative; however, EPA has scheduled a cancellation of all pesticide products containing PCP by February 28, 2027 (EPA 2021).

2,3,7,8-TCDD forms during the manufacture of 2,4,5-TCP. 2,4,5-TCP had been used in cooling towers and in paper, pulp, and leather processing (Hutzinger et al. 1985). 2,4,5-TCP was used to produce the bactericide, hexachlorophene, and phenoxy-herbicides like 2,4,5-T. 2,4,5-T, in turn, was used in the production of a wide variety of herbicides including Silvex (2-[2,4,5-trichlorophenoxy]propionic acid) and Agent Orange (Hutzinger et al. 1985). 2,3,7,8-TCDD was an unintended contaminant of hexachlorophene, which was once used as a disinfectant, and contained <15 µg/kg (ppb) 2,3,7,8-TCDD (IARC 1977; Sine 1990). The 2,3,7,8-TCDD produced is primarily contained in still-bottom waste (waste oils) remaining after hexachlorophene is purified (Freeman et al. 1986). Still-bottom waste and other oils were used in the early 1970s for dust control on roads, parking lots, horse arenas, and other sites around Missouri (Freeman et al. 1986). The herbicide, 2,4,5-T, produced commercially prior to 1965 contained up to 30 mg/kg (ppm) or more 2,3,7,8-TCDD (IARC 1977). The level of 2,3,7,8-TCDD in commercial 2,4,5-T was reduced to <0.05 mg/kg (ppm), and most of the commercial 2,4,5-T available before its registration was discontinued in the United States in 1983 contained <0.02 mg/kg (ppm) 2,3,7,8-TCDD (IARC 1977; Sine 1990). Chlorophenoxy herbicides, such as 2,4-D, are typically formulated as esters or amine salt derivatives (IARC 1986b). Of 16 samples of 2,4-D formulations from Canada analyzed for CDDs in the early 1980s, 8 of 9 ester formulations and 4 of 7 amine salt formulations contained CDDs (IARC 1986b). The 2,4-D ester formulations contained 0.2–1.8 mg/kg (ppm) 1,3,6,8-TCDD (the only TCDD isomer detected), while the 2,4-D amine salt formulations contained 0.02–0.3 mg/kg (ppm) 1,3,6,8-TCDD (IARC 1986b). It should be noted that 1,3,6,8-TCDD is not one of the toxic CDDs with respect to mammals; however, 2,3,7,8-substituted CDDs/CDFs have been reported in 2,4-D from Russia (Schecter et al. 1993).

Agricultural and wartime uses of trichlorophenol-based herbicides such as 2,4,5-T and Silvex also have resulted in release of 2,3,7,8-TCDD at low concentrations in many countries (EPA 1987b). 2,4,5-T was used in aerial spraying operations for weed control on crops, along fence rows, ditch banks, farm roadways, pastures, and rangeland (Bovey 1980). Non-farm uses of 2,4,5-T included tree and bush control on rights-of-way, roadways, fire lanes, and railroads (Bovey 1980). Agent Orange, used as a defoliant in the Vietnam War from 1962 to 1970, was contaminated with an average of 2 ppm of 2,3,7,8-TCDD (Czuczwa and Hites 1986a, 1986b; Wolfe et al. 1985). An estimated 10–11 million gallons were applied in South Vietnam (EPA 1987b; Wolfe et al. 1985). This volume of Agent Orange contained an estimated 368 pounds of 2,3,7,8-TCDD (Wolfe et al. 1985). Agent Orange is an equal parts mixture of the butyl esters of 2,4,5-T and 2,4-D (Josephson 1983). These herbicides were used extensively in silviculture for control of deciduous trees in conifer forests before their use was

discontinued (EPA 1987b). The use of Silvex, an herbicide closely related to 2,4,5-T, was discontinued in the United States in 1984 (Sine 1990).

5.3.2 Water

Estimated releases of 1,295 g (~2.85 pounds [<1 metric ton]) of dioxin compounds including CDDs to surface water from 799 domestic manufacturing and processing facilities in 2021, accounted for about <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2022). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs). These releases are summarized in Table 5-2.

CDDs can enter water by a number of different mechanisms including urban runoff, combined sewer overflows (CSOs), and direct discharge by industrial facilities and POTWs; deposition of particulates from combustion sources, runoff and drift from the use of chlorophenol-based pesticides; and leaching from chlorophenol-containing waste sites (Huntley et al. 1997; Muir et al. 1986a; Pereira et al. 1985; Shear et al. 1996). Direct application or drift of 2,4,5-T or Silvex into water resulted in release of TCDD to surface water (Norris 1981); however, the contribution of CDDs from pesticide drift is now negligible since most CDD-containing pesticides have been banned.

CDDs/CDFs, specifically 2,3,7,8-TCDD and 2,3,7,8-TCDF, were also present in effluent and sludges from pulp and paper mills that employed the bleached kraft process (Clement et al. 1989; EPA 1991a; Swanson et al. 1988). 2,3,7,8-TCDD was detected in seven of nine bleached pulps at concentrations ranging from not detected (<1 ppt) to 51 ppt (median 4.9 ppt; mean 13 ppt) (Amendola et al. 1989). It was also detected in wastewaters from four of five paper mills at levels ranging from not detected (<0.006 ppt) to 3.6 ppt (Amendola et al. 1989). Changes in the commercial bleaching process have significantly reduced the levels of CDDs/CDFs in paper products. The use of chlorine dioxide rather than elemental chlorine in the bleaching procedure essentially eliminates the formation of 2,3,7,8-TCDD and 2,3,7,8-TCDF in finished products and effluents (Axegård 2019).

5.3.3 Soil

Estimated releases of 72,093 g (~159 pounds [<1 metric ton]) of dioxin compounds including CDDs to soil from 799 domestic manufacturing and processing facilities in 2021, accounted for about 96% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2022). An

additional 230 g (~0.46 pounds [<1 metric ton]), constituting about <1% of the total environmental emissions, were released via underground injection (TRI21 2022). These releases are summarized in Table 5-2.

Historically, CDDs have been deposited onto soil through pesticide applications and disposal of CDD-contaminated industrial wastes, and via land application of paper mill sludges (EPA 1991a). Atmospheric fall-out of CDD-laden particulates and gases appears to be the predominant source of CDDs to soil (Hutzinger et al. 1985).

In February of 2023, a large train derailment occurred in East Palestine, Ohio. The derailment and subsequent fire released CDDs, CDFs, and many other chemicals into nearby soils (EPA 2023; NTSB 2023). Monitoring data from this event are discussed in Section 5.5.3.

The commercial production of trichlorophenol, as well as various derivative products such as 2,4,5-T and other biocides, yielded large quantities of waste products containing substantial concentrations of CDDs; however, these substances are no longer used in the United States. Extensive contamination of the environment with 2,3,7,8-TCDD occurred in Missouri in the early 1970s as a result of the spraying of horse arenas, roads, and parking lots with mixtures of used oil and chemical waste (Tiernan et al. 1985). The chemical waste, formed during the manufacture of 2,4,5-TCP and then used to make hexachlorophene, contained several hundred ppm of 2,3,7,8-TCDD (Tiernan et al. 1985). Several thousand gallons of this waste were dispersed over a sizable area of southwestern and eastern Missouri during the 1970s. Concentrations of 2,3,7,8-TCDD in soil samples from Times Beach, Missouri, which had been heavily contaminated, were 4.4–317 ppb (Tiernan et al. 1985).

In Seveso, Italy, an explosion occurred during the production of 2,4,5-T and a cloud of toxic material including 2,3,7,8-TCDD was released (Cerlisi et al. 1989; Mocarelli et al. 1988, 1991). Debris from the cloud covered an area of approximately 700 acres (2.8 km^2). The total amount of 2,3,7,8-TCDD released during the accident was estimated to be 1.3 kg. Soil samples from this industrial accident were measured in three areas: zone A, the most contaminated zone where residents were evacuated; zone B, the moderately contaminated area where residents were advised not to eat locally raised produce; and zone R, where 2,3,7,8-TCDD contamination in soil was lowest of the three areas. Mean soil concentrations in these three areas were: 230 $\mu g/m^2$ (maximum 5,477 $\mu g/m^2$) in zone A, 3 $\mu g/m^2$ (maximum 43.9 $\mu g/m^2$) in zone B, and 0.9 $\mu g/m^2$ (maximum 9.7 $\mu g/m^2$) in zone R (Mocarelli et al. 1988).

The migration of chemical waste containing CDDs from disposal sites has also resulted in environmental contamination of sediment. For example, at Love Canal in Niagara Falls, New York, where an estimated 200 tons of 2,4,5-TCP production waste were disposed of during the 1940s and early 1950s, 2,3,7,8-TCDD was detected at high concentrations (up to several hundred ppb) in storm sewer sediments (Smith et al. 1983; Tiernan et al. 1985).

5.4 ENVIRONMENTAL FATE

Combustion-generated CDDs may be transported long distances (as vapors or associated with particulates) in the atmosphere (Czuczwa and Hites 1986a, 1986b; Tysklind et al. 1993). They may eventually be deposited on soils, surface waters, or plant vegetation as a result of dry or wet deposition. CDDs (primarily MCDD, DCDD, and TrCDD) will slowly volatilize from the water column, while the more highly chlorinated CDDs will adsorb to suspended particulate material in the water column and be transported to the sediment (Fletcher and McKay 1993; Muir et al. 1992). CDDs deposited on soils will strongly adsorb to organic matter. CDDs are unlikely to leach to underlying groundwater, but may enter the atmosphere on soil dust particles or enter surface waters on soil particles in surface runoff. Low water solubilities and high lipophilicity indicate that CDDs will bioconcentrate in aquatic organisms, although as a result of their binding to suspended organic matter, the actual uptake by such organisms may be less than predicted. This is also true of uptake and bioconcentration by plants, although foliar deposition and adherence may be significant.

5.4.1 Transport and Partitioning

Air. CDDs have relatively long residence times in the atmosphere, and combustion-generated CDDs associated with particulates can become distributed over large areas (Tysklind et al. 1993). During transport in the atmosphere, CDDs are partitioned between the vapor phase and particle-bound phase (EPA 1991). However, because of the very low vapor pressure of CDDs, the amount present in the vapor phase generally is low as compared to the amount adsorbed to particulates (Paustenbach et al. 1991). The two environmental factors controlling the phase in which the congener is found are vapor pressure and atmospheric temperature (EPA 1991). Congeners with a vapor pressure $<10^{-8}$ mm Hg will be primarily associated with particulate matter while congeners with a vapor pressure $>10^{-4}$ mm Hg will exist primarily in the vapor phase. Those chemicals with vapor pressures between these values can be found in both the vapor phase and associated with particulates (Eisenreich et al. 1981). With a reported vapor

pressure ranging from $7.4x10^{-10}$ to $3.4x10^{-5}$ mm Hg, 2,3,7,8-TCDD falls into the intermediate-duration category.

Gas-particle partitioning of CDDs/CDFs and PCBs was studied in flue gases emitted from two municipal solid waste incinerators located in China. Total CDD/CDFs concentrations in the flue gas ranged from 0.75 to 15 ng m^{-3}, while in the particulate phase, they ranged from 0.14 to 8.1 ng m^{-3} (Han et al. 2017). Lee et al. (2018) studied the vapor-phase particulate-phase monitoring of CDD/CDFs in Taiwan. Since Taiwan is located mostly in the subtropical zone, with higher average temperatures than the United States, many of the CDD/CDFs were observed in the vapor phase. A study on ambient air in southern China found that, in general, during winter months, particulate-phase CDDs increased in fractions, but decreased in the summer months due to the increasing temperature (Tang et al. 2017). Additionally, higher chlorinated CDDs were associated with the particulate phase, while lower chlorinated congeners were predominantly in the vapor phase. Bi et al. (2020) found the total concentration of 17 CDD/CDFs in $PM_{2.5}$ (particles with aerodynamic diameter <2.5 μm) to range from 3.14 to 37.07 pg/m^3 in an industrial area of China.

The detection of CDDs in sediments from Siskiwit Lake, Isle Royale, suggests that CDDs can be transported great distances in air (Czuczwa and Hites 1986a, 1986b). Because this lake is landlocked on a wilderness island in Lake Superior, the only way that CDDs could reach these sediments is by atmospheric fall-out (i.e., by wet and dry deposition). Similar amounts of CDDs were also found in Lake Huron and Lake Michigan sediments, which indicates that atmospheric transport is a source of CDDs found on these Great Lake sites (Czuczwa and Hites 1986a, 1986b; Hutzinger et al. 1985). Atmospheric deposition of TCDD to Lake Erie may contribute up to 2% of the annual input of TCDD to the lake (Kelly et al. 1991). Through pattern analysis of herring gull monitoring data, Hebert et al. (1994) provided evidence that the sources of CDDs in Great Lakes food chains were mainly atmospheric, with the exception of 2,3,7,8-TCDD in Lake Ontario, and several CDDs in Saginaw Bay in Lake Huron where point sources were implicated.

CDDs are physically removed from the atmosphere via wet deposition (scavenging by precipitation), particle dry deposition (gravitational settling of particles), and gas-phase dry deposition (sorption of CDDs in the vapor phase onto plant surfaces) (Rippen and Wesp 1993; Welsch-pausch et al. 1995). Precipitation (rain, sleet, snow) is very effective in removing particle-bound CDDs from the atmosphere (EPA 1991; Koester and Hites 1992a). Table 5-3 summarizes the average ppt scavenging ratios and percentage of washout due to particulates for congener groups of both CDDs and CDFs collected at two

sites in Indiana. The scavenging ratio is the ratio of the concentration of the congener group in rain to the atmospheric concentration of the congener group and is a measure of the effectiveness of rain in removing the congener groups from the atmosphere. Table 5-3 also summarizes the percentages of the congener groups scavenged as particles in rain rather than as dissolved solutes in rain. Total rain scavenging ratios were 10,000–150,000; HpCDDs and OCDD (the congeners most strongly associated with particulates) were the congeners scavenged most efficiently (EPA 1991; Koester and Hites 1992a).

Table 5-3. Rain Scavenging Ratios (RS) and Percent Washout Due to Particulates (%W) for CDDs and CDFs in Ambient Air in Two Midwest Cities

	Bloomington, Indiana		Indianapolis, Indiana	
Congener group	RS	%W	RS	%W
TCDD[a]	–	–	–	–
PeCDD	10,000	50	30,000	67
HxCDD	10,000	88	26,000	69
HpCDD	62,000	93	91,000	78
OCDD	90,000	80	150,000	60

[a]Rarely detected; no calculations performed.

CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; HpCDD = heptachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin

Sources: EPA 1991; Koester and Hites 1992a

Water. Volatilization from water surfaces may be an important environmental fate process for the lower chlorinated congeners but will be significantly slower for the higher chlorinated substances because these substances are more likely to adsorb to suspended solids and sediment in the water column, which attenuates the rate of volatilization. The estimated volatilization half-lives for a MCDD were about 15 hours from a model river and 12 days from a model lake estimated using the EPA software, Estimation Programs Interface Suite™ (EPI Suite™) (EPA 2012b). The estimated volatilization half-lives for OCDD were approximately 8 and 93 days from a model river and lake respectively; however, this does not account for adsorption to suspended particles and sediment, which will slow the rate of volatilization.

Experimentally measured bioconcentration factors (BCFs) for selected CDD congeners in various aquatic species are summarized in Table 5-4. Measurements of the bioconcentration of CDDs tend to increase with the degree of chlorination up to TCDDs, and then decrease as chlorination continues to increase up to and including the OCDD congener (Loonen et al. 1993). The more highly chlorinated congeners, such

as OCDD, appear to have the lowest bioconcentration potential either because they are less bioavailable because of their rapid adsorption to sediment particles (Servos et al. 1989a, 1989b) or because their large molecule size may interfere with transport across biological membranes (Bruggeman et al. 1984; Muir et al. 1986a, 1986b).

Table 5-4. Bioconcentration Factors (BCFs) for Aquatic Organisms

Organism	Congener	Exposure period (days)	Media	BCF	References
Aquatic plants					
Oedogonium cardiacum *Elodea nuttali* *Ceratophylum demeusum*	2,3,7,8-TCDD	1–50	Water/ sediment	208–2,083	Isensee 1978; Tsushimoto et al. 1982; Yockim et al. 1978
Invertebrates					
Physa sp. *Helosoma* sp. *Daphnia magna*	2,3,7,8-TCDD	1–32	Water/ sediment	702–7,125	Isensee 1978; Yockim et al. 1978
Chironomus sp. *Hexagenia* sp. *Paragnetina* sp. *Pteronarcys* sp. *Acroneuria* sp.	1,3,6,8-TCDD	4	Water/ sediment	1,375–18,439 (sand) 304–111,345 (silt)	Muir et al. 1983
Chironomus sp. *Hexagenia* sp. *Paragnetina* sp. *Pteronarcys* sp.	OCDD	4	Water/ sediment	173–2,854 (sand) 331–2,296 (silt)	Muir et al. 1983
Fish					
Carp (*Cyprinus carpio*)	2,3,7,8-TCDD	71	Water	66,000	Cook et al. 1991
Rainbow trout fry (*Oncorhynchus mykiss*)	1,2,3,7-TCDD 1,3,6,8-TCDD 1,2,3,4,7-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,4,6,7-HpCDD OCDD	5	Water	874–1,577 1,400–2,938 810 1,715–2,840 1,059–1,790 34–136	Muir et al. 1986a, 1986b
Fathead minnow (*Pimephales promelas*)	1,2,3,7-TCDD 1,3,6,8-TCDD 1,2,3,4,7-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,4,6,7-HpCDD OCDD	5	Water	2,018–2,458 5,565–5,840 1,200–1,647 2,630–5,834 513–515 2,226	Muir et al. 1986a, 1986b
Fathead minnow (*P. promelas*)	2,3,7,8-TCDD	71	Water	128,000	Cook et al. 1991

Table 5-4. Bioconcentration Factors (BCFs) for Aquatic Organisms

Organism	Congener	Exposure period (days)	Media	BCF	References
Fathead minnow (*P. promelas*)	2,3,7,8-TCDD		Water/ sediment	2,500	Tsushimoto et al. 1982
	2,3,7,8-TCDD		Water/ sediment	5,800	Adams et al. 1986
Mosquitofish (*Gambusia affinis*)	OCDD	104	Experimental lake	>9,000	Servos et al. 1989b
White sucker (*Catostomus commersoni*)	2,3,7,8-TCDD		Water/ sediment	4,875	Yockim et al. 1978

HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; OCDD = octachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin

BCF values measured in fish exposed to both water and sediment were much lower than equivalent exposures to water only and ranged from 2,500 to 5,800 (Adams et al. 1986; Cook et al. 1991; Tsushimoto et al. 1982) (Table 5-4). Loonen et al. (1993) also reported that bioaccumulation of CDDs was reduced in the presence of sediment and that the effects of sediment increased with increasing hydrophobicity (degree of chlorination) of the congeners. BCFs were reduced by 15–82% for various CDD/CDF congeners, with the greatest reduction associated with OCDD. In water-only exposure studies, BCF values for fish exposed to 2,3,7,8-TCDD ranged from 37,900 to 128,000 (Cook et al. 1991; Mehrle et al. 1988). Much lower BCF values of 1,400–5,840 and 34–2,226 have been reported for fish exposed to 1,3,6,8-TCDD and OCDD, respectively (Muir et al. 1986a, 1986b). Similarly, the lower BCFs for HpCDD in fathead minnows and OCDD in rainbow trout fry relative to the other CDDs tested resulted from lower uptake efficiencies from water. Elimination half-lives for TCDDs and PeCDDs were similar and rapid, averaging about 2.6 days in trout fry and 3 days in minnows. Elimination half-lives for HxCDD and HpCDD were longer, averaging about 16 days in rainbow trout and 20 days in fathead minnows (Muir et al. 1986b). The results of these studies also indicate that BCFs of the higher chlorinated CDDs (HxCDD, HpCDD, OCDD) from water are much lower than would be predicted based on their K_{ow} values. Servos et al. (1989a, 1989b) also noted that the BCF values were less than predicted based on the K_{ow} values; the study authors suggested that BCFs reported in the literature may underestimate the true BCF, unless the BCFs were calculated using truly dissolved CDD concentrations in the water column rather than total dissolved concentrations, which would include complexes with large molecules of dissolved organic carbon.

Whereas the term bioconcentration is defined as the uptake of a chemical from water only, the term bioaccumulation refers to the combined uptake of a chemical from both dietary sources (e.g., food) and water. A bioaccumulation factor (BAF) that includes the ingestion route of uptake can be calculated based on fish uptake from water, food, and sediment (Sherman et al. 1992). Estimated BAFs for MCDD through OCDD calculated using EPI Suite™ (EPA 2012b) are provided in Table 5-5.

Table 5-5. Estimated Upper Trophic Bioaccumulation Factors (BAFs) for MCDD Through OCDD

Congener	Log BAF
MCDD	2.9
DCDD	3.3
TrCDD	3.9
TCDD	6.1
PeCDD	5.7
HxCDD	4.7
HpCDD	4.8
OCDD	4.6

DCDD = dichlorodibenzo-*p*-dioxin; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; MCDD = monochlorodibenzo-*p*-dioxin; OCDD = octachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin; TrCDD = trichlorodibenzo-*p*-dioxin

Source: EPA 2012b

Several studies have examined the disposition and metabolism of CDDs in fish. Studies on the disposition of 2,3,7,8-TCDD in rainbow trout and yellow perch indicate that fatty tissues (visceral fat, carcass, skin, and pyloric caeca) typically contain the bulk of 2,3,7,8-TCDD (78–90%) with only a small percentage (2–5%) associated with the skeletal muscle (Kleeman et al. 1986a, 1986b). For other congeners, such as 1,3,6,8-TCDD and OCDD, the greatest proportion of the total body burden is concentrated in the bile, with lesser concentrations in liver > caeca > kidney > spleen > skin > muscle (Muir et al. 1986a, 1986b). Differences in the distribution among various species may be a function of the exposure pathway (i.e., dietary versus water uptake) and differences in metabolic breakdown rates. For example, both the parent compound and metabolites of 2,3,7,8-TCDD and 1,3,6,8-TCDD were present in the bile of fish exposed under laboratory conditions (Branson et al. 1985; Muir et al. 1986a, 1986b). Kleeman et al. (1986b) reported the presence of several polar metabolites in the gall bladder of yellow perch exposed to a single dose of [^{14}C]-2,3,7,8-TCDD. One week later, the gall bladder, skin, skeletal muscle, and kidneys were removed. In contrast to liver, muscle, and kidney where the parent compound accounted for 96–99% of the extractable [^{14}C], the gall bladder contained almost entirely

2,3,7,8-TCDD metabolites, at least one of which was a glucuronide conjugate. Although the metabolic breakdown was slow, it is clear that CDDs can be transformed by fish to polar metabolites that are subsequently excreted in the bile.

The primary route of exposure to CDD congeners for lower trophic organisms (e.g., phytoplankton and various aquatic invertebrates) is uptake from the water column or from interstitial water (between sediment particles). Certain benthic organisms accumulate highly lipophilic compounds (e.g., PCBs and CDDs/CDFs) from water at the water/sediment interface (the concentration of a lipophilic compound is generally higher at this interface than in the water column) and via intake of phytoplankton, zooplankton, and suspended particulate materials that contain higher concentrations of these chemicals than the surrounding water (Porte and Albaiges 1993; Pruell et al. 1993; Secor et al. 1993). For the higher trophic level organisms, such as foraging fish, predaceous fish, and piscivorous wildlife, the predominant route of exposure is via food chain transfer, with negligible contributions from CDDs in water and sediment (Muir and Yarechewski 1988). Exposure through direct consumption of CDD-contaminated sediment and detritus may occur in some bottom-feeding species such as carp and white suckers (Kuehl et al. 1987a, 1987b; Servos et al. 1989a, 1989b). Under natural conditions, in which a high proportion of these hydrophobic CDD compounds are sorbed to suspended and dissolved organic matter, direct uptake of these CDDs from water is not expected to be substantial (Muir et al. 1986a, 1986b). The estimated BCFs in such cases may not be a good indicator of the experimental bioaccumulation measured in the field. Another reason for the difference between estimated BCFs and experimentally measured bioaccumulation values is the ability of some aquatic organisms to metabolize and eliminate specific CDD congeners from their bodies and thereby change the congener profile pattern in their tissues.

The bioavailability of CDDs/CDFs from municipal incinerator fly ash and sediment to freshwater fish has been studied in experimental situations. Like the BCF and BAF values, the biota-sediment-accumulation factor (BASF) (ratio of contaminant concentration in the organism normalized to lipid content to the concentration in fly ash or sediment, normalized to organic carbon content) generally decreased with an increasing degree of chlorination (Kuehl et al. 1985, 1987b, 1987c). The BASF values for benthic (bottom-dwelling) fish (e.g., carp, catfish) are generally higher than for those pelagic (water column) species (e.g., bass, trout, sunfish) because of the higher lipid content and increased exposure to contaminated sediments for the benthic species (Paustenbach et al. 1992).

Freshwater aquatic invertebrates have been shown to bioaccumulate CDDs/CDFs through water, sediment, and food pathways (Isensee 1978; Muir et al. 1985; Yockim et al. 1978). The range in

experimentally determined BCF values for freshwater invertebrates is presented in Table 5-4. As discussed previously, exposure to CDDs from sediment and water containing dissolved organic material markedly decreases the BCF values, especially for the more highly chlorinated CDDs. Sediment-dwelling organisms (e.g., *Chironomous* sp. larvae and *Hexagenia* sp. nymphs), stoneflies, and other predaceous nymphs showed poor accumulation of OCDD in comparison to 1,3,6,8-TCDD (Muir et al. 1985). The lower bioaccumulation of OCDD was attributed to greater adsorption of the OCDD onto sediment particles and organic matter, and the reduced uptake across biological membranes due to large molecular size. The potential ingestion of sediments during burrowing activities by sediment-dwelling insects was believed to result in greater tissue concentrations of CDDs than those observed for predaceous insects. It is also possible that predaceous insects may metabolize 1,3,6,8-TCDD more effectively, leading to a greater rate of elimination. Sediment-dwelling organisms are important food sources for fish and other predaceous insects; consequently, if rapid elimination of 1,3,6,8-TCDD and low accumulation of OCDD occur in the natural environment, bioaccumulation of these congeners in trophically higher-level organisms may not be significant (Muir et al. 1985).

Marine invertebrates have also shown an ability to bioaccumulate CDDs/CDFs to varying degrees in their tissues (Brown et al. 1994; Cai et al. 1994; Conacher et al. 1993; Hauge et al. 1994; Rappe et al. 1991), although no information on BCF values was found in the literature. Interestingly, several investigators have reported that shellfish species (crustaceans and mollusks) are better indicators of CDD/CDF contaminant levels than fish because their tissues contain larger numbers and higher residues of CDD/CDF congeners in addition to the 2,3,7,8-TCDD congeners and other 2,3,7,8-substituted congeners that are selectively accumulated in fish species (Brown et al. 1994; Conacher et al. 1993; Rappe et al. 1991). This is in contrast to what is observed in fish and fish-eating birds, in which there is selective retention of congeners with the 2,3,7,8-substitution positions occupied, which may be due to an increased ability to metabolize and eliminate non-2,3,7,8-substituted CDD/CDF congeners (Brown et al. 1994; Rappe et al. 1991). The use of shellfish species as target organisms in CDD/CDF-monitoring studies is recommended as these species provide a better overall representation of both the magnitude and congener-specific nature of the environmental contamination (Petreas et al. 1992). Conacher et al. (1993) present an example where use of a shellfish species provides a much higher estimate of exposure to CDDs/CDFs as well as to total CDD equivalent toxicity (TEQs) than use of a fish species. This difference in congener bioaccumulation profiles between fish and shellfish species is a result of the ability of fish to metabolize CDDs/CDFs. Both the parent congeners and metabolites of 2,3,7,8-TCDD and 1,3,6,8-TCDD were present in the bile of fish exposed under laboratory conditions (Branson et al. 1985; Muir et al. 1986a). Kleeman et al. (1986a, 1986b) reported the presence of several polar metabolites,

including glucuronide conjugates, in various fish exposed to 2,3,7,8-TCDD. Despite the slowness of the metabolic breakdown processes, it is clear that CDDs can be transformed within fish to polar metabolites that are subsequently excreted with the bile. It does not appear from the results obtained in studies conducted to date that shellfish species have the same ability to metabolize and eliminate non-2,3,7,8-substituted CDDs/CDFs (Brown et al. 1994; Cai et al. 1994).

It is apparent from the available data that ingestion of contaminated fish and shellfish is an important exposure pathway for CDDs/CDFs in humans.

CDDs have been found to accumulate in both surface and rooted aquatic vegetation, with BCF values ranging from 208 to 2,083 (Table 5-4) (Isensee 1978; Tsushimoto et al. 1982; Yockim et al. 1978). Corbet et al. (1983) reported that a rooted plant species (*Potemageton pectimatus*) and a surface-dwelling duckweed (*Lemna* sp.) accumulated concentrations of 1,3,6,8-TCDD of 280 and 105 ng/g (dry weight), respectively, following exposure to water containing 1,000 ng/L (ppt). The maximum concentrations were observed 8 days post-application and represented 6% of the total TCDD applied. These results are similar to those reported by Tsushimoto et al. (1982) in an outdoor pond study, in which a maximum bioaccumulation of 2,3,7,8-TCDD in the pond weeds, *Elodea nuttali* and *Ceratophyllon demersum*, equivalent to a BCF of 130 occurred after 5 days of exposure. In both studies, the tissue concentrations reached equilibrium in approximately 20 days and remained constant until the end of the experiment (approximately 58 and 170 days, respectively). These experimental data indicate that CDDs can accumulate in aquatic plant species through waterborne exposure.

Like many fish, several species of fish-eating birds have shown the ability for preferential bioaccumulation of 2,3,7,8-TCDD and other 2,3,7,8-substituted CDDs and TCDFs. Jones et al. (1994) monitored TEQ values for 2,3,7,8-TCDD in double-crested cormorants from three of the Great Lakes: Superior, Michigan, and Huron. Biomagnification factors (BMFs, the ratio of the concentration of TCDD-equivalents in bird eggs to concentrations in forage fish) were found to range from 11.7 to 56.8 (mean, 31.3). In another study, all the CDDs and CDFs detected in double-crested cormorant and Caspian tern eggs were 2,3,7,8-substituted (Yamashita et al. 1992). Concentrations of 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD/1,2,3,6,7,8-HxCDD/1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD were 5.3–20, 3.2–9.4, 10–20, 3.6–11, and 7.8–16 pg TEQ/g, respectively, for double-crested cormorant eggs, and 8.2–22, 3.3–6.4, 8.7–17, 2.4–6.0, and 9.7–21 pg TEQ/g, respectively, for Caspian tern eggs. This same pattern was also reported to occur in California peregrine falcons and their eggs (Jarman et al. 1993). For this species, mean concentrations were 5.7 pg TEQ/g 2,3,7,8-TCDD, 11 pg

TEQ/g 1,2,3,7,8-PeCDD, 2 pg TEQ/g 1,2,3,4,7,8-HxCDD, 11 pg TEQ/g 1,2,3,6,7,8-HxCDD, 1.3 pg TEQ/g 1,2,3,7,8,9-HxCDD, 3.8 pg TEQ/g 1,2,3,4,6,7,8-HpCDD, and 5.3 pg TEQ/g OCDD in eggs. Fish-eating birds are exposed to CDDs primarily through their diet. A rapid decline in contaminant levels in eggs of fish-eating birds, therefore, reflects a rapid decrease in contaminant levels of their prey. This has been shown to occur in great blue heron chicks in British Columbia (Sanderson et al. 1994) in areas where CDD/CDF levels in pulp and paper mill effluents decreased substantially within a few years. The great blue heron chicks also showed an increased hepatic microsomal EROD activity in the areas of highest contamination. This indicates that the induction of CYP1A1 has occurred, and that the AhR-mediated process, by which 2,3,7,8-TCDD and related chemicals exert their toxicities, has been activated.

Ankley et al. (1993) studied the uptake of persistent polychlorinated hydrocarbons by four avian species at upper trophic levels of two aquatic food chains. Concentration of 2,3,7,8-TCDD TEQs were evaluated in Forster's tern and common tern chicks and in tree-swallow and red-winged-blackbird nestlings from several areas in the watershed. Young birds accumulated small concentrations of 2,3,7,8-TCDD and several other 2,3,7,8-substituted CDDs and CDFs, including 1,2,3,6,7,8-HxCDD, 2,3,7,8-TCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,4,6,7,8-HpCDF, 1,2,3,7,8-PeCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD. The general trend in concentrations of CDDs from the greatest to least was Forster's tern = common tern > tree swallow > red-winged blackbird. The similarity in concentrations between the two tern species is expected given that they are both piscivores, they have similar life histories, and the two colonies are in close proximity. The greater concentrations in the tree swallows than in the red-winged blackbirds were somewhat unexpected given the presumed similarity of the diets (both species are insectivores). The study authors suspected that the red-winged blackbirds foraged more on relatively uncontaminated upland food sources than the tree swallows, which fed primarily on chironomids emerging from the bay.

Sediment and Soil. Adsorption is an important process affecting transport of hydrophobic compounds such as CDDs. The organic carbon fraction of the soil is believed to be the most important factor governing the degree of adsorption of hydrophobic organic contaminants. CDDs adsorb more strongly to soils with a higher organic carbon content than to soils with low organic carbon content (Yousefi and Walters 1987). Because of their very low water solubilities and vapor pressures, CDDs found below the surface soil (top few mm) are strongly adsorbed and show little vertical migration, particularly in soil with high organic carbon content (Yanders et al. 1989). Vertical movement of CDDs in soil may result from the saturation of sorption sites of the soil matrix, migration of organic solvents, or human or animal activity (Hutzinger et al. 1985). Adsorption/desorption of 2,3,7,8-TCDD in contaminated soils was studied by Des Rosiers (1986). Soil samples were taken from an abandoned 2,4,5-T manufacturing

facility and a scrap metal yard in New Jersey and from horse arenas, roadways, and residential property in Missouri. Historically, these samples were contaminated with either chemical residues or waste oils containing 2,3,7,8-TCDD. Mean log organic carbon partition coefficient (K_{oc}) values were 7.39–7.58 (Des Rosiers 1986). This K_{oc} range indicates that 2,3,7,8-TCDD is immobile in soil (Swann et al. 1983). However, the mobility of 2,3,7,8-TCDD in soil will increase if organic co-solvents that can solubilize 2,3,7,8-TCDD are present in the soil (Podoll et al. 1986). This situation might occur at a hazardous waste site. In one study, only 1.5% of the CDDs applied to soil surfaces had leached to a depth of 2.5 cm below the soil surface after 15 months. Leaching of the CDDs through the soil was primarily associated with carriers such as petroleum oil (Orazio et al. 1992).

A model has been developed to describe the vertical transport of low-volatility organic chemicals in soil (Freeman and Schroy 1986). The model was used to make predictions on the transport of 2,3,7,8-TCDD at the Eglin Air Force Base Agent Orange biodegradation test plots (Freeman and Schroy 1986). Trenches 10 cm deep were dug in the soil, and Agent Orange containing 40 ppb of 2,3,7,8-TCDD was applied to the trench bottom. The model predicted a vertical movement of 2,3,7,8-TCDD, buried in 1972, through the soil column. Soil-column-profile data confirm the vertical movement of 2,3,7,8-TCDD from core samples taken in 1984 (Freeman and Schroy 1986). The 2,3,7,8-TCDD in the Eglin Air Force Base biodegradation plots moved through the entire 10 cm of the soil column in 12 years (Freeman and Schroy 1986). The rates of migration and loss of 2,3,7,8-TCDD in contaminated soil were studied under natural conditions in experimental plots at the Dioxin Research Facility, Times Beach, Missouri (Yanders et al. 1989). The TCDD concentration profiles of sample cores taken at Times Beach in 1988 (mean range 78–160 ppb) were virtually the same as those in cores taken in 1984 (mean range 76–162 ppb). The results show that little movement and essentially no loss due to volatilization of 2,3,7,8-TCDD had occurred in the experimental plots in the 4 years since the Dioxin Research Facility was established (Yanders et al. 1989).

Estimated log K_{oc} values for MCDD through OCDD calculated using EPI Suite™ (EPA 2012b) are provided in Table 5-6. The first method reports the estimation using a molecular connectivity index (MCI) method and the second value is an estimation using a correlation with the log K_{ow}.

Table 5-6. Estimated Log K_{oc} for MCDD through OCDD

CDD	Log K_{oc} (MCI)	Log K_{oc} (K_{ow} QSAR)
MCDD	4.4	4.1
DCDD	4.6	4.9

Table 5-6. Estimated Log K_{oc} for MCDD through OCDD

CDD	Log K_{oc} (MCI)	Log K_{oc} (K_{ow} QSAR)
TrCDD	5.2	4.5
TCDD	5.4	4.8
PeCDD	5.6	4.7
HxCDD	5.8	5.6
HpCDD	6.1	5.5
OCDD	6.3	5.6

CDD = chlorinated dibenzo-*p*-dioxin; DCDD = dichlorodibenzo-*p*-dioxin; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; MCDD = monochlorodibenzo-*p*-dioxin; MCI = molecular connectivity index; OCDD = octachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; QSAR = quantitative structure-activity relationship; TCDD = tetrachlorodibenzo-*p*-dioxin; TrCDD = trichlorodibenzo-*p*-dioxin

Source: EPA 2012b

Other Media. Maize (corn) and bean cultivations grown in soils spiked with 22–1,066 ppt 2,3,7,8-TCDD showed 2,3,7,8-TCDD concentrations in roots ranging from 16 to 1,278 ppt for maize and from 37 to 1,807 for beans (Facchetti et al. 1986). The soil-grown crops did not show a significant increase of 2,3,7,8-TCDD in above-ground parts, either as a function of time or with increasing concentration of the pollutant in the soil (Facchetti et al. 1986). Using two soils with differing organic matter content, it was shown that for both zucchini and pumpkin, uptake of CDDs by the root and translocation to the shoots and fruit were important mechanisms and may explain why fruits in the *Cucurbita* genus tend to have higher levels of CDDs than other fruits (Hülster et al. 1994). Inui et al. (2008, 2011) also studied the uptake of CDDs in three different zucchini cultivars and found accumulation to be significantly higher in the black beauty and gold rush variety as compared to the patty green cultivar.

Uptake of [^{14}C]-labeled OCDD was studied in a closed, aerated-soil plant system for 7 days after application of the OCDD to soil (Schroll et al. 1994). The BCF (concentration of [^{14}C] equivalent to the OCDD in plant dry matter divided by [^{14}C]-labeled OCDD in dry soil) was 0.742 in carrot root and 0.085 in carrot shoots grown on OCDD-contaminated soil as compared to a BCF of not determinable and 0.084 in the control carrot root and shoots, respectively. There was no transport of [^{14}C]-labeled OCDD between the roots and shoots or vice versa. The residues in roots were due only to root uptake from the soil; those in shoots were due only to foliar uptake from the air.

Müller et al. (1993) studied transfer pathways of CDD/CDFs to fruit. The study authors found that homologue patterns of CDDs/CDFs in soil were different from those in both apples and pears grown in

the contaminated soil. Concentrations of CDDs/CDFs were 1–4 ng/kg (fresh weight) and were 4–8 times higher in the peel than in the pulp. The study authors suggested that airborne CDDs/CDFs are a major source of contamination of fruits grown in contaminated soil. Müller et al. (1994) conducted field studies of CDD transfer pathways from soil to several edible plant varieties (carrots, lettuce, and peas). Plants were grown in soil with 5 ng TEQ/kg or total CDD/CDF concentrations of 363 ng/kg dry weight (control plots) and 56 ng TEQ/kg or total CDD/CDF concentrations of 3,223 ng/kg dry weight on the contaminated plots. CDD/CDF concentrations in carrot peels were 3 times higher on the contaminated plots than on the control plots. This was the result of a 10-fold increase in the CDD/CDF levels in the carrot peel. CDD/CDF concentrations in lettuce (17.7 and 21.1 ng/kg dry weight) and in peas (7.1 ng/kg dry weight) were not any higher when grown on the contaminated plot as compared to the control plots and were much lower than concentrations in the carrots (47.3 and 47.5 ng/kg dry weight). This indicates that the CDD/CDFs in the lettuce and peas from both plots were of atmospheric origin. The CDD/CDF homologue pattern in the contaminated soil showed that OCDFs and HpCDFs were the two most prevalent congeners, while the CDD/CDF homologue pattern from the peel of carrots grown on the contaminated plots contained TCDF, PeCDF, and HxCDF. Levels of TCDD were the lowest of all CDD/CDF homologues in both contaminated soils and carrot peels. The homologue profile in lettuce samples was largely dominated by lower chlorinated CDFs (TCDF and PeCDF) and higher chlorinated CDDs (HpCDD and OCDD), a profile often found in samples of atmospheric deposition (Eitzer and Hites 1989a, 1989b). The lowest CDD/CDF levels of this study were found in peas, with pea pods showing higher levels than seeds. The homologue profile was dominated by lower chlorinated CDFs and higher chlorinated CDDs similar to the profile found in lettuce.

Since most of the CDDs released into the atmosphere settle onto water and soil surfaces, foliar deposition is the major route of vegetative contamination (Travis and Hattemer-Frey 1987). The translocation of foliar-applied 2,3,7,8-TCDD has been studied (Kearney et al. 1971). Labeled 2,3,7,8-TCDD was applied to the center leaflet of the first trifoliate leaf of 3-week-old soybean plants and the first leaf blade of 12-day-old oat plants. The compound was applied in an aqueous surfactant solution to enhance leaf adsorption and to keep the water-insoluble TCDD in solution. Plants were harvested 2, 7, 14, and 21 days after treatment, dissected into treated and untreated parts, and analyzed. 2,3,7,8-TCDD was not translocated from the treated leaf to other plant parts. Very little 2,3,7,8-TCDD was lost from soybean leaves, while a gradual loss (38% in 21 days) did occur from oat leaves (Kearney et al. 1971). The study authors considered volatilization to be a possible mechanism for removal of 2,3,7,8-TCDD, but photolysis may also have contributed to the loss.

McCrady and Maggard (1993) measured the uptake and elimination mechanisms for 2,3,7,8-TCDD applied to grass foliage in a closed-laboratory system using [^{3}H]-TCDD. The [^{3}H]-2,3,7,8-TCDD was injected into the chamber as a vapor originating from a [^{3}H]-2,3,7,8-TCDD generator. The total recovered radioactivity was 74%. Plant foliage accounted for 59% and the air and other chamber components accounted for 6 and 9%, respectively. This indicated that plant foliage was a major sink for [^{3}H]-2,3,7,8-TCDD vapor. Less than 0.2% was recovered from the soil and associated with root tissues, further verifying an airborne mechanism of [^{3}H]-2,3,7,8-TCDD uptake and negligible translocation. The study authors also demonstrated that both photodegradation and volatilization were primary loss mechanisms for [^{3}H]-2,3,7,8-TCDD. The photodegradation half-life (first-order kinetics) of 2,3,7,8-TCDD sorbed to grass and exposed to natural sunlight was 44 hours, while the half-life for volatilization of 2,3,7,8-TCDD from grass foliage was 128 hours.

5.4.2 Transformation and Degradation

Air. CDDs slowly degrade in the atmosphere by reacting with photochemically produced hydroxyl radicals. Using the gas-phase hydroxyl radical reaction rate constants and an average 12-hour daytime hydroxyl radical concentration of 1.5×10^6 molecules cm^{-3}, the atmospheric vapor phase lifetimes of CDDs are estimated to range from about 0.5 days for MCDD to 9.6 days for OCDD, with TCDD having a lifetime of 0.8–2 days (Atkinson 1991). Particulate-phase CDDs have been shown to have much longer atmospheric half-lives as compared to the vapor phase CDDs (Atkinson 1991). Based on the photolysis lifetimes of CDDs in solution, it is expected that vapor-phase CDDs will also undergo photolysis in the atmosphere, although reactions with hydroxyl radicals will predominate. For TCDD, the photolytic lifetime ranges from 1.3 to 7.1 days, depending on the season (faster in summer and slower in winter).

Particulate-bound CDDs are removed by wet or dry deposition with an atmospheric lifetime ≥10 days (Atkinson 1991) and, to a lesser extent, by photolysis. Miller et al. (1987) measured photolysis of 2,3,7,8-TCDD sorbed onto small-diameter fly ash particulates suspended in air. The results indicated that fly ash confers photostability to the adsorbed 2,3,7,8-TCDD. The study authors reported little (8%) to no loss of 2,3,7,8-TCDD on the fly ash samples after 40 hours of illumination in simulated sunlight. Koester and Hites (1992b) studied the photodegradation of CDDs naturally adsorbed to five fly ash samples (two from coal-fired plants, two from municipal incinerators, and one from a hospital incinerator). Although the study authors reported that CDDs underwent photolysis in solution and on silica gel, no significant degradation was observed in 11 photodegradation experiments conducted for periods ranging from 2 to 6 days.

The selected transformation of the more and less chlorinated CDDs has been demonstrated by the analysis of CDDs found in soil samples compared with atmospheric concentrations of CDDs at the emission source (Marklund et al. 1991; Yamamoto and Fukushima 1993). Soil samples contained progressively greater concentrations of HpCDD and OCDD with increasing distance from the emission source, indicating that photolysis of the less chlorinated congeners was occurring (Eitzer 1993). In the air, the low vapor pressure of OCDD results in its partitioning primarily to the particulate phase rather than the vapor phase; therefore, atmospheric photodegradation is less likely to occur for this tightly bound congener (Eitzer 1993).

Water. Photolysis is the major route of CDD disappearance in aqueous solutions (Hutzinger et al. 1985). While photolysis is a relatively slow process in water, CDDs are rapidly photolyzed under certain conditions (i.e., when exposed to UV light of the appropriate wavelength and in the presence of an organic hydrogen donor). These hydrogen donors can be expected to be present in chlorophenol pesticides either as formulation solvents (e.g., xylene or petroleum hydrocarbons), as active constituents of the formulation (e.g., the alkyl esters of 2,4-D and 2,4,5-T), or as natural organic films on soils (Crosby et al. 1973). The photolytic behavior of CDDs in an organic solvent or in a water-organic solvent, however, may not accurately reflect the photolytic behavior of these compounds in natural waters (Hutzinger et al. 1985). For example, Choudhry and Webster (1989) reported that photolysis of 1,3,6,8-TCDD was slower in natural pond-water solutions than was predicted from studies with laboratory solutions. Conversely, Friesen et al. (1990) reported that photolysis of PeCDD and HpCDD proceeds faster in a pond or lake-water solutions than was predicted or measured in a laboratory solution. In general, however, lower chlorinated CDDs are degraded faster than higher chlorinated congeners. Chlorine atoms in the lateral positions (e.g., 2, 3, 7, 8) are also more susceptible to photolysis than are chlorine atoms in the para positions (e.g., 1, 4, 6, 9) (Choudhry and Hutzinger 1982; Crosby et al. 1973; Hutzinger et al. 1985).

Podoll et al. (1986) used the quantum yield data of Dulin et al. (1986) for a water:acetonitrile solution to calculate seasonal half-life values for dissolved 2,3,7,8-TCDD at 40 degrees north latitude in clear near-surface waters. Photolysis half-lives for dissolved 2,3,7,8-TCDD in sunlight ranged from 118 hours in winter, to 51 hours in fall, to 27 hours in spring, to 21 hours in summer (Podoll et al. 1986). Choudhry and Webster (1989) studied photolysis of a series of CDDs in a water:acetonitrile solution (2:1 v/v). The study authors estimated the midday midsummer sunlight photolysis half-lives values at 40 degrees north latitude in clear near-surface waters as follows: 1,3,6,8-TCDD (0.3 days), 1,2,3,7-TCDD (1.8 days),

1,2,3,4,7-PeCDD (15 days), 1,2,3,4,7,8-HxCDD (6.3 days), 1,2,3,4,6,7,8-HpCDD (47 days), and OCDD (18 days) near the surface of water bodies (Choudhry and Webster 1989). Sunlight photolysis half-lives were also reported for the spring, fall, and winter for 1,2,3,4,6,7,8-HpCDD (57, 88, and 156 days, respectively) and for OCDD (21, 31, and 50 days, respectively) (Choudhry and Webster 1989). Photolysis half-lives for 1,2,3,4,6,7,8-HpCDD and OCDD in water-acetonitrile solutions irradiated at 313 nm were reported to be 8 and 7.7 days, respectively (Choudhry and Webster 1987, 1989). The half-lives of 1,3,6,8-TCDD and OCDD in lake water were reported as 2.6 and 4 days, respectively, with removal by partitioning to the lake sediments (Servos et al. 1992).

The photodegradation profiles of 2,3,7,8-TCDD, 1,3,6,8-TCDD, and 1,2,3,4-TCDD in 1,4-dioxane solutions at various wavelengths under xenon lamp irradiation were studied (Koshioka et al. 1989a, 1989b, 1989c). Reductive dechlorination reactions were observed in the photolysis of TCDD isomers. After 200 minutes of irradiation with a xenon lamp, 2,3,7,8-TCDD formed 2,3,7-TrCDD, 2,7-DCDD, 2,8-DCDD, 2-MCDD, and DD. Photodegradation half-lives of 2,3,7,8-TCDD at the maximal photodegradation wavelengths of 252.6 and 318.6 nm were 72.6 and 29.7 minutes, respectively (Koshioka et al. 1989b, 1989c). After 267 minutes of irradiation with a xenon lamp, 1,3,6,8-TCDD formed 1,3,6-TrCDD, 1,3-DCDD, 1,6-DCDD, 1-MCDD, 2-MCDD, and DD, while 1,2,3,4-TCDD formed 1,2,3-TrCDD, 1,2,4-TrCDD, 1,2-DCDD, 1,3-DCDD, 1,4-DCDD, 2,3-DCDD, 1-MCDD, 2-MCDD, and DD (Koshioka et al. 1989a).

The photolytic half-lives of 2,3,7,8-TCDD in isooctane were estimated to be 40 minutes with a light source at 0.5 meters and 3 hours with a light source at 1 meter (Stehl et al. 1973). Very little change was observed in OCDD on exposure to artificial sunlight. Approximately 20% photolysis of OCDD was observed in isooctane at the end of 18 hours and about 6% photolysis of OCDD was observed after 20 hours of exposure in 1-octanol (Stehl et al. 1973). Irradiation of PCP dissolved in sodium hydroxide at a wavelength of 300 nm (equivalent to sunlight) for 16 hours produced OCDD (Crosby and Wong 1976). OCDD then underwent photoreduction to HpCDD as a PCP photolysis product.

Under equivalent light exposure conditions, photolytic half-lives were determined for each of the individual TCDD isomers in dilute hydrocarbon solution and as a diffuse molecular dispersion on a clean soft-glass surface (Nestrick et al. 1980). The photolytic behavior of 2,3,7,8-TCDD was atypical compared to other TCDD isomers. In a hydrocarbon solution, 2,3,7,8-TCDD had the fastest decomposition rate (half-life 56.8 minutes) and 1,4,6,9-TCDD had the slowest decomposition rate (half-life 8,400 minutes [5.8 days]). The half-lives of the remaining TCDD isomers were 153–1,388 minutes

(2.55–23.1 hours). However, as a diffuse molecular dispersion on a glass surface, the 2,3,7,8-TCDD had the slowest decomposition rate (half-life 8,400 minutes [5.8 days]), and 1,4,6,9-TCDD had the second slowest decomposition rate (half-life 830 minutes [13.8 hours]). The half-lives of the remaining TCDDs were 121–560 minutes (2–9.3 hours). The majority of TCDD isomers photolytically decomposed faster on a glass surface than in a hydrocarbon solution under conditions of equivalent light intensity. 2,3,7,8-TCDD and 1,4,6,9-TCDD possess the highest degree of symmetry within the group, and these isomers demonstrated the largest change in the photodecomposition rate for surface and solution reactions, with the changes being in opposite directions. Additional photolysis tests were conducted using more highly chlorinated CDD congeners. In a hydrocarbon solution, the half-lives of 1,2,3,4,6,7,8-HpCDD, 1,2,3,4,6,7,9-HpCDD, and OCDD were 1,800 minutes (1.3 days), 3,300 minutes (2.3 days), and 1,460 minutes (1.01 days), respectively, and 3,140 minutes (2.18 days), 2,400 minutes (1.67 days), and 48,900 minutes (33.96 days), respectively, on a glass surface (Nestrick et al. 1980).

2,3,7,8-TCDD decomposed rapidly when dissolved in methanol and exposed to UV light (Plimmer et al. 1973). Rate measurements showed that 2,3,7,8-TCDD is more rapidly photolyzed in methanol than OCDD (Plimmer et al. 1973). The photolysis half-lives for 2,3,7,8-TCDD, 1,2,3,4,6,7,8-HpCDD, 1,2,3,4,6,7,9-HpCDD, and OCDD in *n*-hexadecane solution were 56.8 minutes, 1,800 minutes (1.25 days), 3,300 minutes (2.29 days), and 1,460 minutes (1.01 days), respectively (Mamantov 1984).

Solution-phase photolysis of HpCDD and OCDD has been reported (Dobbs and Grant 1979). Solutions of these CDDs in hexane (approximately 1 μg/mL) were exposed to natural sunlight as well as to fluorescent blacklight. The photolytic half-life for OCDD exposed to both types of radiation was 16 hours. HpCDD was generated by photolysis of OCDD (Dobbs and Grant 1979). The photolytic half-lives of 1,2,3,4,6,7,9-HpCDD and 1,2,3,4,6,7,8-HpCDD were 28 hours and 11 hours, respectively (Dobbs and Grant 1979).

It has been suggested that the potential for biological degradation of 2,3,7,8-TCDD in a wide variety of environmental samples is low (Arthur and Frea 1989). The fate of 2,3,7,8-TCDD in sediment and water from two lakes in Wisconsin was examined (Ward and Matsumura 1978). After incubation periods of up to 589 days, little metabolism of 2,3,7,8-TCDD was detected. The slight metabolism that was detected was stimulated by the presence of sediment and the addition of nutrients (Ward and Matsumura 1978). Also, 2,3,7,8-TCDD does not hydrolyze in water (EPA 1982; Miller et al. 1987).

Sediment and Soil. Photolysis of 2,3,7,8-TCDD on soils is a relatively slow process compared to photolysis in an aqueous media (Kieatiwong et al. 1990). 2,3,7,8-TCDD applied to soil or a solid surface seems to be extremely resistant to the action of sunlight and decomposes very slowly (Plimmer et al. 1973). A methanol solution of 2,3,7,8-TCDD (2.4 ppm) applied to glass plates coated with soil and illuminated 96 hours with a fluorescent UV lamp remained unchanged at the end of the period (Plimmer et al. 1973). Organic solvents added to the soil, however, can enhance the extent of photolysis. Use of a solvent mixture of tetradecane and 1-butanol to TCDD-treated soil, combined with exposure to sunlight, resulted in 61–85% photodegradation of TCDD after 60 days. The solvent was effective in transporting TCDD from deeper in the soil column (60 cm) to the soil surface via evaporation. At the soil surface, photodegradation could occur. TCDD concentrations at 60 cm decreased from 23.8 ng/g (ppb) to 7.1 ng/g (ppb) after 60 days (McPeters and Overcash 1993).

Photolysis of OCDD (10 mg/kg) on soils resulted in production of the lower chlorinated CDDs, notably 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, three HxCDD isomers substituted at the 2,3,7,8-positions, and 1,2,3,4,6,7,8-HpCDD. Photolysis of OCDD occurred in mean soil depths between 0.06 and 0.13 mm (Miller et al. 1989b). Approximately 30–45% of OCDD was lost by day 5 of irradiation; no further significant loss of OCDD was observed following 10 additional days of irradiation. Although photolysis only occurred at shallow soil depths and the conversion of OCDD to the more toxic TCDD, PeCDD, and HxCDD homologues was small (0.5–1%) compared with the photodechlorination to HpCDD (67%), photolysis of OCDD may represent a significant source of these toxic isomers (Miller et al. 1989b).

The loss of 2,3,7,8-TCDD in contaminated soil has been studied under natural conditions in experimental plots at the Dioxin Research Facility, Times Beach, Missouri (Yanders et al. 1989). The 2,3,7,8-TCDD concentration profiles of sample cores taken at Times Beach in 1988 were virtually the same as those in cores taken in 1984. The study authors concluded that the loss of 2,3,7,8-TCDD due to photolysis at Times Beach was minimal in the 4 years covered by the study (Yanders et al. 1989). Estimates of the half-life of TCDD on the soil surface range from 9 to 15 years, whereas the half-life in subsurface soil may range from 25 to 100 years (Paustenbach et al. 1992).

A white rot fungus *(Phanerochaete chrysosporium)* has demonstrated the ability to degrade 2,3,7,8-TCDD in laboratory experiments (Bumpus et al. 1985; Des Rosiers 1986). In cultures containing 1.25 nmol of the 2,3,7,8-TCDD substrate, 27.9 pmol were mineralized to CO_2 in 30 days (2.23% metabolism) increasing to 49.5 pmol in 60 days (3.96% metabolism) (Des Rosiers 1986). It was suggested that the ability of this fungus to metabolize 2,3,7,8-TCDD is dependent on its extracellular

lignin-degrading enzyme system (Bumpus et al. 1985; Des Rosiers 1986). Valli et al. (1992) reported that 2,7-DCDD also was degraded by *P. chrysosporium* via the removal of both aromatic chlorines before aromatic ring cleavage took place.

Cultures of *Pseudomonas testosteroni*, of an unidentified bacterium isolated from soil from Seveso, Italy, and of a mixture of 6 unidentified bacterial strains isolated from Seveso soil were incubated aerobically with [^{14}C]-2,3,7,8-TCDD for 12, 35, or 54 weeks (Philippi et al. 1982). Results showed the occurrence of a polar metabolite of [^{14}C]-2,3,7,8-TCDD, which amounted to approximately 1% of the input material and was found to be a hydroxylated derivative of [^{14}C]-2,3,7,8-TCDD (Philippi et al. 1982).

Approximately 100 strains of pesticide-degrading microorganisms were tested for their ability to degrade 2,3,7,8-TCDD (Matsumura and Benezet 1973). The organisms were maintained in liquid axenic culture, and the production of metabolites from ring-labeled [^{14}C]-2,3,7,8-TCDD was measured. Five strains were identified that showed some ability to degrade [^{14}C]-2,3,7,8-TCDD. The degradative organisms included a fungus *(Trichoderma viride)*, a bacterium *(Pseudomonas putida)*, and three organisms referred to by coded numbers (Matsumura and Benezet 1973).

To determine the persistence of 2,3,7,8-TCDD, concentrations of 1, 10, and 100 ppm of unlabeled 2,3,7,8-TCDD were added to 300 g samples of silty loam and sandy soils and then assayed periodically for residues (Kearney et al. 1971). Measurements of 2,3,7,8-TCDD residues after 20, 40, 80, 160, and 350 days of incubation at 28°C in foil-sealed beakers indicated a relatively slow degradation process in both soils. After 350 days, 56% of the initially applied 2,3,7,8-TCDD was recovered from the sandy soil, while 63% was recovered from the silty clay loam for all concentrations (Kearney et al. 1971).

Parsons (1992) studied the influence of suspended sediment on the biodegradation of several CDDs. In this study, aqueous solutions of a mixture of 2-chloro-, 1,3-dichloro, 2,8-dichloro-, and 1,2,4-trichloro CDDs were incubated for 24 days with 100 mg/L suspended sediment. Subsequently, the degradation of the CDDs in the sediment suspensions by *Alcaligenes* sp. strain JB1 was compared to that in solutions without sediment. The amounts of all four CDD compounds degraded in the sediment suspensions after 7 days were greater than those initially present in the dissolved phase, based on their calculated sediment-water partition coefficients. The sorbed fractions were, therefore, sufficiently desorbed to be partly degraded. However, the biodegradation rates were slower in the sediment suspensions than in the solutions. The results indicate that sorbed fractions of CDDs formed after relatively short incubation periods are sufficiently labile to be available for biodegradation after desorption. Evidence that the

presence of sediment lowers biodegradation rates in sediment suspension, however, implies that longer residence times, such as those observed under field conditions, may also lead to a significant lowering of the biodegradation rates in soil. This will apply even more to the more highly chlorinated CDD congeners. In another study, the degradation of highly chlorinated CDD congeners (5–7 chlorine/ molecule) was studied for a period of 6 months in anaerobic microcosm incubations using PCB-contaminated Hudson River sediments and creosote-contaminated aquifer samples from Pensacola, Florida (Adriaens and Grbic-Galic 1994). The study authors reported (pseudo-first order) half-life values for 1,2,3,4,6,7,8-HpCDD of 4.1 and 2.9 years for the Hudson River and Pensacola aquifer-incubated microcosm samples, respectively. The half-life values for 1,2,3,4,7,8-HxCDD were 2 and 2.9 years for the Hudson River and Pensacola aquifer-incubated microcosm samples, respectively. The 1,2,4,6,8,9/1,2,4,6,7,9-HxCDD congeners were found not to be degraded, which was presumably due to the low concentration spiked. The study authors reported that tentative identification of the degradation products indicate that para-dechlorination was the preferential route of reduction, as has been observed with 1,2,3,4,5,6,7,8-HpCDD in aquifer microcosms. This observation is contrary to photolytic dechlorination patterns of soil-sorbed CDDs.

Beurskens et al. (1995) reported that an anaerobic microbial consortium enriched from Rhine River sediments was able to remove chlorine substituents from CDDs. A model CDD, 1,2,3,4-TCDD, was reductively dechlorinated to both 1,2,3- and 1,2,4-TrCDD. These TrCDD compounds were further dechlorinated to 1,3- and 2,3-DCDD and trace amounts of 2-MCDD. The TrCDD compounds were detected at low concentrations, but the 1,3- and 2,3-DCDD were detected at higher concentrations. The anaerobic culture dechlorinates 1,2,3,4-TCDD at a relatively rapid rate with a half-life value estimated at 15.5 days (first-order kinetics). The formation of metabolites with a conserved 2,3-substitution pattern from 1,2,3,4-TCDD indicates that dechlorination of highly chlorinated CDDs may result in metabolites that are potentially more toxic than the parent compounds.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to CDDs depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of CDDs in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on CDD levels monitored or estimated in the environment, it should be noted that the amount of the chemical identified analytically is not necessarily equivalent to the amount that is bioavailable and that every measurement is accompanied with a certain analytical error.

Table 5-7 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-8.

Table 5-7. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.0003 fg/m^3 (2,3,7,8-TCDD)[b]	Friedman et al. 2012
Drinking water	10 pg/L (ppq) (2,3,7,8-TCDD)[c]	EPA 2007a (Method 8290)
Surface water and groundwater	0.3 fg/L (2,3,7,8-TCDD)	Friedman et al. 2012
Soil	0.2 pg/g (ppt) (2,3,7,8-TCDD)	Nestrick et al. 1986
Sediment	1 pg/g (ppt) (2,3,7,8-TCDD)[c]	EPA 2007a (Method 8290)
Whole blood	1.25 pg/L (ppq) (2,3,7,8-TCDD); 3.8 pg/g lipid basis	CDC 2024a; Patterson et al. 1987

[a]Detection limits based on using appropriate sample mass/volume, preparation and analytics. These limits may not be possible in all situations.
[b]Detection limits in air are dependent upon the sampling time/sampling volume. Typical detection limits are in the pg/m^3 range; however, this study had extended sampling times and large volume collections (>150 m^3) ensuring very low detection limits.
[c]The detection limits and quantitation levels in this method are usually dependent on the level of interferences rather than instrumental limitations.

ppq = parts per quadrillion; ppt = parts per trillion; TCDD = tetrachlorodibenzo-*p*-dioxin

Table 5-8. Summary of Environmental Levels of Chlorinated Dibenzo-*p*-Dioxins

Media	Low	High	For more information
Outdoor air (pg/m^3)	<LOD	24	Section 5.5.1
Indoor air (pg/m^3)	<LOD	131.5	Section 5.5.1
Surface water (pg/L)	<LOD	20	Section 5.5.2
Groundwater (pg/L)	<LOD	3,900,000	Section 5.5.2
Drinking water (pg/L)	<LOD	230	Section 5.5.2
Food (pg/g)	<LOD	65	Section 5.5.4
Soil (pg/g)	<LOD	$2x10^9$	Section 5.5.3

LOD = limit of detection

Detections of CDDs in air, water, and soil at NPL sites are summarized in Table 5-9.

Table 5-9. Chlorinated Dibenzo-*p*-Dioxin Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
2,3,7,8-TCDD					
Water (ppb)	7.05×10^{-4}	6.37×10^{-4}	401	8	5
Soil (ppb)	6.2	12.5	49.4	95	56
Air (ppbv)			No data		
TCDD[b]					
Water (ppb)			No data		
Soil (ppb)	3.5	6.25	35.1	21	11
Air (ppbv)			No data		
1,2,3,7,8-PeCDD					
Water (ppb)			No data		
Soil (ppb)	1.1	0.369	58.3	5	4
Air (ppbv)			No data		
PeCDD[b]					
Water (ppb)			No data		
Soil (ppb)	3.1	2.97	29.1	17	10
Air (ppbv)			No data		
1,2,3,4,7,8-HxCDD					
Water (ppb)			No data		
Soil (ppb)	4	1.56	38.4	7	6
Air (ppbv)			No data		
1,2,3,6,7,8-HxCDD					
Water (ppb)			No data		
Soil (ppb)	26	4.14	74.5	5	5
Air (ppbv)			No data		
1,2,3,7,8,9-HxCDD					
Water (ppb)			No data		
Soil (ppb)	10.4	3.55	38.6	6	5
Air (ppbv)			No data		
HxCDD[b]					
Water (ppb)			No data		
Soil (ppb)	7.8	10.6	26	28	17
Air (ppbv)			No data		
1,2,3,4,6,7,8-HpCDD					
Water (ppb)			No data		
Soil (ppb)	22.6	36.4	56.7	10	9
Air (ppbv)			No data		

Table 5-9. Chlorinated Dibenzo-*p*-Dioxin Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
HpCDD[b]					
Water (ppb)	2.5	2.62	1,380	7	4
Soil (ppb)	4.9	10.6	45.4	36	20
Air (ppbv)			No data		
OCDD					
Water (ppb)	4.57	2.63	2,660	8	5
Soil (ppb)	21	77.7	64.2	47	29
Air (ppbv)			No data		

[a]Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022). Pathways do not necessarily involve exposure or levels of concern.
[b]Refers to summation of the other isomers in the homologues instead of the specified isomer.

5.5.1 Air

The National Dioxin Air Monitoring Network (NDAMN) was established by the EPA in 1998 to determine background air concentrations of CDDs, CDFs, and dioxin-like PCBs in the United States (EPA 2013). Congener-specific data from June 1998 through November 2004 at 34 NDAMN stations (4 urban stations, 23 rural stations, and 7 remote stations) throughout the United States are shown in Table 5-10. Large sampling times and large volumes of collected air guaranteed low detection limits and a high detection frequency. The maximum concentration of 23,953 fg/m^3 (23.953 pg/m^3) was observed for OCDD.

Table 5-10. Congener-specific Monitoring Data from the National Dioxin Air Monitoring Network 1998–2004

Congener	Detection frequency (%)	Mean (fg/m^3)	SD (fg/m^3)
2,3,7,8-TCDD	85	0.6	1.2
1,2,3,7,8-PeCDD	89	3.1	5.9
1,2,3,4,7,8-HxCDD	94	4.2	10.4
1,2,3,6,7,8-HxCDD	97	7.3	15.3
1,2,3,7,8,9-HxCDD	96	7.2	15.3
1,2,3,4,6,7,8-HpCDD	100	102.3	234.6

Table 5-10. Congener-specific Monitoring Data from the National Dioxin Air Monitoring Network 1998–2004

Congener	Detection frequency (%)	Mean (fg/m^3)	SD (fg/m^3)
OCDD	100	352.8	973.4

HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; OCDD = octachlorodibenzo-*p*-dioxin; SD = standard deviation; TCDD = tetrachlorodibenzo-*p*-dioxin

Source: EPA 2013

High levels of CDDs and CDFs were predicted to have arisen following the terrorist attacks at the World Trade Center (WTC) complex in New York City on September 11, 2001 (Rayne et al. 2005). Predicted gas-phase concentrations in Manhattan 6 weeks after the attack were estimated to be as high as 822 fg/m^3 (0.822 pg/m^3) for 2,3,7,8-TCDD at Church and Warren Streets. This location also had the highest predicted combined CDF/CDD TEQ of 2,730 fg/m^3 (2.730 pg/m^3).

Monitoring data in the vicinity of the Passaic River and Newark Bay New Jersey from May 2008 to August 2009, measured vapor-phase concentrations of mono- to octaCDDs (Friedman et al. 2012). Lower chlorinated congeners (2,7-/2,8-DCDD) were detected and likely resulted from photochemical conversion of triclosan in Newark Bay. The highest concentration of these congeners was about 7 pg/m^3. 2,4,7-TrCDD was also detected in atmospheric samples at levels up to 1 pg/m^3. Other higher chlorinated congeners were not detected in vapor-phase air samples.

Lin et al. (2010) studied atmospheric levels of CDDs and CDFs in the air of Taiwan in the vicinity of water treatment facilities. Average atmospheric levels in pg/m^3 were as follows: 2,3,7,8-TCDD, 0.009; 1,2,3,7,8-PeCDD, 0.043; 1,2,3,4,7,8-HxCDD, 0.062; 1,2,3,6,7,8-HxCDD, 0.144; 1,2,3,7,8,9-HxCDD, 0.112; 1,2,3,4,6,7,8-HpCDD, 1.86; and OCDD, 6.06. Levels were consistently higher in the spring as compared to summer, fall, and winter months.

As part of the Stockholm Convention on Persistent Organic Pollutants (POPs) Global Monitoring Plan (GMP), a study was conducted between 2017 and 2019 to monitor dioxin-like POPs in developing countries (Abad et al. 2022). The results were expressed as TEQ and included 195 measurements from 42 developing nations. The findings indicated that there was a noticeable downward trend for CDD/CDF TEQs only in Latin American nations and that the highest levels were determined to be in Asian nations. Results from a GMP study conducted in Brazil showed that mass concentrations of CDDs/CDFs in Sao Paulo declined approximately 50% from 0.0265 to 0.0133 pg/m^3 from 2010 to 2015 (Hu et al. 2019).

Concentrations of individual CDDs were typically <0.01 pg/m^3. Similar monitoring studies were conducted in a rural area of Mexico (Sinaloa) from 2016 to 2018 as part of the GMP (Valenzuela et al. 2022). Ten CDFs and seven CDD congeners were monitored in the ambient air. The predominant CDDs detected were 1,2,3,4,6,7,8,9-OCDD with concentrations of 0.154–0.164 pg/m^3 and 1,2,3,4,6,7,8-HpCDD with concentrations of 0.044–0.048 pg/m^3.

Table 5-11 provides additional air concentrations of CDDs in indoor air, outdoor air, and over oceans.

Table 5-11. Concentrations of CDDs in Ambient Indoor and Outdoor Air in North America and Oceans

Site	Sampling year	CDD	Concentration (pg/m^3)	Reference
Binghampton, New York	1985	2,3,7,8-TCDD	0.23–0.47	Smith et al. 1986
Binghampton, New York	1985	Total TCDD	1.0–1.3	Smith et al. 1986
Chicago, Illinois (outdoor)	2004–2007	ΣCDDs/CDFs	1.3±0.10	Venier et al. 2009
Eagle Harbour, Michigan (outdoor)	2004–2007	ΣCDDs/CDFs	0.12±0.013	Venier et al. 2009
Sturgeon Point, New York	2004–2007	ΣCDDs/CDFs	0.74±0.083	Venier et al. 2009
Sleeping Bear Dunes, (outdoor) Michigan	2004–2007	ΣCDDs/CDFs	0.40±0.093	Venier et al. 2009
Calcasieu Parish, Louisiana outdoor)	2001–2002	ΣCDDs/CDFs	0.0027–0.0924	Gibbs et al. 2003
Minneapolis-St. Paul (outdoor, winter)	1988	2,3,7,8-TCDD	0.015–0.019	Reed et al. 1990
Minneapolis-St. Paul (outdoor, winter)	1988	Total HpCDD	0.5–4.1	Reed et al. 1990
Minneapolis-St. Paul (outdoor, winter)	1988	OCDD	0.74–8.2	Reed et al. 1990
Minneapolis-St. Paul (outdoor, summer)	1988	Total HpCDD	0.204–0.246	Reed et al. 1990
Minneapolis-St. Paul (outdoor, summer)	1988	OCDD	0.018–0.024	Reed et al. 1990
Bloomington, Iowa	1985–1988	Total TCDD	0.0013 (vapor) 0.0002 (particulate)	Eitzer and Hites 1989b
Bloomington, Iowa	1985–1988	Total PeCDD	0.026 (vapor) 0.013 (particulate)	Eitzer and Hites 1989b
Bloomington, Iowa	1985–1988	Total HxCDD	0.033 (vapor) 0.115 (particulate)	Eitzer and Hites 1989b

Table 5-11. Concentrations of CDDs in Ambient Indoor and Outdoor Air in North America and Oceans

Site	Sampling year	CDD	Concentration (pg/m^3)	Reference
Bloomington, Iowa	1985–1988	Total HpCDD	0.0058 (vapor) 0.065 (particulate)	Eitzer and Hites 1989b
Joint Base Balad in Iraq	2007	2,3,7,8-TCDD	0.06 (average all sites)	Masiol et al. 2016
Joint Base Balad in Iraq	2007	1,2,3,7,8-PeCDD	0.15 (average all sites)	Masiol et al. 2016
Joint Base Balad in Iraq	2007	1,2,3,4,7,8-HxCDD	0.12 (average all sites)	Masiol et al. 2016
Joint Base Balad in Iraq	2007	1,2,3,6,7,8-HxCDD	0.26 (average all sites)	Masiol et al. 2016
Joint Base Balad in Iraq	2007	1,2,3,7,8,9-HxCDD	0.48 (average all sites)	Masiol et al. 2016
Joint Base Balad in Iraq	2007	1,2,3,4,6,7,8-HpCDD	1.27 (average all sites)	Masiol et al. 2016
Joint Base Balad in Iraq	2007	OCDD	1.43 (average all sites)	Masiol et al. 2016
North Atlantic	2010–2011	ΣCDDs[a]	0.011 (gas) 0.0095 (aerosol)	Morales et al. 2014
South Atlantic	2010–2011	ΣCDDs[a]	0.013 (gas) 0.040 (aerosol)	Morales et al. 2014
Indian Ocean	2010–2011	ΣCDDs[a]	0.012 (gas) 0.023 (aerosol)	Morales et al. 2014
South Pacific	2010–2011	ΣCDDs[a]	0.0065 (gas) 0.010 (aerosol)	Morales et al. 2014
North Pacific	2010–2011	ΣCDDs[a]	0.012 (gas) 0.0081 (aerosol)	Morales et al. 2014
Global	2010–2011	ΣCDDs[a]	0.011 (gas) 0.020 (aerosol)	Morales et al. 2014

[a]Sum of TCDD, PeCDD, HxCDD, HpCDD, and OCDD congeners.

CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorodibenzofuran; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; OCDD = octachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin

Indoor household dust samples gathered by a vacuum cleaner from rooms with furniture treated with a wood-preserving formulation were analyzed for CDDs (Christmann et al. 1989). The wood-preserving formulation contained PCP, which was known to be contaminated with CDDs, particularly HxCDD, HpCDD, and OCDD. OCDD was the most abundant congener found in the dust samples at an average concentration of 191 µg/kg (ppb), followed by HpCDD (20 µg/kg), HxCDD (2.5 µg/kg), PeCDD (0.9 µg/kg), and TCDD (0.2 µg/kg) (Christmann et al. 1989).

Indoor air concentrations of CDD/CDFs were measured in kindergarten classrooms in West Germany to evaluate releases from wood preservatives (e.g., PCP) that may have been used in building materials (Päpke et al. 1989a). Measured indoor air concentrations of total CDDs/CDFs were 1.46–4.27 pg/m^3, while measured outdoor air concentrations were 0.61–78.97 pg/m^3. The 2,3,7,8-substituted congeners predominated with mean concentrations as follows: OCDD (131.5 pg/m^3), 1,2,3,4,6,7,8-HpCDD (77 pg/m^3), 1,2,3,4,6,7,8-HpCDF (51 pg/m^3), and OCDF (25.3 pg/m^3).

Measured indoor air samples collected in an office building in Binghamton, New York, 2 years after a fire in an electrical transformer that contained PCBs and tri- and tetrachlorobenzenes had concentrations of 2,3,7,8-TCDD ranging from 0.23 to 0.47 pg/m^3 (0.017–0.036 ppq) (Smith et al. 1986). The 2,3,7,8-TCDD isomer constituted 23–30% of the 1.0–1.3 pg/m^3 (0.076–0.099 ppq) total TCDDs. The limit of detection for these samples was approximately 0.003 pg/m^3 (Smith et al. 1986).

Background levels of CDDs in air were measured in a semi-rural location in Elk River, Minnesota, located about 25 miles northwest of Minneapolis-St. Paul (Reed et al. 1990). No major industrial or commercial activity occurred in the area at the time of the study. Ambient air samples were collected in the winter and summer of 1988. 2,3,7,8-TCDD was not detected in any of the ambient air samples taken in the summer (detection limits for 2,3,7,8-TCDD were 0.005–0.065 pg/m^3 [0.0004–0.0046 ppq]). 2,3,7,8-TCDD was noted in a wintertime sample at concentrations of 0.015 pg/m^3 (0.0011 ppq) and 0.019 pg/m^3 (0.0014 ppq). Detection limits in the remaining wintertime samples for 2,3,7,8-TCDD were 0.005–0.01 pg/m^3 (0.0004–0.0007 ppq). Wintertime CDD concentrations were greater than those observed for summertime. The study authors noted that this may be a result of increased numbers of combustion sources operating during the winter months. The wintertime CDD congener profile showed increasing concentrations with increasing chlorine substitutions. Average wintertime ambient air concentrations of HpCDD and OCDD were approximately 0.5–4.1 pg/m^3 (0.029–0.236 ppq) and 0.74–8.2 pg/m^3 (0.039–0.436 ppq), respectively (Reed et al. 1990). Average summertime ambient air concentrations of HpCDD and OCDD were approximately 0.204–0.246 pg/m^3 (0.011–0.014 ppq) and 0.018–0.024 pg/m^3 (0.001–0.0013 ppq), respectively (Reed et al. 1990). The study authors found that, in general, the more highly chlorinated congeners were present at higher concentrations than the less chlorinated congeners.

A long-term study (1985–1988) of CDDs in the ambient atmosphere of Bloomington, Indiana (a suburban area), was carried out to provide baseline data against which the impact of a future incinerator on local

CDD concentrations could be judged (Eitzer and Hites 1989b). Ambient air samples were analyzed for the presence of CDDs in both the particulate-bound phase and the vapor-phase forms. At the four sites sampled, the concentrations of CDDs (TCDD, PeCDD, HxCDD, HpCDD, and OCDD) increased with an increasing level of chlorination. All sites showed that the less chlorinated CDDs have a higher vapor-phase fraction than the more chlorinated CDDs. In addition, all sites showed OCDD to be the most abundant CDD, averaging from 0.44 to 0.69 pg/m^3 (0.023–0.032 ppq) (detection limit 0.001 pg/m^3 [$5.3x10^{-5}$ ppq]) (Eitzer and Hites 1989b). A seasonal effect was seen on the proportion of the total atmospheric burden present in the vapor phase. During the warm summer months, the total vapor-to-particle bound ratio was as great as 2, whereas in the winter, it was <0.5. At warm temperatures, most of the less chlorinated CDDs are found in the vapor phase, whereas at cooler temperatures more of the CDDs were associated with the particle phase (Eitzer and Hites 1989b).

An extensive multi-year monitoring program for CDDs/CDFs was conducted at eight sampling locations in the Los Angeles South Coast Air Basin from 1987 to 1989 (Hunt and Maisel 1992). The monitoring network, which monitored for both vapor and particulates, included several sites situated in residential areas as well as sites in the vicinity of suspected CDD/CDF sources. Monitoring results indicated that 2,3,7,8-TCDD was virtually undetected. The most commonly detected 2,3,7,8-substituted congener was OCDD followed by 1,2,3,4,6,7,8-HpCDD. The predominance of 1,2,3,4,6,7,8-HpCDD as the most persistent congener is associated with stationary or mobile combustion source emissions. 1,2,3,4,6,7,8-HpCDD was found at all seven sampling sessions at a mean concentration of 1.140 pg/m^3. OCDD also was found at all seven sampling sessions at a mean concentration of 2.883 pg/m^3. The mean total TCDD concentration was 0.114 pg/m^3 and was measured during only three sampling sessions (Hunt and Maisel 1992).

The concentrations of CDDs in the ambient air at several sites in metropolitan Dayton, Ohio, have been determined (Tiernan et al. 1989). No CDDs (TCDD, PeCDD, HxCDD, HpCDD, and OCDD) were found in rural regions, with average detection limits ranging from 0.03 pg/m^3 (TCDD) to 1.44 pg/m^3 (OCDD). The rural area was outside the impact zone of air pollutants from any regional industrial sources. CDDs in the industrialized regions appear to originate from a combination of sources, including municipal waste incinerators, motorized vehicles, and a polyvinyl chloride (PVC)-coated metal incinerator, the latter being a major source of these pollutants. Suburban/roadside area samples were taken at ground level at a distance of about 3 m from a street intersection through which approximately 60,000 cars passed each day. Other sampling sources were on the roofs of buildings in the downtown Dayton area, which lay in the emissions path from municipal solid-waste incinerators. TCDDs and PeCDDs (detection limits

0.01 and 0.03 pg/m^3, respectively) were not detected in the suburban/roadside area but were detected in the municipal waste-incinerator areas at 0.24 and 0.38 pg/m^3, respectively. HpCDD was detected in both the suburban/roadside areas and the municipal waste-incinerator areas at concentrations of 0.41 pg/m^3 (0.024 ppq) and 3.34 pg/m^3 (0.19 ppq), respectively. OCDD was also detected in the suburban/roadside areas (1.09 pg/m^3 [0.058 ppq]) and the municipal waste incinerator areas (4.69 pg/m^3 [0.25 ppq]). Concentrations of HxCDD were lower than HpCDD and OCDD, 0.05 pg/m^3 (0.003 ppq) in the suburban/roadside areas and 2.56 pg/m^3 (0.160 ppq) in the vicinity of the municipal waste incinerators (Tiernan et al. 1989).

Air samples were collected in Ohio in 1987 at an industrial area, an urban area downwind of a municipal incinerator, a high-traffic density area, and a rural area (Edgerton et al. 1989). No 2,3,7,8-TCDD was detected in any of the air samples with detection limits of <0.24 pg/m^3 (0.02 ppq) in any of the areas. The ambient concentrations of CDDs collected in the urban area were as follows: total HpCDD, 1.0–1.1 pg/m^3 (0.058–0.063 ppq); OCDD, 1.0–1.2 pg/m^3 (0.053–0.064 ppq); PeCDD, 0.1 pg/m^3 (0.03 pg/m^3); and total HxCDD, 0.6–0.63 pg/m^3 (0.038–0.039 ppq) (detection limit not specified). Concentrations of CDDs in the industrial area were: total HpCDD, 0.41–1.0 pg/m^3 (0.024–0.058 ppq), OCDD, 0.51–1.1 pg/m^3 (0.027–0.058 ppq), and total HxCDD, 0.43–0.78 pg/m^3 (0.027–0.049 ppq). Concentrations of total HpCDD, OCDD, and total HxCDD in the high-traffic density area were 0.56 pg/m^3 (0.032 ppq), 0.96 pg/m^3 (0.051 ppq), and 0.15 pg/m^3 (0.008 ppq), respectively. Ambient air concentrations of total HpCDD, OCDD, and total HxCDD in the rural area were 0.48 pg/m^3 (0.028 ppq), 0.5 pg/m^3 (0.027 ppq), and 0.33 pg/m^3 (0.021 ppq), respectively. PeCDD was not detected in the industrial, high-traffic, or rural areas (Edgerton et al. 1989).

Air monitoring at Windsor, Ontario, downwind of a proposed municipal solid-waste incinerator in Detroit, Michigan, between 1987 and 1988 found a mean total CDD concentration of 2.12 pg/m^3. A sampling station located in a rural area 30 miles away provided background total CDD concentrations of 0.51 mg/m^3. At both stations, the primary congeners were HpCDD and OCDD in the particulate phase, whereas TCDD and PeCDD were not detected in the vapor or particulate phases above the detection limit (Bobet et al. 1990).

In conclusion, most of the measurements of CDDs in air tend to be very close to current detection limits. CDDs are found at the greatest concentrations in particulate-phase urban air with OCDD being the most prevalent congener. Concentrations of all CDDs are highest in the air near industrial areas or other point sources such as open burn pits. Rural areas usually have very low or unquantifiable levels of all CDDs.

In urban and suburban areas, concentrations of CDDs may be greater during colder months of the year when furnaces and wood stoves are used for home heating.

5.5.2 Water

The Water Quality Portal is a tool of publicly available water-quality data from the U.S. Geological Survey (USGS), EPA, and over 400 state, federal, tribal, and local agencies. Data from 2020–2021 showed that no CDD congeners were detected in either surface water or groundwater measurements (WQP 2022). Typically, surface water levels of CDDs are near or below detection limits unless there is a nearby emission source.

Khairy and Lohmann (2020a, 2020b) measured levels of CDDs and CDFs in porewater at four locations in the lower Passaic River, New Jersey. Due to industrial activities, this area is historically known for its contamination with PCBs and CDDs/CDFs. The data from this study are summarized in Table 5-12. Porewater concentrations of CDDs (pg/L) at four locations of the lower Passaic River were obtained during four sampling periods.

Table 5-12. Porewater Concentrations of CDDs (pg/L) at Four Locations of the Lower Passaic River Obtained During Four Sampling Periods

Congener	06/2015–08/2015	08/2015–10/2015	10/2015–12/2015	12/2015–02/2016
River Bank Park, Lower Passaic River				
2-MCDD	<LOD	<LOD	<LOD	<LOD
2,7-/2,8-DCDD	5.36	4.92	4.24	4.87
1,2,4-TrCDD	0.21	0.27	0.26	0.29
1,3,6,8-TCDD	0.12	0.10	0.13	0.16
1,3,7,8-TCDD	<LOD	<LOD	<LOD	<LOD
2,3,7,8-TCDD	0.14	0.14	0.11	0.11
1,2,8,9-TCDD	<LOD	<LOD	<LOD	<LOD
1,2,3,4,7-PeCDD	<LOD	<LOD	<LOD	<LOD
1,2,3,4,7,8-HxCDD	<LOD	<LOD	<LOD	<LOD
1,2,3,6,7,8-HxCDD	0.03	0.03	0.04	0.03
1,2,3,7,8,9-HxCDD	<LOD	<LOD	<LOD	<LOD
1,2,3,4, 6,7,8-HpCDD	0.05	0.05	0.07	0.07
1,2,3,4,6,7,8,9-OCDD	0.11	0.11	0.09	0.10

Table 5-12. Porewater Concentrations of CDDs (pg/L) at Four Locations of the Lower Passaic River Obtained During Four Sampling Periods

Congener	06/2015–08/2015	08/2015–10/2015	10/2015–12/2015	12/2015–02/2016
Bridge Street, Passaic River				
2-MCDD	<LOD	<LOD	NA	NA
2,7-/2,8-DCDD	4.341	4.589	NA	NA
1,2,4-TrCDD	0.315	0.307	NA	NA
1,3,6,8-TCDD	0.098	0.096	NA	NA
1,3,7,8-TCDD	0.042	0.031	NA	NA
2,3,7,8-TCDD	0.150	0.161	NA	NA
1,2,8,9-TCDD	<LOD	<LOD	NA	NA
1,2,3,4,7-PeCDD	<LOD	<LOD	NA	NA
1,2,3,4,7,8-HxCDD	<LOD	<LOD	NA	NA
1,2,3,6,7,8-HxCDD	<LOD	<LOD	NA	NA
1,2,3,7,8,9-HxCDD	<LOD	<LOD	NA	NA
1,2,3,4,6,7,8-HpCDD	0.026	0.020	NA	NA
1,2,3,4,6,7,8,9-OCDD	0.017	0.019	NA	NA
Doremus Street, Passaic River				
2-MCDD	<LOD	<LOD	<LOD	<LOD
2,7-/2,8-DCDD	6.38	5.74	5.47	4.68
1,2,4-TrCDD	0.234	0.262	0.277	0.230
1,3,6,8-TCDD	0.113	0.108	0.134	0.135
1,3,7,8-TCDD	<LOD	<LOD	<LOD	<LOD
2,3,7,8-TCDD	0.146	0.156	0.139	0.115
1,2,8,9-TCDD	<LOD	<LOD	<LOD	<LOD
1,2,3,4,7,8-HxCDD	<LOD	<LOD	<LOD	<LOD
1,2,3,6,7,8-HxCDD	<LOD	<LOD	<LOD	<LOD
1,2,3,7,8,9-HxCDD	<LOD	<LOD	<LOD	<LOD
1,2,3,4,6,7,8-HpCDD	0.023	0.031	0.028	0.032
1,2,3,4,6,7,8,9-OCDD	0.020	0.024	0.024	0.026
Passaic Ave, Passaic River				
2-MCDD	<LOD	<LOD	<LOD	<LOD
2,7-/2,8-DCDD	8.36	7.48	5.90	5.93
1,2,4-TrCDD	0.28	0.23	0.19	0.23
1,3,6,8-TCDD	0.14	0.13	0.10	0.09
1,3,7,8-TCDD	0.07	0.07	0.07	0.07
2,3,7,8-TCDD	0.15	0.15	0.12	0.11
1,2,8,9-TCDD	<LOD	<LOD	<LOD	<LOD
1,2,3,4,7,8-HxCDD	<LOD	<LOD	<LOD	<LOD
1,2,3,6,7,8-HxCDD	<LOD	<LOD	<LOD	<LOD
1,2,3,7,8,9-HxCDD	<LOD	<LOD	<LOD	<LOD

Table 5-12. Porewater Concentrations of CDDs (pg/L) at Four Locations of the Lower Passaic River Obtained During Four Sampling Periods

Congener	06/2015–08/2015	08/2015–10/2015	10/2015–12/2015	12/2015–02/2016
1,2,3,4,6,7,8-HpCDD	0.05	0.05	0.04	0.03
1,2,3,4,6,7,8,9-OCDD	0.03	0.03	0.03	0.03

CDD = chlorinated dibenzo-*p*-dioxin; DCDD = dichlorodibenzo-*p*-dioxin; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; LOD = limit of detection; MCDD = monochlorodibenzo-*p*-dioxin; NA = not applicable; OCDD = octachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin; TrCDD = trichlorodibenzo-*p*-dioxin

Source: Khairy and Lohmann 2020b

A second monitoring study in the vicinity of the Passaic River and Newark Bay New Jersey from May 2008 to August 2009, measured mono- to octaCDD congeners in surface and bottom waters (Friedman et al. 2012). Measured concentrations were generally low with the highest measured concentration observed for the 2,7-/2,8-DCDD congeners, which were ≤20 pg/L. Dissolved concentrations for most congeners did not vary between location, depth, or sampling period. The maximum 2,3,7,8-TCDD concentration was 0.023 pg/L and OCDD was never detected. Previous monitoring results from the late 1990s to early 2000s observed levels of 2,3,7,8-TCDD ranging from 0.036 to 0.120 pg/L and OCDD concentrations ranging from 0.200 to 0.350 pg/L.

Precipitation samples collected in a rural location (Dorset, Ontario) over an 8-month period between 1986 and 1987 were analyzed for CDDs (Tashiro et al. 1989a, 1989b). No TCDDs were found in any samples at detection limits of 4–30 ppq (pg/L). OCDD concentrations were found in three samples in the 60–1,200 ppq (pg/L) range. Lower concentrations of HpCDD (70 ppq [pg/L]) were also found (Tashiro et al. 1989a). Precipitation samples were also collected in 1987–1988 in urban and rural locations in Canada (Tashiro et al. 1989b). Varying levels of OCDD were detected throughout the sampling period, mainly at the rural location. OCDD was the only CDD detected at the rural site. OCDD concentrations ranged from 35 to 230 ppq, with the median value being slightly below 100 ppq. No seasonal pattern of OCDD concentrations was observed. OCDD was detected in only two of the urban precipitation samples at concentrations of 33 and 15 ppq (pg/L) (Tashiro et al. 1989b). Rain collected at Bloomington, Indiana, between June 1987 and July 1988 showed low concentrations of total CDDs, although OCDD was the most prominent congener in all samples at concentrations ranging from below the detection limit of 0.1–220 pg/L. Total TCDD was detected in only 3 of 28 samples at concentrations <9 pg/L (EPA 1991c).

Lin et al. (2010) studied concentrations of CDDs and CDFs in drinking water in Taiwan to better understand how atmospheric deposition influence these concentrations. Tap water levels (averaged at three different plants) in pg/L were as follows: 2,3,7,8-TCDD, 0.0001–0.005; 1,2,3,7,8-PeCDD, 0.0002–0.0006; 1,2,3,7,8-PeCDD, 0.0001–0.0006; 1,2,3,7,8-PeCDD, 0.0002–0.0013; 1,2,3,7,8,9-HxCDD, 0.0002–0.0010; 1,2,3,4,6,7,8-HpCDD, 0.0022- 0.0088; and OCDD, 0.0139–0.0416. The study authors found tap water levels for total CDDs/CDFs to be approximately 55% less than levels in source water and that atmospheric deposition to uncovered water treatment facilities likely increased the levels in finished water.

During 1986, a survey of 20 community water systems throughout the state of New York was conducted to evaluate CDD/CDF concentrations (Meyer et al. 1989). The sampling sites selected were representative of major surface water sources in the state used to obtain drinking water. The sites included surface water sources receiving industrial discharges and those known to contain CDD-contaminated fish, as well as water sources from more remote areas. Raw water sampled at the Lockport, New York, facility contained concentrations of TCDDs (1.7 ppq [pg/L]) as well as concentrations of TCDFs to OCDFs (18, 27, 85, 210, and 230 ppq [pg/L], respectively). These data show that the CDF congener group concentrations increased with increasing chlorine numbers. TCDFs were also detected in finished water sampled at the Lockport facility (duplicate samples contained 2.1 and 2.6 ppq). Except for a trace of OCDF detected at one other location, no other CDDs/CDFs were detected in finished water at any of the other 19 community water systems surveyed.

Groundwater in the vicinity of an abandoned wood treatment facility was sampled from monitoring wells constructed at depths of 6.1–30.5 m and was analyzed for CDDs in January 1984 (Pereira et al. 1985). Concentrations of HxCDD, HpCDD, and OCDD in groundwater samples taken from wells at a depth of 6.1 m were 61, 1,500, and 3,900 ppt, (61,000, 1,500,000, and 3,900,00 pg/L), respectively. The study authors noted that the high concentrations of CDDs in the sample from a depth of 6.1 m probably resulted from the presence of microemulsions of oil that were difficult to separate from the sample. Groundwater samples collected from deeper wells (12.2–30.5 m) contained HxCDD, HpCDD, and OCDD at concentration ranges of not detected to 21 ppt (21,000 pg/L), not detected to 34 ppt (34,000 pg/L), and not detected to 539 ppt (539,000 pg/L), respectively (Pereira et al. 1985).

In conclusion, CDDs are rarely detected in drinking water at ppq levels or higher. Raw water samples generally have higher concentrations of CDDs than finished drinking water samples because conventional water treatment processes remove the CDDs along with the particulates from raw water. In groundwater

samples collected near industrial sites, CDDs have been detected at concentrations up to 3,900 ppt (3,900,000 pg/L).

5.5.3 Sediment and Soil

Following the train derailment and subsequent fire that occurred February 3, 2023, in East Palestine, Ohio, testing began on soil samples collected in the affected area at various sampling depths. Sampling data from March of 2023 showed soil levels of CDD congeners often >1,000 ppt. Comprehensive data are available from the EPA website: https://www.epa.gov/east-palestine-oh-train-derailment/epa-residential-commercial-and-agricultural-soil-sampling#summary. Table 5-13 shows residential, commercial, and agricultural soil sampling data collected by Norfolk Southern for a surface soil (depth 0.0–0.1 feet) on March 12, 2023 (EPA 2023).

Table 5-13. CDD Levels in a Soil Sample Taken from a Sampling Location in East Palestine, Ohio, March 12, 2023

CDD congener	Soil levels ppt (pg/g)
1,2,3,4,6,7,8-HpCDD	2,600
1,2,3,4,7,8-HxCDD	37
1,2,3,6,7,8-HxCDD	99
1,2,3,7,8,9-HxCDD	62
1,2,3,7,8-PeCDD	17
2,3,7,8-TCDD	2.3
OCDD	27,000

CDD = chlorinated dibenzo-*p*-dioxin; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; LOD = limit of detection; NA = not applicable; OCDD = octachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin

Source: EPA 2023

As part of a National Dioxin Study, EPA conducted a 2-year nationwide monitoring program to assess the extent of 2,3,7,8-TCDD contamination (EPA 1987c). Environmental samples (including soil, sediment, water, and fish) were analyzed for 2,3,7,8-TCDD concentrations at seven different tiers of sites (including NPL, various industrial, urban, and pristine rural sites). Soil concentrations at most of the Tier 1 and 2 sites (i.e., sites classified as or expected to be classified as NPL sites) were in the ppb range, although at a few of the sites where 2,4,5-TCP production waste storage or disposal occurred, concentrations were as high as 2,000 ppm (2×10^9 ppt). Offsite soil contamination of concern (in the ppb range) was confirmed at 7 of these 100 Tier 1 and 2 sites. At 11 of 64 Tier 3 sites (facilities and associated disposal sites where

2,4,5-TCP and its derivatives were formulated into pesticide products), soil concentrations exceeded 1 ppb, but in 7 of the 11 sites where contamination was found, only 1 or 2 samples exceeded 1 ppb. At 15 of 26 Tier 5 sites (areas where 2,4,5-TCP and other pesticide derivatives had been or were currently being used), soil concentrations were generally >1 ppt with one detection at 6 ppb (6,000 ppt). Two-thirds of all detections at the Tier 5 sites were <5 ppt. At 3 of 18 Tier 6 sites (organic chemical and pesticide manufacturing facilities where production processes could have resulted in 2,3,7,8-TCDD being introduced into the waste streams), soil concentrations exceeded the 1 ppt detection limit, although these concentrations were limited to one or two samples per site. In general, 2,3,7,8-TCDD was detected infrequently and at very low concentrations in background soil samples taken at sites (urban and rural areas) that did not have previously known sources of 2,3,7,8-TCDD contamination (1 ppt detection limit). Only 17 of 221 urban sites and 1 of 138 rural sites in Tier 7 (background sites not expected to have contamination) had detectable levels of 2,3,7,8-TCDD, with 11.2 ppt being the highest concentration reported (Des Rosiers 1987; EPA 1987c).

Background levels of CDDs in soil were measured at Elk River, Minnesota, a semi-rural area located about 25 miles northwest of Minneapolis-St. Paul (Reed et al. 1990). No major industrial or commercial activity occurred in the area at the time of the study. The soil data reflected generally low background concentrations of CDDs. 2,3,7,8-TCDD, total TCDD, and PeCDD were not detected (detection limit range 0.75–2.9 ppt). OCDD represented the highest baseline levels, ranging from 340 to 3,300 ppt. Levels of total HpCDD were 62–640 ppt, while levels of total HxCDD were 12–99 ppt (Reed et al. 1990).

Birmingham (1990) analyzed soil samples from industrial, urban, and rural sites in Ontario, Canada, and some Midwestern U.S. states for CDDs and CDFs. The concentrations of CDD/CDF in rural soils were generally not detectable, although HpCDDs and OCDD were found in a few samples. In urban soils, the tetra- through octa-congener groups were measured for both CDDs and CDFs. The HpCDDs and OCDD dominated the homologue profile and were 2 orders of magnitude greater than concentrations in rural soils. These urban soils also contained measurable quantities of TCDDs, PeCDDs, and HxCDDs. Industrial soils did not contain any TCDDs or PeCDDs, but they did contain the highest concentrations of the HpCDDs, OCDD, TCDFs, HpCDFs, and OCDFs. In an earlier study, soil concentrations of 2,3,7,8-TCDD were measured in industrialized areas of a group of mid-western and mid-Atlantic states (Illinois, Michigan, New York, Ohio, Pennsylvania, Tennessee, Virginia, and West Virginia) (see Table 5-14) (Nestrick et al. 1986). Many of the samples were taken within 1 mile of major steel, automotive, or chemical manufacturing facilities or of municipal solid-waste incinerators. The data show that in these typical industrialized areas, 2,3,7,8-TCDD soil concentrations are below 0.01 ppb (range, not

detected to 9.4 ppt). The widespread occurrence of 2,3,7,8-TCDD in U.S. urban soils at levels of 0.001–0.01 ppb suggests that local combustion sources, including industrial and municipal waste incinerators, are the probable sources of the trace 2,3,7,8-TCDD soil concentrations found in those locations (Nestrick et al. 1986). Soil samples collected in the vicinity of a sewage sludge incinerator were compared with soil samples from rural and urban sites in Ontario, Canada (Pearson et al. 1990). Soil in the vicinity of the incinerator showed a general increase in CDD concentration with increasing degrees of chlorination. Of the CDFs measured, only OCDF was detected (mean concentration, 43 ppt). Rural woodlot soil samples contained only OCDD (mean concentration, 30 ppt). Soil samples from undisturbed urban parkland revealed only concentrations of HpCDDs and OCDD, but all CDF congener groups from TCDF to OCDF were present. The parkland samples showed an increase in concentrations from the HpCDDs to OCDD and PeCDFs to OCDF. The TCDFs were found at the highest concentration (mean, 29 ppt) of all the CDF congener groups.

Table 5-14. 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) Levels Measured in Soil Samples Collected in 1984 from Industrialized Areas of U.S. Cities

Sample location	2,3,7,8-TCDD (ppt)
Lansing, Michigan	3 (0.7)[a] ND (0.8)
Gaylord, Michigan	ND (0.2)
Detroit, Michigan	3.6 (0.7) 2.1 (0.4)
Chicago, Illinois	9.4
Middletown, Ohio	ND (0.3) ND (0.3)
Barberton, Ohio	5.6
Akron, Ohio	6.3
Nashville, Tennessee	0.8 (0.3)
Pittsburgh, Pennsylvania	2.6 (0.5)
Marcus Hook, Pennsylvania	0.4 (0.3)
Philadelphia, Pennsylvania	0.9 (0.3)
Clifton Heights, Pennsylvania	ND (0.4)
Brooklyn, New York	2.6 (0.4)
South Charleston, West Virginia	ND (0.4)

Table 5-14. 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) Levels Measured in Soil Samples Collected in 1984 from Industrialized Areas of U.S. Cities

Sample location	2,3,7,8-TCDD (ppt)
Arlington, Virginia	ND (0.4)
Newport News, Virginia	0.4 (0.3)

[a]Values in parentheses show the detection limit, 2.5 times noise, when the experimental result is <10 times the measured detection limit.

ND = not detected; ppt = parts per trillion

Source: Nestrick et al. 1986

In conclusion, soil concentrations of CDDs are typically higher in urban areas than in rural areas. Soil concentrations associated with industrial sites are clearly the highest, with CDD levels ranging from the hundreds to thousands of ppt. In general, as the degree of chlorination increases, the concentrations increase. HpCDD and OCDD congeners are generally found at higher concentrations in soil and sediments than the TCDD, PeCDD, and HxCDD congeners.

Levels of CDD congeners were monitored in sediment at four locations in the lower Passaic River, New Jersey during a monitoring study conducted in July 2015 (Khairy and Lohmann 2020a, 2020b). Due to industrial activities, this area is historically known for its contamination with PCBs and CDDs/CDFs. Ranges of values in ppt (pg/g) were reported as: 2-MCDD <LOD–2.0; 2,7,2,8-DCDD 38.5–308; 1,2,4-TtrCDD 5.3–29.0; 1,3,6,8-TCDD 1.9–39.2; 1,3,7,8-TCDD, 2.2–8.9; 2,3,7,8-TCDD 43.7–170.7; 1,2,3,4,7-PeCDD 0.9–2.8; 1,2,3,4,7,8-HxCDD 6.9–18.0; 1,2,3,6,7,8-HxCDD <LOD–38.2; 1,2,3,7,8,9-HxCDD 3.1–6.6; 1,2,3,4,6,7,8-HpCDD 92.0–229.3; and 1,2,3,4,6,7,8,9-OCDD 1,100.1–2,792.1.

Sediment samples collected in 1985–1986 from estuarine areas (Passaic River and Newark Bay), near a Newark, New Jersey, facility that manufactured 2,4,5-T between 1948 and 1969, contained high concentrations of 2,3,7,8-TCDD and OCDD (Bopp et al. 1991). Concentrations of OCDD in the sediment were many times higher than concentrations of 2,3,7,8-TCDD. The study indicated that there probably was a significant regional source (i.e., combustion and/or use of the wood preservative, PCP) for OCDD, a source that is lacking in significant concentrations of 2,3,7,8-TCDD relative to the local industrial source. A high correlation was found between 2,3,7,8-TCDD and 2,3,7,8-TCDF concentrations. Sediment core samples from a depth of 108–111 cm contained 2,3,7,8-TCDD at a concentration of 21,000 ppt, the highest concentration measured in the study. This residue value

corresponds to deposition of sediments that occurred during the late 1950s to early 1960s during active 2,4,5-T production at the industrial site. Maximum concentrations of TCDD in the sediment cores corresponded to the period of maximum 2,4,5-T production, with more recently deposited sediments containing lower concentrations of TCDD. This study established the persistence of 2,3,7,8-TCDD and 2,3,7,8-TCDF in anaerobic sediments on a time scale of several decades (Bopp et al. 1991).

Ehrlich et al. (1994) identified the relative contributions of various sources of CDDs/CDFs to deposited sediments of Newark Bay using polytopic vector analysis, a multivariate statistical technique, and monitoring data collected from 1991 to 1993 at 62 sampling locations. The study authors also concluded that the 2,3,7,8-substituted CDD/CDF patterns in the sediments of Newark Bay are consistent with discharges from multiple sources. Huntley et al. (1997) reported that combined sewer overflows may contribute substantially to surface sediment contamination of the nearby Passaic River. Several such sources that have existed over the past century in the vicinity include scrap metal refineries, pulp and paper mills, copper smelters, chemical manufacturing plants, municipal sewage treatment plants, and industrial/municipal incinerators (EPA 1987c). 2,3,7,8-TCDD sediment concentrations ranged from below the detection limit (22 ppt) to 21,000 ppt, whereas OCDD concentrations were 3.1–42,000 ppt, although other sources of OCDD were thought to contribute to the elevated levels of OCDD (Bopp et al. 1991; Wenning et al. 1992). Maximum levels of CDDs from this monitoring study conducted from December 1991 to March 1993 are approximately an order of magnitude greater than the levels reported by Khairy and Lohmann (2020a, 2020b) during a monitoring study conducted in 2015.

Highly stratified sediments from Green Lake in upstate New York had CDD concentrations that could be correlated with atmospheric deposition. CDDs could be detected as far back as 1860–1865 at a total CDD concentration of 7 ppt; 98% of all CDDs detected were OCDD. The CDD sediment profile showed a strong increase after 1923 and continued to increase until 1984 (the last year analyzed), with a maximum concentration of >900 ppt, of which 75% was OCDD (Smith et al. 1992).

In another study, surficial (surface) sediment samples taken from the Saginaw River and Bay and from southern Lake Huron showed that CDDs are ubiquitous in the samples studied, including the most remote locations (Czuczwa and Hites 1984). The concentrations were highest in those sediments collected closest to urban areas and lowest in open-lake cores. This indicates that the most of the CDDs found in these samples are anthropogenic in origin (Czuczwa and Hites 1984). The CDDs found closest to urban areas may be related to point source industrial inputs as well as atmospheric deposition, while CDDs found at the remote sites are likely to be only atmospheric in origin. In dated sediment cores, CDDs were

absent before 1940. Thus, the study authors suggested that accumulation of CDDs in the environment is a recent phenomenon and is related to industrial activities (Czuczwa and Hites 1986a, 1986b). Surface sediments taken from the Great Lakes showed that CDDs were ubiquitous in the sediments. OCDD was predominant at concentrations of 560–4,800 ppt (dry weight) (Czuczwa and Hites 1986a, 1986b). The sediments also contained relatively high concentrations of HpCDD. The less chlorinated CDDs were not found in the sediments (Czuczwa and Hites 1986a). Sediment samples were collected from five sampling stations in the western basin of Lake Ontario near the mouth of the Niagara River and were analyzed for 2,3,7,8-TCDD (Onuska et al. 1983). Measurable quantities of 2,3,7,8-TCDD were present in sediment at two of the stations. The highest concentration of 2,3,7,8-TCDD (13 ppt) was found at a depth of 3–5 cm, followed by a concentration of 4 ppt at a depth of 3 cm, and 3 ppt at a depth of 13–14 cm. Concentrations of 2,3,7,8-TCDD in the rest of the sediment samples were below the detection limit (0.1 ppt) (Onuska et al. 1983).

Surficial sediments collected from Jackfish Bay on the north shore of Lake Superior, near a pulp and paper manufacturer, contained moderate concentrations of TCDFs (range of geometric mean, 2.4–6,223 ppt) and OCDD (range of geometric mean, 12–250 ppt) congeners, with trace (<60 ppt) concentrations of other congeners (Sherman et al. 1990). The OCDF and OCDD profile for a sediment core collected from Moberly Bay was similar to the surficial sediment pattern. These congener groups predominated at all sediment depths where detectable concentrations occurred. Low concentrations of the HpCDD, PeCDF, and HpCDF congeners also were detected. The concentration profile of the HpCDF congener group showed a relatively high value that dropped abruptly to nondetectable (<60 ppt) below a sediment depth of 10 cm. This abrupt change corresponded to a date of 1973 that reflected an operational change at the pulp mill.

Biosolids obtained from wastewater or sewage treatment facilities are applied to agricultural lands to add nutrients to the soils used for commercial farming applications. CDDs were detected in biosolids collected in 32 U.S. states and the District of Columbia from 94 wastewater treatment plants by the EPA in its 2001 national sewage sludge survey (EPA 2007b). Minimum levels of CDDs ranged from about 0.1 (2,3,7,8-TCDD) to 1 ng/kg (OCDD).

In conclusion, CDD congener profiles in sediment generally reflect those exhibited by the contamination source or sources. High concentrations of HxCDDs, HpCDDs, and OCDDs in sediment are usually the result of anthropogenic inputs via industrial processes and releases or urban runoff, and concentrations

generally increase with the degree of chlorination, but decrease with distance from the source (McKee et al. 1990).

5.5.4 Other Media

Foods. The FDA conducted limited analyses for the higher chlorinated CDDs (HxCDD, HpCDD, and OCDD) in market-basket samples collected from 1979 to 1984 under the FDA's Total Diet Program (Firestone et al. 1986). Food samples found to contain PCP residues >0.05 μg/g (ppm) were analyzed for 1,2,3,4,6,7,8-HpCDD and OCDD. In addition, selected samples of ground beef, chicken, pork, and eggs from the market-basket survey were analyzed for these CDD congeners (wet weight basis), regardless of the results of the PCP analysis. HxCDD was not found in any of the foods sampled; however, the detection limit (10–40 pg/g [ppt]) was very high. Generally low concentrations (<300 pg/g [ppt]) of HpCDD and OCDD were found in bacon, chicken, pork chops, and beef liver. Several beef livers had higher concentrations of OCDD residues (614–3,830 pg/g), and one beef liver contained 428 pg/g (ppt) of HpCDD. HxCDD, HpCDD, and OCDD were not detected in milk, ground beef, or seafood samples, but the detection limits (10–40 ppt) were very high. No CDDs were found in 17 egg samples collected in various parts of the United States. OCDD was detected in 2 of 18 pork samples (27 ppt and 53 ppt) and in 2 of 16 chicken samples (29 ppt and 76 ppt). One chicken sample with PCP residues (>0.05 μg/g) contained concentrations of 1,2,3,4,6,7,8-HpCDD (28 ppt) and OCDD (252 ppt). The CDD residues (21–1,610 pg/g) in eggs from Houston, Texas, and Mena, Arkansas, with PCP residues >0.05 μg/g collected in 1982 and 1983–1984, respectively, contained 1,2,3,4,6,7,8-HpCDD concentrations of 21–588 ppt and OCDD concentrations of 80–1,610 ppt. These residues were attributed to local PCP contamination problems in these areas (Firestone et al. 1986). Milk samples contaminated with PCP at levels of 0.01–0.05 μg/g PCP contained no detectable CDDs.

The most recent FDA market basket analysis for CDDs and CDFs was the 2004 study in which more than 200 different food types were collected and analyzed for 17 different CDD or CDF congeners obtained from commercial supermarkets located in Boston, Massachusetts; Syracuse, New York; and Pittsburgh, Pennsylvania (FDA 2006). The entire data set for the years 2000–2004 may be obtained from the FDA website at: https://www.fda.gov/food/process-contaminants-food/dioxin-analysis-resultsexposure-estimates. The highest detected level was for OCDD (65 pg/g) in a sample of liver (beef/calf), which is orders of magnitude lower than OCDD residues in beef livers from previous surveys. The entire data output for any given year is too large to be reproduced in this document; however, results for food items

collected in the 2004 market basket survey in which there was a specific detected amount are provided in Table 5-15 (FDA 2007).

Table 5-15. Detections of CDD Congeners in Food Items from the 2004 FDA Market Basket Survey

Product description	Congener description	Amount found (pg/g [ppt])	LOD (pg/g [ppt])
Liver (beef/calf), pan-cooked with oil	1,2,3,4,6,7,8-HpCDD	6.8	0.006
Beef roast, chuck, oven-roasted	1,2,3,4,6,7,8-HpCDD	5.1	0.003
Frankfurter (beef/pork), boiled	1,2,3,4,6,7,8-HpCDD	2.9	0.003
Beef, ground, regular, pan-cooked	1,2,3,4,6,7,8-HpCDD	2.3	0.002
Mushrooms, raw	1,2,3,4,6,7,8-HpCDD	2	0.009
Salami, luncheon-meat type (not hard)	1,2,3,4,6,7,8-HpCDD	1.3	0.001
Catfish, pan-cooked with oil	1,2,3,4,6,7,8-HpCDD	1.3	0.005
Meatloaf, beef, homemade	1,2,3,4,6,7,8-HpCDD	1.2	0.001
Butter, regular (salted)	1,2,3,4,6,7,8-HpCDD	1.2	0.003
Beef steak, loin/sirloin, broiled	1,2,3,4,6,7,8-HpCDD	1	0.001
Burrito with beef, beans, and cheese, from Mexican carry-out	1,2,3,4,6,7,8-HpCDD	0.92	0.001
Chili con carne with beans, canned	1,2,3,4,6,7,8-HpCDD	0.86	0.002
Cream cheese	1,2,3,4,6,7,8-HpCDD	0.78	0.0043
Cheese, cheddar, natural (sharp/mild)	1,2,3,4,6,7,8-HpCDD	0.75	0.002
Baby food, vegetables and beef	1,2,3,4,6,7,8-HpCDD	0.74	0.003
Pork sausage (link/patty), oven-cooked	1,2,3,4,6,7,8-HpCDD	0.68	0.002
Quarter-pound hamburger on bun, fast-food	1,2,3,4,6,7,8-HpCDD	0.61	0.001
Quarter-pound cheeseburger on bun, fast-food	1,2,3,4,6,7,8-HpCDD	0.52	0.003
Cheese, Swiss, natural	1,2,3,4,6,7,8-HpCDD	0.49	0.003
Green beans, canned	1,2,3,4,6,7,8-HpCDD	0.47	0.006
Margarine, regular (salted)	1,2,3,4,6,7,8-HpCDD	0.47	0.002
Cheese, American, processed	1,2,3,4,6,7,8-HpCDD	0.43	0.002
Baby food, turkey and rice	1,2,3,4,6,7,8-HpCDD	0.43	0.003
Taco/tostada with beef and cheese, from Mexican carry-out	1,2,3,4,6,7,8-HpCDD	0.42	0.004

Table 5-15. Detections of CDD Congeners in Food Items from the 2004 FDA Market Basket Survey

Product description	Congener description	Amount found (pg/g [ppt])	LOD (pg/g [ppt])
Bologna (beef/pork)	1,2,3,4,6,7,8-HpCDD	0.41	0.001
Spaghetti with meat sauce, homemade	1,2,3,4,6,7,8-HpCDD	0.4	0.001
Chicken with vegetables in sauce, from Chinese carry-out	1,2,3,4,6,7,8-HpCDD	0.4	0.001
Refried beans, canned	1,2,3,4,6,7,8-HpCDD	0.39	0.001
Green beans, fresh/frozen, boiled	1,2,3,4,6,7,8-HpCDD	0.38	0.003
Lettuce, leaf, raw	1,2,3,4,6,7,8-HpCDD	0.38	0.002
Baby food, chicken noodle dinner	1,2,3,4,6,7,8-HpCDD	0.36	0.004
Carrot, baby, raw	1,2,3,4,6,7,8-HpCDD	0.33	0.002
Vegetable oil	1,2,3,4,6,7,8-HpCDD	0.31	0.008
Sour cream	1,2,3,4,6,7,8-HpCDD	0.3	0.001
Pizza, cheese and pepperoni, regular crust, from pizza carry-out	1,2,3,4,6,7,8-HpCDD	0.29	0.002
Spinach, fresh/frozen, boiled	1,2,3,4,6,7,8-HpCDD	0.28	0.009
Potato, mashed, prepared from fresh	1,2,3,4,6,7,8-HpCDD	0.26	0.001
Broccoli, fresh/frozen, boiled	1,2,3,4,6,7,8-HpCDD	0.25	0.003
Summer squash, fresh/frozen, boiled	1,2,3,4,6,7,8-HpCDD	0.23	0.004
Beets, canned	1,2,3,4,6,7,8-HpCDD	0.23	0.001
Beef and vegetable stew, canned	1,2,3,4,6,7,8-HpCDD	0.22	0.005
Mayonnaise, regular, bottled	1,2,3,4,6,7,8-HpCDD	0.21	0.003
Corn, canned	1,2,3,4,6,7,8-HpCDD	0.2	0.001
Eggs, scrambled with oil	1,2,3,4,6,7,8-HpCDD	0.19	0.002
Ice cream, regular, vanilla	1,2,3,4,6,7,8-HpCDD	0.19	0.001
Sour cream dip, any flavor	1,2,3,4,6,7,8-HpCDD	0.19	0.001
Salad dressing, creamy/buttermilk type, regular	1,2,3,4,6,7,8-HpCDD	0.19	0.001
Sweet roll/Danish pastry	1,2,3,4,6,7,8-HpCDD	0.18	0.002
Baby food, cereal, barley, dry, prepared with water	1,2,3,4,6,7,8-HpCDD	0.18	0.002
Half and half cream	1,2,3,4,6,7,8-HpCDD	0.17	0.001
Baby food, mixed vegetables	1,2,3,4,6,7,8-HpCDD	0.17	0.005
Sweet potatoes, canned	1,2,3,4,6,7,8-HpCDD	0.17	0.001
Milk shake, chocolate, fast-food	1,2,3,4,6,7,8-HpCDD	0.16	0.001

Table 5-15. Detections of CDD Congeners in Food Items from the 2004 FDA Market Basket Survey

Product description	Congener description	Amount found (pg/g [ppt])	LOD (pg/g [ppt])
Eggs, boiled	1,2,3,4,6,7,8-HpCDD	0.16	0.001
Sandwich cookies with creme filling	1,2,3,4,6,7,8-HpCDD	0.16	0.004
Candy bar, milk chocolate, plain	1,2,3,4,6,7,8-HpCDD	0.16	0.001
Pork chop, pan-cooked with oil	1,2,3,4,6,7,8-HpCDD	0.14	0.002
Peanut butter, creamy	1,2,3,4,6,7,8-HpCDD	0.14	0.002
Cornbread, homemade	1,2,3,4,6,7,8-HpCDD	0.14	0.003
Pumpkin pie, fresh/frozen	1,2,3,4,6,7,8-HpCDD	0.14	0.004
Mixed vegetables, frozen, boiled	1,2,3,4,6,7,8-HpCDD	0.14	0.001
Doughnut, cake-type, any flavor	1,2,3,4,6,7,8-HpCDD	0.14	0.003
White beans, dry, boiled	1,2,3,4,6,7,8-HpCDD	0.14	0.002
Brownie	1,2,3,4,6,7,8-HpCDD	0.13	0.005
Pork and beans, canned	1,2,3,4,6,7,8-HpCDD	0.12	0.003
Ice cream, light, vanilla	1,2,3,4,6,7,8-HpCDD	0.099	0.001
Baby food, macaroni, tomato, and beef	1,2,3,4,6,7,8-HpCDD	0.096	0.001
Soup, Oriental noodles (ramen noodles), prepared with water	1,2,3,4,6,7,8-HpCDD	0.087	0.006
Milk, whole, fluid	1,2,3,4,6,7,8-HpCDD	0.084	0.001
Sugar cookies	1,2,3,4,6,7,8-HpCDD	0.082	0.004
Chocolate chip cookies	1,2,3,4,6,7,8-HpCDD	0.081	0.002
Potato chips	1,2,3,4,6,7,8-HpCDD	0.077	0.004
Infant formula, milk-based, high iron, ready to feed	1,2,3,4,6,7,8-HpCDD	0.071	0.001
Soup, bean with bacon/pork, canned, condensed, prepared with water	1,2,3,4,6,7,8-HpCDD	0.057	0.002
Bread, whole wheat	1,2,3,4,6,7,8-HpCDD	0.035	0.001
Bread, white, enriched	1,2,3,4,6,7,8-HpCDD	0.032	0.002
Frankfurter (beef/pork), boiled	1,2,3,6,7,8-HxCDD	0.69	0.002
Beef roast, chuck, oven-roasted	1,2,3,6,7,8-HxCDD	0.59	0.003
Butter, regular (salted)	1,2,3,6,7,8-HxCDD	0.51	0.003
Beef, ground, regular, pan-cooked	1,2,3,6,7,8-HxCDD	0.34	0.002
Cream cheese	1,2,3,6,7,8-HxCDD	0.32	0.0021
Mushrooms, raw	1,2,3,6,7,8-HxCDD	0.27	0.009
Meatloaf, beef, homemade	1,2,3,6,7,8-HxCDD	0.26	0.001

Table 5-15. Detections of CDD Congeners in Food Items from the 2004 FDA Market Basket Survey

Product description	Congener description	Amount found (pg/g [ppt])	LOD (pg/g [ppt])
Beef steak, loin/sirloin, broiled	1,2,3,6,7,8-HxCDD	0.247	0.001
Cheese, cheddar, natural (sharp/mild)	1,2,3,6,7,8-HxCDD	0.23	0.002
Liver (beef/calf), pan-cooked with oil	1,2,3,6,7,8-HxCDD	0.22	0.002
Salami, luncheon-meat type (not hard)	1,2,3,6,7,8-HxCDD	0.22	0.001
Catfish, pan-cooked with oil	1,2,3,6,7,8-HxCDD	0.21	0.003
Cheese, Swiss, natural	1,2,3,6,7,8-HxCDD	0.19	0.003
Burrito with beef, beans, and cheese, from Mexican carry-out	1,2,3,6,7,8-HxCDD	0.19	0.003
Chili con carne with beans, canned	1,2,3,6,7,8-HxCDD	0.16	0.002
Quarter-pound hamburger on bun, fast-food	1,2,3,6,7,8-HxCDD	0.16	0.001
Cheese, American, processed	1,2,3,6,7,8-HxCDD	0.15	0.003
Quarter-pound cheeseburger on bun, fast-food	1,2,3,6,7,8-HxCDD	0.15	0.003
Taco/tostada with beef and cheese, from Mexican carry-out	1,2,3,6,7,8-HxCDD	0.14	0.005
Sour cream	1,2,3,6,7,8-HxCDD	0.13	0.001
Baby food, vegetables and beef	1,2,3,6,7,8-HxCDD	0.09	0.004
Baby food, beef and noodles/beef stroganoff	1,2,3,6,7,8-HxCDD	0.088	0.004
Pizza, cheese and pepperoni, regular crust, from pizza carry-out	1,2,3,6,7,8-HxCDD	0.084	0.003
Ice cream, regular, vanilla	1,2,3,6,7,8-HxCDD	0.071	0.001
Lasagna with meat, frozen, heated	1,2,3,6,7,8-HxCDD	0.071	0.003
Potato, mashed, prepared from fresh	1,2,3,6,7,8-HxCDD	0.07	0.002
Sour cream dip, any flavor	1,2,3,6,7,8-HxCDD	0.062	0.004
Beef stroganoff with noodles, homemade	1,2,3,6,7,8-HxCDD	0.059	0.003
Half and half cream	1,2,3,6,7,8-HxCDD	0.057	0.001
Beef and vegetable stew, canned	1,2,3,6,7,8-HxCDD	0.056	0.002
Pork sausage (link/patty), oven-cooked	1,2,3,6,7,8-HxCDD	0.054	0.002

Table 5-15. Detections of CDD Congeners in Food Items from the 2004 FDA Market Basket Survey

Product description	Congener description	Amount found (pg/g [ppt])	LOD (pg/g [ppt])
Milk shake, chocolate, fast-food	1,2,3,6,7,8-HxCDD	0.053	0.001
Lamb chop, pan-cooked with oil	1,2,3,6,7,8-HxCDD	0.053	0.003
Bologna (beef/pork)	1,2,3,6,7,8-HxCDD	0.05	0.001
Spaghetti with meat sauce, homemade	1,2,3,6,7,8-HxCDD	0.049	0.001
Candy bar, milk chocolate, plain	1,2,3,6,7,8-HxCDD	0.046	0.001
Ice cream, light, vanilla	1,2,3,6,7,8-HxCDD	0.04	0.001
Eggs, boiled	1,2,3,6,7,8-HxCDD	0.035	0.003
Milk, whole, fluid	1,2,3,6,7,8-HxCDD	0.034	0.001
Eggs, scrambled with oil	1,2,3,6,7,8-HxCDD	0.034	0.003
Pumpkin pie, fresh/frozen	1,2,3,6,7,8-HxCDD	0.034	0.004
Lettuce, leaf, raw	1,2,3,6,7,8-HxCDD	0.033	0.002
Baby food, beef and broth/gravy	1,2,3,6,7,8-HxCDD	0.032	0.002
Chicken with vegetables in sauce, from Chinese carry-out	1,2,3,6,7,8-HxCDD	0.027	0.002
Brown gravy, canned or bottled	1,2,3,6,7,8-HxCDD	0.027	0.003
Vegetable oil	1,2,3,6,7,8-HxCDD	0.025	0.004
Green beans, fresh/frozen, boiled	1,2,3,6,7,8-HxCDD	0.024	0.005
Cornbread, homemade	1,2,3,6,7,8-HxCDD	0.02	0.003
Infant formula, milk-based, high iron, ready to feed	1,2,3,6,7,8-HxCDD	0.02	0.001
Cottage cheese, creamed, low fat (2% milk fat)	1,2,3,6,7,8-HxCDD	0.02	0.003
Pork chop, pan-cooked with oil	1,2,3,6,7,8-HxCDD	0.018	0.001
Beets, canned	1,2,3,6,7,8-HxCDD	0.018	0.003
Carrot, baby, raw	1,2,3,6,7,8-HxCDD	0.017	0.001
Margarine, regular (salted)	1,2,3,6,7,8-HxCDD	0.014	0.004
Beef with vegetables in sauce, from Chinese carry-out	1,2,3,6,7,8-HxCDD	0.014	0.005
Corn, canned	1,2,3,6,7,8-HxCDD	0.012	0.001
Mixed vegetables, frozen, boiled	1,2,3,6,7,8-HxCDD	0.01	0.002
Popcorn, microwave, butter-flavored	1,2,3,6,7,8-HxCDD	0.005	0.001
Milk, low fat (2%), fluid	1,2,3,6,7,8-HxCDD	0.002	0.022

Table 5-15. Detections of CDD Congeners in Food Items from the 2004 FDA Market Basket Survey

Product description	Congener description	Amount found (pg/g [ppt])	LOD (pg/g [ppt])
Beef roast, chuck, oven-roasted	1,2,3,7,8,9-HxCDD	0.2	0.003
Frankfurter (beef/pork), boiled	1,2,3,7,8,9-HxCDD	0.15	0.002
Liver (beef/calf), pan-cooked with oil	1,2,3,7,8,9-HxCDD	0.14	0.002
Catfish, pan-cooked with oil	1,2,3,7,8,9-HxCDD	0.14	0.003
Butter, regular (salted)	1,2,3,7,8,9-HxCDD	0.12	0.003
Beef, ground, regular, pan-cooked	1,2,3,7,8,9-HxCDD	0.089	0.002
Cream cheese	1,2,3,7,8,9-HxCDD	0.081	0.0021
Cheese, cheddar, natural (sharp/mild)	1,2,3,7,8,9-HxCDD	0.075	0.004
Meatloaf, beef, homemade	1,2,3,7,8,9-HxCDD	0.069	0.001
Cheese, Swiss, natural	1,2,3,7,8,9-HxCDD	0.062	0.003
Beef steak, loin/sirloin, broiled	1,2,3,7,8,9-HxCDD	0.055	0.001
Cheese, American, processed	1,2,3,7,8,9-HxCDD	0.047	0.006
Salami, luncheon-meat type (not hard)	1,2,3,7,8,9-HxCDD	0.044	0.001
Burrito with beef, beans, and cheese, from Mexican carry-out	1,2,3,7,8,9-HxCDD	0.043	0.003
Sour cream	1,2,3,7,8,9-HxCDD	0.037	0.001
Chili con carne with beans, canned	1,2,3,7,8,9-HxCDD	0.034	0.002
Quarter-pound hamburger on bun, fast-food	1,2,3,7,8,9-HxCDD	0.03	0.001
Sweet roll/Danish pastry	1,2,3,7,8,9-HxCDD	0.029	0.004
Ice cream, regular, vanilla	1,2,3,7,8,9-HxCDD	0.024	0.001
Potato, mashed, prepared from fresh	1,2,3,7,8,9-HxCDD	0.024	0.002
Sour cream dip, any flavor	1,2,3,7,8,9-HxCDD	0.023	0.002
Baby food, beef and noodles/beef stroganoff	1,2,3,7,8,9-HxCDD	0.022	0.002
Candy bar, milk chocolate, plain	1,2,3,7,8,9-HxCDD	0.021	0.001
Half and half cream	1,2,3,7,8,9-HxCDD	0.019	0.001
Spaghetti with meat sauce, homemade	1,2,3,7,8,9-HxCDD	0.018	0.001
Eggs, scrambled with oil	1,2,3,7,8,9-HxCDD	0.017	0.001
Lettuce, leaf, raw	1,2,3,7,8,9-HxCDD	0.014	0.003
Ice cream, light, vanilla	1,2,3,7,8,9-HxCDD	0.012	0.001

Table 5-15. Detections of CDD Congeners in Food Items from the 2004 FDA Market Basket Survey

Product description	Congener description	Amount found (pg/g [ppt])	LOD (pg/g [ppt])
Infant formula, milk-based, high iron, ready to feed	1,2,3,7,8,9-HxCDD	0.009	0.001
Milk, whole, fluid	1,2,3,7,8,9-HxCDD	0.008	0.001
Beef roast, chuck, oven-roasted	1,2,3,7,8-PeCDD	0.1	0.004
Cream cheese	1,2,3,7,8-PeCDD	0.091	0.0009
Frankfurter (beef/pork), boiled	1,2,3,7,8-PeCDD	0.089	0.004
Cheese, cheddar, natural (sharp/mild)	1,2,3,7,8-PeCDD	0.066	0.003
Beef, ground, regular, pan-cooked	1,2,3,7,8-PeCDD	0.052	0.004
Meatloaf, beef, homemade	1,2,3,7,8-PeCDD	0.043	0.001
Beef steak, loin/sirloin, broiled	1,2,3,7,8-PeCDD	0.038	0.003
Sour cream	1,2,3,7,8-PeCDD	0.033	0.001
Salami, luncheon-meat type (not hard)	1,2,3,7,8-PeCDD	0.031	0.001
Quarter-pound hamburger on bun, fast-food	1,2,3,7,8-PeCDD	0.029	0.001
Liver (beef/calf), pan-cooked with oil	1,2,3,7,8-PeCDD	0.027	0.003
Chicken potpie, frozen, heated	1,2,3,7,8-PeCDD	0.021	0.001
Burrito with beef, beans, and cheese, from Mexican carry-out	1,2,3,7,8-PeCDD	0.021	0.005
Chicken breast, oven-roasted (skin removed)	1,2,3,7,8-PeCDD	0.018	0.004
Chili con carne with beans, canned	1,2,3,7,8-PeCDD	0.016	0.004
Candy bar, milk chocolate, plain	1,2,3,7,8-PeCDD	0.016	0.001
Ice cream, regular, vanilla	1,2,3,7,8-PeCDD	0.015	0.001
Milk shake, chocolate, fast-food	1,2,3,7,8-PeCDD	0.013	0.001
Half and half cream	1,2,3,7,8-PeCDD	0.013	0.001
Syrup, pancake	1,2,3,7,8-PeCDD	0.01	0.007
Ice cream, light, vanilla	1,2,3,7,8-PeCDD	0.01	0.001
Milk, whole, fluid	1,2,3,7,8-PeCDD	0.009	0.001
Catfish, pan-cooked with oil	2,3,7,8-TCDD	0.026	0.001
Cream cheese	2,3,7,8-TCDD	0.021	0.0025
Salmon, steaks/fillets, baked	2,3,7,8-TCDD	0.021	0.001
Baby food, chicken noodle dinner	2,3,7,8-TCDD	0.015	0.007

Table 5-15. Detections of CDD Congeners in Food Items from the 2004 FDA Market Basket Survey

Product description	Congener description	Amount found (pg/g [ppt])	LOD (pg/g [ppt])
Cheese, cheddar, natural (sharp/mild)	2,3,7,8-TCDD	0.013	0.001
Beef roast, chuck, oven-roasted	2,3,7,8-TCDD	0.011	0.002
Meatloaf, beef, homemade	2,3,7,8-TCDD	0.008	0.001
Sour cream	2,3,7,8-TCDD	0.008	0.001
Ice cream, regular, vanilla	2,3,7,8-TCDD	0.004	0.001
Half and half cream	2,3,7,8-TCDD	0.003	0.001
Milk shake, chocolate, fast-food	2,3,7,8-TCDD	0.002	0.001
Liver (beef/calf), pan-cooked with oil	OCDD	65	0.013
Mushrooms, raw	OCDD	36	0.016
Catfish, pan-cooked with oil	OCDD	12	0.011
Beef roast, chuck, oven-roasted	OCDD	10	0.005
Pork sausage (link/patty), oven-cooked	OCDD	7.3	0.007
Frankfurter (beef/pork), boiled	OCDD	5.6	0.003
Vegetable oil	OCDD	5.5	0.007
Beef, ground, regular, pan-cooked	OCDD	4.9	0.003
Margarine, regular (salted)	OCDD	4.2	0.007
Lettuce, leaf, raw	OCDD	3.7	0.003
Salami, luncheon-meat type (not hard)	OCDD	3.5	0.002
Mayonnaise, regular, bottled	OCDD	3.2	0.004
Peanut butter, creamy	OCDD	2.6	0.004
Spinach, fresh/frozen, boiled	OCDD	2.5	0.015
Baby food, chicken noodle dinner	OCDD	2.5	0.006
Burrito with beef, beans, and cheese, from Mexican carry-out	OCDD	2.4	0.003
Bologna (beef/pork)	OCDD	2.3	0.002
Baby food, vegetables and beef	OCDD	2.3	0.006
Salad dressing, creamy/buttermilk type, regular	OCDD	2.3	0.005
Chili con carne with beans, canned	OCDD	2.1	0.003

Table 5-15. Detections of CDD Congeners in Food Items from the 2004 FDA Market Basket Survey

Product description	Congener description	Amount found (pg/g [ppt])	LOD (pg/g [ppt])
Baby food, cereal, barley, dry, prepared with water	OCDD	2.1	0.003
Baby food, mixed vegetables	OCDD	2	0.007
Meatloaf, beef, homemade	OCDD	1.9	0.001
Baby food, turkey and rice	OCDD	1.7	0.009
Green beans, canned	OCDD	1.6	0.012
Crackers, butter-type	OCDD	1.6	0.002
Butter, regular (salted)	OCDD	1.5	0.003
Sandwich cookies with creme filling	OCDD	1.5	0.006
Brownie	OCDD	1.5	0.008
Chicken with vegetables in sauce, from Chinese carry-out	OCDD	1.5	0.003
Beef steak, loin/sirloin, broiled	OCDD	1.4	0.002
Soup, Oriental noodles (ramen noodles), prepared with water	OCDD	1.4	0.007
Green beans, fresh/frozen, boiled	OCDD	1.3	0.004
Candy bar, milk chocolate, plain	OCDD	1.3	0.001
Refried beans, canned	OCDD	1.3	0.002
Cornbread, homemade	OCDD	1.1	0.004
Carrot, baby, raw	OCDD	1.1	0.003
Pork chop, pan-cooked with oil	OCDD	1	0.002
Baby food, cereal, oatmeal with fruit, prepared with water	OCDD	1	0.004
Broccoli, fresh/frozen, boiled	OCDD	0.97	0.005
Sweet roll/Danish pastry	OCDD	0.9	0.003
Eggs, scrambled with oil	OCDD	0.89	0.003
Pumpkin pie, fresh/frozen	OCDD	0.89	0.005
Fish sticks or patty, frozen, oven-cooked	OCDD	0.87	0.002
Pizza, cheese and pepperoni, regular crust, from pizza carry-out	OCDD	0.85	0.002
Cream cheese	OCDD	0.82	0.014
Sugar cookies	OCDD	0.81	0.005
Cheese, cheddar, natural (sharp/mild)	OCDD	0.78	0.002
Infant formula, soy-based, ready to feed	OCDD	0.78	0.001

Table 5-15. Detections of CDD Congeners in Food Items from the 2004 FDA Market Basket Survey

Product description	Congener description	Amount found (pg/g [ppt])	LOD (pg/g [ppt])
Fried rice, meatless, from Chinese carry-out	OCDD	0.77	0.003
Beets, canned	OCDD	0.74	0.002
Sunflower seeds (shelled), roasted, salted	OCDD	0.74	0.002
Fish sandwich on bun, fast-food	OCDD	0.72	0.002
Eggs, boiled	OCDD	0.65	0.002
Corn, canned	OCDD	0.64	0.001
Potato, mashed, prepared from fresh	OCDD	0.57	0.002
Baby food, macaroni, tomato, and beef	OCDD	0.56	0.004
Sweet potatoes, canned	OCDD	0.54	0.002
Mixed vegetables, frozen, boiled	OCDD	0.53	0.002
Pepper, sweet, green, raw	OCDD	0.5	0.003
Ham, cured (not canned), baked	OCDD	0.47	0.003
Pork and beans, canned	OCDD	0.45	0.005
Coleslaw, mayonnaise-type, from grocery/deli	OCDD	0.41	0.001
Soup, bean with bacon/pork, canned, cond, prepared with water	OCDD	0.39	0.003
Milk, low fat (2%), fluid	OCDD	0.37	0.003
Beef and vegetable stew, canned	OCDD	0.37	0.004
Candy bar, chocolate, nougat, and nuts	OCDD	0.33	0.001
Milk shake, chocolate, fast-food	OCDD	0.31	0.002

CDD = chlorinated dibenzo-*p*-dioxin; FDA = U.S. Food and Drug Administration; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; LOD = limit of detection; PeCDD = pentachlorodibenzo-*p*-dioxin; OCDD = octachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin

Source: FDA 2007

Congener-specific analyses for CDDs and CDFs were performed on 18 dairy, meat, and fish products obtained from a supermarket in upstate New York (Schecter et al. 1994d). Total CDD concentrations (on a wet weight basis) were 0.35–2.91 ppt in fish, 0.6–59.3 ppt for meats, and 0.6–14 ppt in dairy products. A summary of the CDD/CDF concentrations and TEQ concentrations calculated for the 18 foods is

presented in Table 5-16. The TEQs for both the CDDs and CDFs on a wet weight basis for these food samples were 0.02–1.5 ppt: 0.02–0.13 ppt for fish products, 0.03–1.5 ppt for meat products, and 0.04–0.7 ppt for dairy products, with the highest TEQ found in ground beef.

Table 5-16. Dioxins, Dibenzofurans, and Dioxin Toxic Equivalencies (TEQs) in U.S. Foods (ppt or pg/g, Wet Weight)

	Total CDDs/CDFs		
Food type	CDD	CDF	TEQ
Fish			
Haddock	0.75	0.14	0.03
Haddock fillet	0.35	0.07	0.02
Crunchy haddock	2.91	0.51	0.13
Perch	1.55	1.14	0.02
Cod	0.82	0.09	0.02
Meats			
Ground beef	4.1	7.0	1.5
Beef rib sirloin tip	0.6	0.2	0.04
Beef rib steak	30.7	4.6	0.3
Pork chop	59.3	2.5	0.3
Cooked ham	59.3	2.5	0.3
Lamb sirloin	8.95	0.85	0.4
Bologna	3.7	0.4	0.12
Chicken drumstick	0.95	0.14	0.03
Dairy			
Cottage cheese	0.6	0.3	0.04
Soft blue cheese	14.0	5.0	0.7
Heavy cream	5.0	2.0	0.4
Soft cream cheese	4.0	2.0	0.3
American cheese slices	4.0	2.0	0.3

CDDs = chlorinated dibenzo-*p*-dioxin; CDFs = chlorinated dibenzofuran

Source: Schecter et al. 1994d

The EPA and USDA completed the first statistically designed surveys of the occurrence and concentrations of CDDs/CDFs in beef fat (Ferrario et al. 1996; Winters et al. 1996), pork fat (Lorber et al. 1997), poultry fat (Ferrario et al. 1997), and the U.S. milk supply (Lorber et al. 1998). The congener-specific results for various foods are shown in Table 5-17. It is clear from the results, that two congeners (1,2,3,4,6,7,8-HpCDD and 1,2,3,4,6,7,8-OCDD) were typically found at the highest concentrations in all food samples. Concentrations of 2,3,7,8-TCDD were highest in heavy fowl (0.43 ppt) and young turkeys (0.24 ppt); much lower concentrations were found in beef (0.05 ppt), pork (0.10 ppt), young chickens (0.16 ppt), light fowl (0.03 ppt), and milk (0.07 ppt). The total concentrations of CDDs/CDFs were highest in pork fat (75.67 ppt) and milk (15.43 ppt), and ranged from 5.68 to 14.09 ppt for all other types

of foods tested. The TEQ value for CDDs/CDFs combined was highest for pork fat (1.30 ppt), heavy fowl (0.98 ppt), young turkeys (0.93 ppt), and beef fat (0.89 ppt), with lower TEQ values of 0.40–0.82 ppt for young chickens, light fowl, and milk.

Table 5-17. Overall National Averages of the Concentrations (ppt or pg/g) of CDDs in Fat of Meat and Milk on a Lipid Basis[a]

CDD/CDF congener	Beef (n=63)	Pork fat (n=78)	Young chickens (n=39)	Light fowl (n=12)	Heavy fowl (n=12)	Young turkeys (n=15)	Milk (composites) (n=8)
2,3,7,8-TCDD	0.05 (0.03)	0.10 (0.01)	0.16 (0.15)	0.05 (0.03)	0.43 (0.42)	0.24 (0.24)	0.07 (0.07)
1,2,3,7,8-PeCDD	0.35 (0.04)	0.45 (0.01)	0.24 (0.12)	0.15 (0.00)	0.32 (0.22)	0.32 (0.23)	0.32 (0.32)
1,2,3,4,7,8-HxCDD	0.64 (0.18)	0.52 (0.10)	0.18 (0.05)	0.15 (0.00)	0.24 (0.13)	0.16 (0.03)	0.39 (0.39)
1,2,3,6,7,8-HxCDD	1.42 (1.21)	1.10 (0.80)	0.39 (0.33)	0.34 (0.29)	0.71 (0.70)	0.79 (0.77)	1.87 (1.87)
1,2,3,7,8,9-HxCDD	0.53 (0.26)	0.47 (0.04)	0.39 (0.29)	0.15 (0.01)	0.60 (0.51)	0.17 (0.06)	0.55 (0.55)
1,2,3,4,6,7,8-HpCDD	4.48 (4.39)	10.15 (9.93)	1.53 (1.53)	0.93 (0.93)	2.04 (2.02)	0.54 (0.52)	5.03 (5.03)
1,2,3,4,6,7,8,9-OCDD	4.78 (3.26)	52.77 (52.40)	5.31 (5.31)	2.07 (2.07)	7.67 (7.67)	0.75 (0.68)	4.89 (4.89)
CDD/CDF I-TEQ, pg/g	0.89 (0.35)	1.30 (0.46)	0.64 (0.41)	0.40 (0.16)	0.98 (0.80)	0.93 (0.76)	0.82 NR

[a]Concentrations calculated at non-detects (ND) equal one-half the detection limit (results for ND=0 are in parentheses).

CDD = chlorinated dibenzo-*p*-dioxin; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; NR = not reported; OCDD = octachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin; TEQ = toxic equivalency

Sources: Ferrario et al. 1996, 1997; Lorber et al. 1997; Winters et al. 1996

CDDs have been found in infant formulas purchased in the United States (Schecter et al. 1989c). The infant formulas were derived from cow's milk or soybeans. In general, both types of infant formula had very low concentrations of CDDs. 2,3,7,8-TCDD and PeCDD were not detected in cow's milk or soybean formula at detection limits ranging from 0.5 to 1.0 ppt. HxCDD was not detected in soybean formula at the same detection limits. Whole and low fat (2% fat) cow's milk contained total HxCDD at lipid-adjusted concentrations of 3.6 and 3.3 ppt, respectively. Lipid-adjusted levels of HpCDD were found in whole cow's milk formula (6.5 ppt), low fat (2%) cow's milk formula (8 ppt), and soybean formula (2.3–3.0 ppt). OCDD was the most abundant congener in both cow's milk and soybean formula.

Concentrations of OCDD (lipid-adjusted) were as follows: cow's milk formula (15 ppt), low fat (2%) cow's milk formula (21 ppt), and soybean formula (21–36 ppt) (Schecter et al. 1989c).

A study by LaFleur et al. (1990) reported the concentration of 2,3,7,8-TCDD and 2,3,7,8-TCDF in whole milk and half-and-half. The study authors also measured the additional exposure that resulted from migration of these compounds from bleached paperboard containers into the milk over various storage periods. The concentrations of 2,3,7,8-TCDD were 24–25 pg/kg in whole milk and 13–14 pg/kg in half-and-half. The corresponding concentrations of 2,3,7,8-TCDF were 260–280 pg/kg for whole milk and 146–195 pg/kg for half-and-half. The study authors also determined the concentration of 2,3,7,8-TCDD and TCDF for cow's milk obtained directly from a dairy and for milk stored for various time periods in bleached paperboard cartons. On a lipid basis, the concentration of 2,3,7,8-TCDD of control milk obtained directly from the dairy was 0.48 pg/g, and milk stored in paperboard cartons for 24, 48, 120, and 288 hours was 0.95, 1.4, 1.9, and 2.7 pg/g, respectively. The 2,3,7,8-TCDD and 2,3,7,8-TCDF concentrations in the paperboard carton were 4.3 and 25 ppt, respectively. Concentrations of 2,3,7,8-TCDF in the control milk was not detectable, but increased in milk stored in cartons for 24, 48, 120, and 288 hours to 6.8, 10.2, 20.1, and 35.1 pg/g, respectively. The percent migration of the 2,3,7,8-TCDD was 2–6%, while the percentage of migration of the 2,3,7,8-TCDF was 4–18% over the same period (LaFleur et al. 1990).

Similar levels of CDD contamination were reported in two European studies. CDDs were detected in 8 samples of cow's milk in Germany at concentrations ranging from 0.2 ppt for 2,3,7,8-TCDD (detection limit 0.2 ppt) to <10 ppt of OCDD (detection limit not significantly higher than blanks) (Beck et al. 1987). In a Swedish study, only 1 of 10 samples of milk held in either glass bottles or paper cartons contained a detectable level of 2,3,7,8-TCDD (0.46 pg/g milk fat; paper carton; detection limit 0.4 pg/g). Other CDDs were also detected (maximum 7.8 pg/g for OCDD) with the highest concentrations associated with milk packaged in paper cartons, indicating that leaching of CDDs from the paper carton into the milk can occur (Rappe et al. 1990).

Fish and Wildlife. De Vault et al. (1989) collected samples of lake trout and walleye for CDD and CDF analysis from each of the Great Lakes and Lake St. Clair. One of the conclusions of the National Dioxin Study was that fish from the Great Lakes region were among the most severely contaminated in the United States. Fish were analyzed for 8 congeners of CDDs and 10 congeners of CDFs. Total CDD concentrations ranged from 7.2 ng/kg (pg/g) in lake trout from Lake Superior to 64.5 ng/kg (pg/g) in Lake Ontario (wet weight basis). Concentrations of 2,3,7,8-TCDD ranged from 1 ng/kg (pg/g) in lake trout

from Lake Superior to 48.9 ng/kg (pg/g) in lake trout from Lake Ontario. The dominant congener in all but Lake Ontario was 1,2,3,7,8-PeCDD at concentrations ranging from 2.3 ng/kg (pg/g) in Lake Superior to 16.7 ng/kg (pg/g) in Lake Michigan. The only other congener that significantly contributed to the total CDD concentration was 1,2,3,6,7,8-HxCDD, which ranged from 1.3 ng/kg (pg/g) in Lake Superior to 10.9 ng/kg (pg/g) in Lake Michigan. Substantial inter-lake differences exist in the percentage of total CDD contributed by the various congeners. The 2,3,7,8-TCDD congener contributes a relatively small percentage of the total CDD in fish from Lakes Superior, Michigan, and Erie. It is comparatively more important in Lake Huron (32%) and Lake St. Clair (36%) and contributes 76% of the total CDD in Lake Ontario. The results of this study support the widespread contamination of the Great Lakes ecosystem and clearly show that both the concentration of individual congeners and the congener composition of total CDDs in Great Lakes fish vary significantly between lakes and in Lake Michigan between sites. The study authors suggested that these differences may be associated with different sources and loadings of these compounds to each of the Great Lakes (De Vault et al. 1989). This is confirmed by the analysis of sources of CDDs in the Great Lakes, which appear to be both from atmospheric deposition and industrial point sources (Hebert et al. 1994).

More recent data suggest that levels of CDDs in fish from the Great Lakes is decreasing, as emissions have declined over the previous decades. A study conducted on dioxin-like substances in fish of the Great Lakes has shown that there has generally been a large decline in CDD/CDF levels in fish since the 1970s (Gandhi et al. 2019). CDD/CDF levels declined between 1989 and 2013 in lake trout from Lakes Ontario, Huron, and Superior by 91, 78, and 73%, respectively, but increased in Lake Whitefish obtained from Lake Erie by 138%. Using an expanded set of data, from the literature, it was shown the TEQ levels in trout from Lake Ontario decreased from 64 to 2.3 pg/g, which is approximately a 96% decrease. The results of this study on 30 types of fish show overall declining levels of CDD/CDF in fish but local/ regional concerns at some locations in the Great Lakes still exist. Pagano et al. (2018) collected monitoring data for CDDs/CDFs in fish from the Great Lakes from 2004 to 2014. The results of this study as well as other recent monitoring data for some congener specific CDDs are summarized in Table 5-18.

Table 5-18. Levels of CDDs in Fish and Other Aquatic Organisms

Species	Sampling area	CDD	Concentration (pg/g [ppt [wet weight]])	Reference
Walleye	Lake Erie	2,3,7,8-TCDD	0.76 (average) 0.88 (maximum)	Pagano et al. 2018
Walleye	Lake Erie	2,3,7,8-TCDD	0.30 (average) 0.4 (maximum)	Pagano et al. 2018
Lake trout	Lake Erie	2,3,7,8-TCDD	0.60–0.73 0.66 (average)	Pagano et al. 2018
Lake trout	Lake Huron	2,3,7,8-TCDD	1.32–3.32 2.35 (average)	Pagano et al. 2018
Lake trout	Lake Michigan	2,3,7,8-TCDD	0.40–1.27 0.72 (average)	Pagano et al. 2018
Lake trout	Lake Ontario	2,3,7,8-TCDD	2.70–13.5 5.76 (average)	Pagano et al. 2018
Lake trout	Lake Superior	2,3,7,8-TCDD	0.35–0.69 0.49 (average)	Pagano et al. 2018
Lake trout	Lake Superior	2,3,7,8-TCDD	0.17-–0.40 0.28 (average)	Pagano et al. 2018
Lake trout	Lake Champlain	2,3,7,8-TCDD	0.422–1.291 (0.724 average)	Pagano and Garner 2020
White sucker	Lake Superior (St. Louis River area)	Total TCDD	<LOD–1.25	Hoffman et al. 2020
White sucker	Lake Superior (St. Louis River area)	Total PeCDD	<LOD–2.14	Hoffman et al. 2020
White sucker	Lake Superior (St. Louis River area)	Total HxCDD	<LOD–3.94	Hoffman et al. 2020
White sucker	Lake Superior (St. Louis River area)	Total HpCDD	<LOD–3.12	Hoffman et al. 2020
Roach	Rybnicki, Poland	2,3,7,8-TCDD 1,2,3,7,8-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,6,7,8-HxCDD 1,2,3,7,8,9-HxCDD 1,2,3,4,6,7,8-HpCDD OCDD	0.005–0.034 <0.004–0.045 <0.002–0.005 0.007–0.040 <0.002–0.006 <0.010–0.033 <0.024–0.033	Mikolajczyk et al. 2022a, 2022b
Bream	Rybnicki, Poland	2,3,7,8-TCDD 1,2,3,7,8-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,6,7,8-HxCDD 1,2,3,7,8,9-HxCDD 1,2,3,4,6,7,8-HpCDD OCDD	0.021–0.277 0.035–0.490 0.016–0.243 0.038–0.481 0.007–0.068 <0.048–0.381 0.035–0.537	Mikolajczyk et al. 2022a, 2022b

Table 5-18. Levels of CDDs in Fish and Other Aquatic Organisms

Species	Sampling area	CDD	Concentration (pg/g [ppt [wet weight]])	Reference
Roach	Maróz Poland	2,3,7,8-TCDD 1,2,3,7,8-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,6,7,8-HxCDD 1,2,3,7,8,9 -HxCDD 1,2,3,4,6,7,8-HpCDD OCDD	0.003–0.011 0.005–0.014 <0.002–0.009 0.002–0.009 <0.002–0.005 <0.010–0.087 0.024–0.258	Mikolajczyk et al. 2022a, 2022b
Bream	Maróz Poland	2,3,7,8-TCDD 1,2,3,7,8-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,6,7,8-HxCDD 1,2,3,7,8,9 -HxCDD 1,2,3,4,6,7,8-HpCDD OCDD	0.005–0.019 0.008–0.060 0.003–0.026 0.020–0.060 0.003–0.009 0.016–0.060 0.029–0.081	Mikolajczyk et al. 2022a, 2022b
Pike	Maróz Poland	2,3,7,8-TCDD 1,2,3,7,8-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,6,7,8-HxCDD 1,2,3,7,8,9 -HxCDD 1,2,3,4,6,7,8-HpCDD OCDD	0.003–0.014 0.006–0.021 <0.002 0.002–0.013 <0.002 0.010–0.025 <0.029–0.066	Mikolajczyk et al. 2022a, 2022b
Pike	Lipczyno Wielkie Poland	2,3,7,8-TCDD 1,2,3,7,8-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,6,7,8-HxCDD 1,2,3,7,8,9 -HxCDD 1,2,3,4,6,7,8-HpCDD OCDD	0.003–0.029 0.005–0.020 0.002–0.007 0.002–0.033 <0.002–0.005 <0.010–0.016 0.042–0.048	Mikolajczyk et al. 2022a, 2022b
Bream	Łańskie, Poland	2,3,7,8-TCDD 1,2,3,7,8-PeCDD 1,2,3,4,7,8-HxCDD 1,2,3,6,7,8-HxCDD 1,2,3,7,8,9 -HxCDD 1,2,3,4,6,7,8-HpCDD OCDD	0.004–0.076 0.019–0.151 0.003–0.056 0.014–0.130 0.004– 0.010 0.029–0.114 0.028–0.097	Mikolajczyk et al. 2022a, 2022b

CDD = chlorinated dibenzo-*p*-dioxin; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin
LOD = limit of detection; OCDD = octachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin;
TCDD = tetrachlorodibenzo-*p*-dioxin

Data from the Water Quality Portal for 2020–2021 indicated that there were 94 instances of CDDs detected out of 315 fish samples tested. The maximum concentrations were observed for 1,2,3,7,8-PeCDD with values of 30–200 ng/kg (pg/g) obtained from channel catfish, carp, and largemouth bass from McKeller Lake and Nonconnah creek in Tennessee (WQP 2022).

Khairy and Lohmann (2020a, 2020b), measured levels of CDDs and CDFs in four benthic species (i.e., mud crabs, tube worms, clams, and shrimp) collected from the lower Passaic River at different sampling locations. The results for several CDD congeners are provided in Table 5-19.

Table 5-19. Concentrations of CDDs (pg/g Lipid [ppt]) in Benthic Species Collected from the Lower Passaic River

Congener	Range of values in benthic organisms collected at four different locations
2-MCDD	<LOD
2,7/2,8-DCDD	2,750–4,420
1,2,4-TrCDD	<LOD–745
1,3,6,8-TCDD	<LOD–287
1,3,7,8-TCDD	<LOD–1,028
2,3,7,8-TCDD	653–1,969
1,2,8,9-TCDD	<LOD
1,2,3,4,7-PeCDD	<LOD
1,2,3,4,7,8-HxCDD	<LOD
1,2,3,6,7,8-HxCDD	<LOD
1,2,3,7,8,9-HxCDD	<LOD–898
1,2,3,4,6,7,8-HpCDD	484–2,057
OCDD	2,028–8,991

CDD = chlorinated dibenzo-*p*-dioxin; DCDD = dichlorodibenzo-*p*-dioxin; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin LOD = limit of detection; MCDD = monochlorodibenzo-*p*-dioxin; OCDD = octachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin; TrCDD = trichlorodibenzo-*p*-dioxin

Source: Khairy and Lohmann 2020b

A survey of 2,3,7,8-TCDD contamination in benthic (bottom feeding) and predator fish from major U.S. watersheds was conducted for the EPA National Dioxin Study (Kuehl et al. 1989). It was observed that 17 of 90 (19%) samples collected at sites statistically selected by the EPA had detectable levels of 2,3,7,8-TCDD, whereas 95 of 305 (31%) samples from sites chosen by EPA regional laboratories had detectable levels (detection limits 0.5–2 ppt (pg/g) on a wet weight basis). Of the 112 sites where 2,3,7,8-TCDD was detected, 74 samples (67%) were <5 ppt (pg/g), 34 samples (32%) were between 5 and 25 ppt (pg/g), and 4 samples (1%) were >25 ppt (pg/g). A subset of samples collected at sites near the discharges from pulp/paper manufacturing facilities (n=28) had a higher frequency of 2,3,7,8-TCDD contamination above 5 ppt (38%). This subset of samples also contained the sample with the highest level of 2,3,7,8-TCDD contamination (85 ppt (pg/g)). Of the 29 samples collected in the Great Lakes region, 23 (79%) of the sites were found to have detectable levels of 2,3,7,8-TCDD. The most highly contaminated sample, with a concentration of 41 ppt (pg/g), was collected from Lake Ontario near

Oswego, New York. Four of 57 (7%) estuarine or coastal sites had detectable 2,3,7,8-TCDD levels in either fish or shellfish. The levels of contamination in these four samples were 1.08–3.5 ppt (pg/g) (Kuehl et al. 1989). In another study, fish sampled downstream from a bleached kraft paper mill were found to contain higher concentrations of CDDs compared with fish sampled upstream of the paper mill (Hodson et al. 1992). TCDD concentrations in the fish ranged from 1.47 pg/g (wet weight basis) in upstream areas to 15.6 pg/g in fish sampled 2 km downstream. Fish sampled 95 km downstream contained only about half the residues (8.87 pg/g TCDD) of those collected immediately downstream of the facility (Hodson et al. 1992).

Travis and Hattemer-Frey (1991) analyzed data collected as part of the National Dioxin Study regarding 2,3,7,8-TCDD concentrations in fish. The TCDD levels measured in fish from lakes and rivers in the United States confirm that 2,3,7,8-TCDD is bioaccumulating in fish and that low-level contamination of fish is widespread (EPA 1987c). The fish survey included 304 urban areas in the vicinity of population centers or areas with known commercial fishing activity, including sites in the Great Lakes region. The results of this study indicate that only 29% of fish fillets collected at urban sites had detectable concentrations of 2,3,7,8-TCDD (detection limit 1 ppt [pg/g]). The geometric mean for these fillet samples was 0.3 ppt (wet weight basis). Fish samples from the Great Lakes area contained higher concentrations of 2,3,7,8-TCDD than fish from urban areas (e.g., 67 versus 29% contained detectable levels, respectively). In the Great Lakes area, the geometric mean concentrations of 2,3,7,8-TCDD in fish fillets (2.3 ppt [pg/g]) was almost 7 times higher than the concentrations in the fillets from fish collected from urban areas (0.3 ppt [pg/g]). Comparable concentrations of 2,3,7,8-TCDD were detected in bottom-feeding and predator species from the Great Lakes region. Approximately 74% of the fish fillet samples collected from sites near pulp and paper mills contained detectable concentrations of 2,3,7,8-TCDD. The geometric mean concentration for these fillet samples was 0.9 ppt (pg/g). This geometric mean is 3 times higher than for urban fillet concentrations (0.3 ppt [pg/g]) but is approximately 2 times lower than for TCDD concentrations in fillets from the Great Lakes Region (2.3 ppt).

From 1986 to 1989, the National Study of Chemical Residues in Fish (NSCRF) was conducted by the EPA as a follow-on study to the National Dioxin Study (EPA 1992). The purpose of the NSCRF was to assess the concentrations of 60 toxic pollutants (including CDDs and CDFs) in the tissues of benthic and game fish nationwide. Benthic species were analyzed as whole-body samples, while game species were analyzed as fillet samples and all concentrations were on a wet weight basis. A summary of the prevalence and concentrations of 6 CDDs and 9 CDFs detected at 388 sites surveyed nationwide in the NSCRF is presented in Table 5-20. Four of the CDDs and three of the CDFs analyzed were detected at

over 50% (58–89%) of the sites surveyed. The most frequently detected CDD/CDF compounds (1,2,3,4,6,7,8-HpCDD and 2,3,7,8-TCDF) were both found at 89% of the sites. These compounds were also detected at the highest concentrations: 1,2,3,4,6,7,8-HpCDD at 249 ppt (pg/g) and 2,3,7,8-TCDF at 404 ppt (pg/g) (wet weight). 2,3,7,8-TCDD was found at 70% of the sites at a maximum concentration of 204 ppt (pg/g) and a mean of 6.8 ppt (wet weight basis). The NSCRF report further shows that pulp and paper mills that previously used chlorine bleach pulp appeared to be the dominant source of the 2,3,7,8-TCDD and 2,3,7,8-TCDF. Fish collected at sites downstream of pulp and paper mills had significantly higher concentrations of 2,3,7,8-TCDD than fish collected near all other source categories. With respect to source categories, the NSCRF data showed that fish collected downstream of pulp and paper mills (using chlorine bleaching processes) had the highest median 2,3,7,8-TCDD concentrations (5.66 ppt [pg/g]), compared to the next highest source category, refinery/other industrial sites (1.82 ppt [pg/g]), industrial/urban sites (1.40 ppt [pg/g]), Superfund sites (1.27 ppt [pg/g]), and background sites (0.5 ppt). Source categories with the highest 2,3,7,8-TCDD concentrations in fish also had the highest TEQ values. OCDD and OCDFs were not analyzed in tissue because at the time the NSCRF study was initiated (1986), the TEFs were zero for these compounds. In 1989, TEFs for OCDD and OCDFs were increased to 0.001. Consequently, TEQ values presented in the NSCRF report may be underreported for samples collected at sites with sources of OCDD/OCDF (e.g., wood preservers) (EPA 1992).

Table 5-20. Summary of CDDs Detected in Fish Tissue as Part of the EPA National Study of Chemical Residues in Fish[a]

Congener	Percent of sites where detected	Maximum	Mean	Standard deviation	Median
2,3,7,8-TCDD	70	203.6	6.89	19.41	1.38
1,2,3,7,8-PeCDD	54	53.95	2.38	4.34	0.93
1,2,3,4,7,8-HxCDD	32	37.56	1.67	2.39	1.24
1,2,3,6,7,8-HxCDD	69	100.9	4.30	9.25	1.32
1,2,3,7,8,9-HxCDD	38	24.76	1.16	1.74	0.69
1,2,3,4,6,7,8-HpCDD	89	249.1	10.52	25.30	2.83

[a]Concentrations are picograms per gram (pg/g) or parts per trillion (ppt) by wet weight. The mean, median, and standard deviation were calculated using one-half the detection limit for samples that were below the detection limit. In cases where multiple samples were analyzed per site, the value used represents the highest concentration.

CDD = chlorinated dibenzo-*p*-dioxin; EPA = U.S. Environmental Protection Agency; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; NA = not applicable; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin; TEQ = toxic equivalency

Source: EPA 1992

Background concentrations of CDDs in fish were measured in the Mississippi River and Lake Orono in Elk River, Minnesota, a semi-rural location (Reed et al. 1990). No major industrial or commercial activity occurred in the area at the time of the study, and the survey was conducted as a baseline study prior to the operation of the Elk River Electric Generating Station (powered by refuse-derived fuel). None of the fish collected contained measurable amounts of 2,3,7,8-TCDD; however, one of the composites from the Mississippi River contained 3.9 ppt (pg/g) of total TCDD (wet weight basis). Detection limits ranged from 0.28 to 6.6 ppt (pg/g) on a congener- and sample-specific basis and were not individually reported for each result. OCDD was the most abundant congener (average 59 ppt, range 56–62 ppt (pg/g)), followed in decreasing order by total HpCDD (average 19.3, range 15–22 ppt), total HxCDD (average 6.87 ppt, range 2.3–11 ppt (pg/g)), and total PeCDD (average 3.9 ppt, range 3.5–4.5 ppt [pg/g]) (Reed et al. 1990). Lake Orono showed the same pattern, with OCDD being the most abundant congener (average 39 ppt, range 35–43 ppt [pg/g]), followed by total HpCDD (average 10.5, range 10–11 ppt [pg/g]), and total HxCDD (3.0 ppt [pg/g]). PeCDDs were not detected in the Lake Orono samples (Reed et al. 1990).

Contamination of the Spring River in southwest Missouri by 2,3,7,8-TCDD is believed to have resulted from several well-defined point-source waste disposal sites (Crunkilton et al. 1987). Analysis of 31 fish samples (11 different fish species) collected from 1981 to 1983 demonstrated a rapid decline in 2,3,7,8-TCDD concentrations in fish at increasing distances both upstream and downstream from the area of contamination. Mean concentrations of 2,3,7,8-TCDD 0.5 km downstream from the area of contamination were 38 ppt (pg/g) in whole fish and 20 ppt (pg/g) in fish fillets (wet weight basis). Mean concentrations in fish caught more than 14 km downstream were <4 ppt (pg/g) in both whole fish and fillet samples (Crunkilton et al. 1987).

Fish samples (butterfish, flounder, hake, and herring) collected in 1984 from the Atlantic Ocean off Long Branch, New Jersey, contained no detectable levels of 2,3,7,8-TCDD (detection limit <10 pg/g) (wet weight basis) (Firestone et al. 1986). Cod caught in the northwest Atlantic in November 1990 did not have detectable levels of any CDDs in their muscles or ovaries, although 5 of 10 liver samples had OCDD at a mean concentration of 0.8 ppt (pg/g) and TCDD was found in 3 of 10 samples at 0.1 ppt (pg/g) (Hellou and Payne 1993). A 4-year study of marine and freshwater fish and other edible aquatic organisms taken from Canadian waters that received effluents from pulp and paper mills indicated that 2,3,7,8-TCDD was the most prominent CDD found in the fish regardless of the tissue sampled or sampling location. The maximum 2,3,7,8-TCDD concentration detected in the edible organisms sampled

was for crab hepatopancreas tissue (>500 pg/g) (wet weight basis). Whole fish samples also contained greater CDD concentrations than fillet samples (Whittle et al. 1993).

Several studies have been conducted to monitor 2,3,7,8-TCDD concentrations in fish and shellfish in northern New Jersey in the vicinity of a pesticide manufacturing site that allegedly released an estimated 4–8 kg of 2,3,7,8-TCDD over a 20-year period (Bopp et al. 1991). Samples of striped bass, blue crabs, and lobsters collected from Newark Bay and the New York Bight (marine waters directly offshore from New York Harbor) all contained high concentrations (up to 6,200 ppt [pg/g]) (wet weight basis) of 2,3,7,8-substituted TCDD, PeCDD, and CDFs (Rappe et al. 1991). Concentrations of HxCDD and HpCDD were <0.1–220.7 and <0.7–244.9 ppt (pg/g), respectively. The concentrations of 2,3,7,8-TCDD in these marine organisms were higher than any other New Jersey samples and represented the highest concentrations of 2,3,7,8-TCDD reported for aquatic species. The two crustaceans sampled in the study had similar congener patterns; they all contained both a large number and large amounts of CDD and CDF congeners in addition to the 2,3,7,8-substituted chlorinated compounds. In contrast, the striped bass samples contained primarily the 2,3,7,8-chlorine-substituted congeners. Concentrations of 2,3,7,8-TCDD in tissue were 3,700–6,200 ppt (pg/g) in crab hepatopancreas and 100–120 ppt (pg/g) in crab meat. Concentrations of 2,3,7,8-TCDD were lower in the lobster, ranging from 250 to 610 ppt in the hepatopancreas and from 5 to 6 ppt (pg/g) in the meat. Concentrations of 2,3,7,8-TCDD in striped bass muscle tissue were 84–730 ppt (pg/g). In this study, the crustacean samples all contained very complex ion curves for the TCDDs showing 10 major and 5 minor peaks, while the striped bass samples primarily contained the 2,3,7,8-TCDD isomer and a few other isomers. With respect to the PeCDDs, the crustacean samples contained 5–6 peaks including 1,2,3,7,8-PeCDD, while the major isomer found in the striped bass was 1,2,3,7,8-PeCDD (5–10 ppt [pg/g]). Regarding the HxCDDs, the crustacean samples contained three major peaks, one of which was 1,2,3,6,7,8-HxCDD (100–300 ppt (pg/g) in the hepatopancreas), while the striped bass samples contained concentrations <1 ppt. The HpCDD congeners (1,2,3,4,6,7,9- and 1,2,3,4,6,7,8-) were detected in crustacean hepatopancreas tissue ranging from 31.7 to 411.9 ppt (pg/g), while meat samples contained 0.00–8.5 ppt (pg/g). Striped bass tissue samples contained 4–11.4 ppt (pg/g). Concentrations of OCDD were 50.5–94.6 ppt in crustacean hepatopancreas tissues and 6.3–78.8 ppt (pg/g) in meat samples, while concentrations in striped bass were 5.1–49.5 ppt (pg/g) (Rappe et al. 1991).

Concentrations of CDDs/CDFs were also evaluated in a bivalve mollusk, the soft-shelled clam *(Mya arenaria)* in Newark Bay, Arthur Kill, and Raritan Bay (Brown et al. 1994). Clams from Newark Bay contained 11–20 ppt (pg/g) TCDD, 3.5–5 ppt (pg/g) TCDF, and 13–25 ppt (pg/g) TEQ; those from Arthur

Kill contained 4.8–7.7 ppt (pg/g) TCDD, 3.1–5.1 ppt (pg/g) TCDF, and 6.8–11 ppt (pg/g) TEQ; and those from Raritan Bay contained 0.5–1.1 ppt (pg/g) TCDD, 2–4.6 ppt (pg/g) TCDF, and 1.2–2.1 ppt (pg/g) TEQ (wet weight basis). Concentrations decreased with increasing distance from the suspected pesticide plant site near Newark Bay. The study authors also showed that the clams could eliminate TCDD and TCDF when they were removed to clean water sites. The half-lives of the TCDD, TCDF, and TEQ were calculated to be 45, 111, and 66 days, respectively.

CDDs were determined in pooled samples of ringed seal *(Phoca hispida)* blubber, beluga whale *(Delphinapterus leucas)* blubber, and polar bear *(Ursus maritimus)* liver and fat collected from several areas throughout the Canadian north (Norstrom et al. 1990). All seal samples and all but one polar bear sample had detectable levels of 2,3,7,8-TCDD (wet weight) ranging from 2 to 37 ppt, but 2,3,7,8-TCDD was not found in beluga blubber (<2 ppt [pg/g]). OCDD concentrations in seal blubber and polar bear samples ranged from not detected (<8 ppt [pg/g]) to 43 ppt (pg/g). No biomagnification of TCDD or OCDD occurred from seal to bear fat. The highest concentrations of 2,3,7,8-TCDD and OCDD in seals and bears were found in the central Canadian Arctic Archipelago, and the lowest concentrations were found in the Hudson Bay area. The reason for higher concentrations of 2,3,7,8-TCDD and OCDD in the Arctic than in sub-Arctic areas is thought to be transpolar movement of aerosols from combustion-related sources originating in Eurasia (Norstrom et al. 1990). CDDs and CDFs were determined in caribou tissue samples from seven herds across the Canadian Arctic (Hebert et al. 1996). In contrast to marine mammals, concentrations for caribou were extremely low, sub-ng/kg (lipid basis), for all congeners except OCDD and 1,2,3,7,8-PeCDD in one herd. OCDD was found in most of the samples at concentrations ranging from <0.2 ng/kg in fat to 4.7 ng/kg in adipose tissue. The one pooled liver sample analyzed from the Yukon had an OCDD concentration of 11 ng/kg (lipid basis). 2,3,7,8-TCDD was detected in adipose tissue samples of two herds in the eastern Canadian Arctic at levels of 0.73 and 0.14 ng/kg, but was not detected in tissue samples from other herds at detections limits as low as 0.03 ng/kg (lipid basis).

Consumer Products

Cigarettes and cigarette smoke. CDDs have been detected in cigarettes and cigarette smoke. Lofroth and Zebuhr (1992) detected CDD/CDF concentrations in both mainstream (collected directly on a glass fiber filter) and sidestream smoke (emitted into an acrylic box and then collected on a glass fiber filter) from a single brand of commercially available Swedish cigarettes. The study authors reported that the mainstream smoke from 20 cigarettes contained about 18 pg TEQ (1 pg TEQ per cigarette), while

sidestream smoke contained 39 pg TEQ (2 pg TEQ per cigarette). No particular isomer contributed more than 20% to the total TEQ value. Most isomers were not present at concentrations above the detection limits (0.3–1.3 pg), with the exception of 1,2,3,4,6,7,8-HpCDD (6.8 pg), 1,2,3,4,6,7,8-HpCDF (4 pg), and OCDD (7.3 pg). An earlier study that used low-resolution mass spectrometry for analysis of CDDs in cigarette smoke obtained by a continuous smoking process (all cigarette tobacco gave rise to mainstream smoke) found that HpCDD was the most abundant homologue detected, accounting for >90% of the total CDDs (Muto and Takizawa 1989).

Paper products. CDDs can be formed during pulp bleaching, and as a result, they have been found in many different types of paper products that previously employed elemental chlorine in the bleaching process. 2,3,7,8-Substituted CDDs were determined in different samples of coffee-filter paper (Beck et al. 1988, 1989d). 2,3,7,8-TCDD was the most abundant congener detected at a mean concentration of 3.85 ppt (range 1.6–7.3 ppt). OCDD was detected at a mean concentration of 2.05 ppt (range 0.7–3.5 ppt). PeCDDs, HxCDDs, and HpCDDs were identified at concentrations of 0.03–0.7 ppt. In an earlier study, HxCDD was the most abundant homologue detected in coffee filters (2.1 ppt) and 2,3,7,8-TCDD was found at concentrations of 1 ppt (Beck et al. 1988). Coffee brewed without filters did not contain any detectable CDDs; however, coffee brewed with one filter showed leaching of TCDDs from the paper into the coffee. An FDA study of the migration of TCDD from paper products that come in contact with food found that TCDD was present in all paper products at concentrations ranging from 0.5 ppt for coated paper trays to 13 ppt for coated paper cups (average 2–8.5 ppt). Migration of TCDD from the paper into the food ranged from below detectable limits for coated juice cartons to 24% for coffee filters. Most CDDs migrated in the range of 4–8%. The TEQ estimated concentration values ranged from 1.5 ppt for coffee filters to 140 ppt for paper plates (Cramer et al. 1991).

Changes in the commercial bleaching process have significantly reduced the levels of CDDs/CDFs in paper products. The use of chlorine dioxide rather than elemental chlorine in the bleaching procedure essentially eliminates the formation of 2,3,7,8-TCDD and 2,3,7,8-TCDF in finished products (Axegård 2019). Almost all new paper mills use elemental chlorine-free bleaching and other techniques such as oxygen delignification, which reduce the amount of lignin in the pulp and thus lower the need for bleaching chemicals (Axegård 2019). Moreover, the elimination of unchlorinated dioxin containing precursers that were found in some mineral oils formerly used in the paper milling process has also lowered the formation of CDDs/CDFs in paper products.

Dyes and pigments. Malisch (1994) reported the presence of CDDs/CDFs in colored candle wax produced with the dye pigment Violet 23, which is derived from chloranil. The three candle samples with the highest contamination contained 1.8, 1.4, and 0.8 ng TEQ/kg (ppt). The study author also noted that candles of the same color could have highly different CDD/CDF concentrations based on the composition of dye pigments used in the manufacturing process.

Three pigments used in fabric dyeing that are derived from chloranil include the dioxazine pigments Violet 23 and Direct Blue 106 and 108 (Williams et al. 1992). Concentrations of the congeners OCDD and OCDF predominated in the pigment Blue 106 and were 18,066–41,953 ng/g (ppb) for OCDD and 1,006–12,463 ng/g (ppb) for OCDF. Pigment Blue 108 contained much lower concentrations of CDDs/CDFs, although OCDD and OCDF were also the predominant congeners detected at 23 and 11 ng/g, respectively. Violet 23 contained higher CDD/CDF concentrations than Direct Blue 108, but lower concentrations than Direct Blue 106. OCDD concentrations were 806–11,022 ng/g (ppb), while OCDF concentrations were 125–3,749 ng/g (ppb). The TEQ values for Direct Blue 106, Direct Blue 108, and Violet 23 were 35.4, 0.1, and 9.1 ng/g (ppb), respectively.

Textile products. A study has identified sources of CDDs/CDFs found in textiles. Horstmann and McLachlan (1994) detected CDD/CDF concentrations in new textile products ranging from <50 pg/g to as high as 290,000 pg/g. The study authors believe that textile finishing processes are not the source of the high CDD/CDF concentrations because of the randomness of the textiles with high concentrations. Since PCP was still being used in developing countries at the time the study was conducted, especially for purposes of preserving cotton during sea transport, the study authors hypothesized that this is a likely source.

Dry-cleaning fluid residues. Chemical analysis of dry-cleaning solvent residues collected in Germany prior to 1993 indicated that residues from machines using perchloroethylene contained an average concentration of 256 ppb CDD/CDF, with 2,3,7,8-TCDD being detected in 21 of 28 samples; however, the HpCDD and OCDD congeners comprised between 90 and 95% of the CDDs/CDFs found (Towara et al. 1992). Horstmann and McLachlan (1994) detected CDD/CDF residues in used dry-cleaning fluid and concluded that the source of the CDD/CDF residues in the dry-cleaning fluid were introduced by dry-cleaning new, unwashed textiles that had been treated with PCP.

Motor vehicle exhaust. CDDs have been identified in automobile exhaust emissions (Marklund et al. 1987, 1990). 2,3,7,8-TCDD was found in car exhaust from four Swedish cars running on leaded gasoline

at levels of <0.05–0.3 ng/24.8 km (0.002–0.01 ng/km) running cycle. PeCDD was also found in the exhaust of cars running on leaded gasoline at levels of 6–98 ng/24.8 km (0.24–3.95 ng/km). No CDDs were found in samples where unleaded gasoline was used at detection limits of 0.05 ng (2,3,7,8-TCDD) and 0.3 ng (PeCDD) (Marklund et al. 1987).

From the research conducted on CDD emissions from vehicles running on leaded and unleaded gasoline, it is clear that CDD emissions are typically less in cars running on unleaded gasoline. It should be noted, however, that because the use of leaded gasoline is no longer permitted in the vast majority of domestic automobiles in the United States, this source of CDD emissions to the air should have been significantly reduced (EPA 1996a).

5.6 GENERAL POPULATION EXPOSURE

Consumption of food (including human milk) is by far the most important pathway for exposure to CDDs for the general population, representing >90% of the total daily intake (Beck et al. 1989a; Hattemer-Frey and Travis 1989; Liem and van Zorge 1995; Rappe 1992; Schaum et al. 1994; Schecter et al. 1994a, 1994d, 1996a). Other pathways of exposure include inhalation of CDDs from municipal, medical, and industrial waste incinerators and other incineration and combustion processes (~2% of the daily intake), and ingestion of drinking water (<0.1% of the daily intake) (Schaum et al. 1994; Travis and Hattemer-Frey 1987).

The U.S. Department of Agriculture (USDA) Food Safety and Inspection Service (FSIS) examined levels of dioxin like compounds measured in FSIS-regulated meat and poultry (Dearfield et al. 2013). Several different exposure scenarios based upon EPA derived actual consumption pattern scenarios and recommended consumption guidelines were considered given the amount of beef or poultry consumed by a specific age group. They concluded that a typical U.S. adult daily exposure of dioxin-like substances in FSIS-regulated products is below the EPA-established RfD. The mean dioxin exposure from beef products based upon U.S. consumption rates is provided in Table 5-21.

Table 5-21. Mean Dioxin Exposure from Beef, Based on Beef Consumption

Demographic	Amount of beef consumed g/kg per day	Mean DLC[a] pg-TEQ/kg-body weight per day (non-lean beef)[b]	Mean DLC pg-TEQ/kg-body weight per day lean beef)
Whole population	0.77	0.098	0.031
Birth to 1 year	0.34	0.043	0.014
1–2 years	1.38	0.175	0.056
3–5 years	1.42	0.180	0.058
6–12 years	1.11	0.141	0.045
13–19 years	0.83	0.105	0.034
20–49 years	0.73	0.093	0.030
Females 13–49 years	0.60	0.076	0.024
≥50 years	0.58	0.074	0.024

[a]Non-lean beef 19.24% fat; lean beef 6.16% fat.
[b]DLC = dioxin-like compounds, includes 17 CDDs/CDFs and 4 non-ortho PCBs.

CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; PCB = polychlorinated biphenyl; TEQ = toxic equivalency

Source: Dearfield et al. 2013

An estimate of the daily intake of 2,3,7,8-TCDD by adults in the general U.S. population from ingestion of contaminated food items and drinking water and inhalation of ambient air is given in Table 5-22. Since levels of CDDs and CDFs have declined in environmental media, including food items, as emissions have been reduced, these estimated intakes are likely higher than current intakes. The average daily adult intake of 2,3,7,8-TCDD estimated by the model was 47 pg/day (Hattemer-Frey and Travis 1989) with a lower bound daily intake of 8 pg/day and an upper bound daily intake of 300 pg/day. Food, especially meat and dairy products, accounted for 98% of the total daily intake of 2,3,7,8-TCDD. Hattemer-Frey and Travis (1989) estimated that the average daily intake of 2,3,7,8-TCDD for an adult in the United States from meat alone was 23 pg/day, accounting for 50% of the total daily intake of 2,3,7,8-TCDD from food sources. The average daily intakes of 2,3,7,8-TCDD from milk, produce, and fish were 13 pg/day (27%), 5 pg/day (11%), and 5 pg/day (10%), respectively, of the total daily intake in the United States (Hattemer-Frey and Travis 1989). However, for certain subpopulations (recreational and subsistence fishers), fish consumption may be a more important source of CDDs. The maximum daily intake of 2,3,7,8-TCDD for residents of the Great Lakes region who regularly consume fish from the Great Lakes was estimated to be 390–8,400 pg/day (EPA 1985); however, levels of CDDs and CDFs in fish in the Great Lakes have dropped dramatically since the time of this study (Gandhi et al. 2019). For example, the 40-year trend of five major CDD/CDF congeners including 2,3,7,8-TCDD in lake trout from

Lake Ontario were shown to decrease approximately 96% from the late 1970s to 2013 (Gandhi et al. 2019). Inhalation of ambient air and ingestion of water are not major pathways of human exposure, accounting for only 2% (1 pg/day) and <0.01% ($6.5x10^{-3}$ pg/day), respectively, of the total daily intake of 2,3,7,8-TCDD (Hattemer-Frey and Travis 1989). The percentage of daily intake of 2,3,7,8-TCDD estimated by Hattemer-Frey and Travis (1989) from each exposure pathway agrees closely with estimates made by Schaum et al. (1994) for intakes of total CDDs/CDFs (Table 5-23). However, quantitatively, the estimates differ by a factor of 2–3 because Hattemer-Frey and Travis (1989) considered only 2,3,7,8_TCDD, while Schaum et al. (1994) based their estimates on all CDDs and CDFs. Lorber et al. (2009) estimated a decrease in dietary exposure to 17 CDD/CDFs of approximately 33% from the mid-1990s to the early 2000s using data from food samples collected between 2001 and 2004 by the FDA.

Table 5-22. Estimated Average Daily Intake of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) by the General U.S. Population

Source/pathway	Daily intake (pg/day)	Percentage of total daily intake
Ambient sources (total)	1.01	2
Air/inhalation	1	2
Water/ingestion	$6.5x10^{-3}$	<0.01
Soil/ingestion	–	–
Food sources (total)/ingestion	46	98
Produce	5	11
Milk	13	27
Meat	23	50
Fish	5	10
Total intake	47	100

Source: Hattemer-Frey and Travis 1989

Table 5-23. Estimated Daily Background Exposure to Chlorinated Dibenzo-*p*-Dioxins (CDDs) and Chlorinated Dibenzofurans in the General U.S. Population

Source	Daily intake (pg/day)	Percentage of total daily intake
Ambient sources (total)	3	2.5%
Air	2.2	1.8
Water	0.008	0.01
Soil	0.8	0.7
Food (total)	116	97%
Produce	–	–
Milk and milk products	42	35
Milk	18	15
Cheese	24	20

Table 5-23. Estimated Daily Background Exposure to Chlorinated Dibenzo-*p*-Dioxins (CDDs) and Chlorinated Dibenzofurans in the General U.S. Population

Source	Daily intake (pg/day)	Percentage of total daily intake
Meat/meat products/eggs	66.1	55
Pork	12	10
Beef	37	30.8
Chicken	13	11
Eggs	4.1	3.4
Fish and fish oil	7.8	6.6
Total exposure	120	100%

Source: Schaum et al. 1994

The FDA calculated exposure to CDDs/CDFs based upon data from its 2001–2004 Total Diet Study in which commercially sold food items are collected from different regions of the country and analyzed for specific CDD and CDF congeners (FDA 2006). The dietary exposure estimates from these data are provided in Table 5-24.

Table 5-24. Dietary CDD/CDF Exposure Estimate (pg WHO-TEQ/kg Body Weight/Month) by Food Category from TDS Foods Collected in 2001–2004

Group	Dairy and mixtures	Eggs and mixtures	Fats, oils, mixtures	Fish and mixtures	Fruits, vegetables and mixtures	Meat and mixtures	Poultry and mixtures	Other foods and mixtures	Total
All groups	1.5	0.1	0.2	0.9	0.5	4.5	0.2	1.8	9.6
Infants 6–11 months infants	6.0	0.3	0.1	0.2	1.5	2.4	0.6	1.7	12.8
Children 2 years	7.4	0.5	0.3	0.9	1.3	9.2	0.4	3.5	23.5
Children 6 years	5.0	0.2	0.3	0.8	0.7	7.5	0.3	3.6	18.5
Children 10 years	3.4	0.2	0.1	0.5	0.5	5.4	0.3	2.7	13.1
Females 14–16 years	1.2	0.1	0.1	0.6	0.3	3.5	0.2	1.9	7.8
Males 14–16 years	1.9	0.1	0.1	0.6	0.3	4.6	0.2	2.9	10.7
Women 25–30 years	1.0	0.1	0.1	0.8	0.3	2.6	0.2	1.5	6.6

Table 5-24. Dietary CDD/CDF Exposure Estimate (pg WHO-TEQ/kg Body Weight/Month) by Food Category from TDS Foods Collected in 2001–2004

Group	Dairy and mixtures	Eggs and mixtures	Fats, oils, mixtures	Fish and mixtures	Fruits, vegetables and mixtures	Meat and mixtures	Poultry and mixtures	Other foods and mixtures	Total
Men 25–30 years	1.0	0.2	0.1	0.4	0.3	4.3	0.2	1.9	8.4
Women 40–45 years	0.8	0.1	0.1	0.7	0.4	3.1	0.2	1.2	6.6
Men 40–45 years	1.1	0.1	0.1	0.7	0.4	4.1	0.3	1.2	7.9
Women 60–65 years	0.7	0.1	0.1	1.1	0.4	2.5	0.2	0.7	5.7
Men 60–65 years	0.8	0.2	0.2	1.1	0.4	3.7	0.2	0.9	7.4
Women >70 years	0.8	0.1	0.1	0.9	0.5	2.3	0.2	0.7	5.6
Men >70 years	1.1	0.1	0.2	1.0	0.5	3.1	0.2	0.8	7.1

CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; TDS = Total Diet Study; TEQ = toxic equivalency; WHO = World Health Organization

Source: FDA 2006

The National Academy of Science (NAS) has also estimated dioxin (CDD and CDF congeners) intake from meat, poultry, and fish for various age and demographic groups using a subset of data from the FDA's Total Diet Study; these estimates, for consumers of high and low amounts of animal products, are presented in Table 5-25 (NAS 2003).

Table 5-25. Estimated Intake of CDDs and CDFs from Meat, Poultry, and Fish

	TEQ intake[a] (pg/kg body weight/day)
Males and females, 1–5 years of age (not breastfeeding)	1.76–1.26
Males and females, 6–11 years of age	1.14–0.77
Males, 12–19 years of age	0.89–0.47
Males, ≥20 years of age	0.69–0.40
Females, 12–19 years of age, not pregnant or lactating	0.69–0.47
Females, ≥20 years of age, not pregnant or lactating	0.59–0.38

Table 5-25. Estimated Intake of CDDs and CDFs from Meat, Poultry, and Fish

	TEQ intake[a] (pg/kg body weight/day)
Females, pregnant or lactating	0.65–0.54
Males and females, ≥1 years of age, including pregnant or lactating	0.78–0.64

[a]Includes CDD and CDF congeners only; range represents average intake for consumers of high and low (<3 ounces) intakes of meat, poultry, and fish. TEQs calculated using 0.5 (LOD) for non-detects.

CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; LOD = limit of detection; TEQ = toxic equivalency

Source: NAS 2003

Based on their congener-specific analysis of 18 food samples collected in Binghamton, New York, Schecter et al. (1994d) estimated that the U.S. mean daily exposure to CDD equivalents for an adult (65 kg body weight) were 18–192 pg TEQs, depending on how not-detected values were treated. This is equal to a daily adult intake of CDDs/CDFs of 0.3–3.0 pg TEQs/kg body weight. The study authors reported that total CDDs were 0.35–2.91 ppt (wet weight) in fish, 0.6–59.3 ppt in meat products, and 0.6–14 ppt in dairy products. The total CDD/CDF TEQ values were 0.023–0.13 ppt for fish, 0.03–1.5 for meat products, and 0.04–0.7 for dairy products. The study authors reported that a vegetarian diet (vegan diet with no consumption of dairy products) might have health advantages by lowering daily intakes to only 2% of the level estimated for persons consuming fish, meat, and dairy products (Schecter et al. 1994a, 1994d). An ovo-lacto vegetarian diet that contains eggs and dairy products would not achieve this same reduction level. These same authors estimated the U.S. mean daily exposure to CDD equivalents based on an expanded analysis of 100 food samples collected in supermarkets in Binghamton, New York; Chicago, Illinois; Louisville, Kentucky; Atlanta, Georgia; and San Diego, California (Schecter et al. 1996a). For 1995, the study authors reported that the estimated U.S. mean daily exposure to CDDs/CDFs TEQs for an adult (65 kg body weight) ranged from 34 to 167 pg TEQs. This is equivalent to a daily adult intake of CDDs/CDFs of 0.52–2.57 pg TEQs/kg body weight. If PCB TEQs are also considered (where TEF values are available), the daily adult intake ranges from 1.16 to 3.57 pg TEQ/kg body weight/day. A follow-up to this study was published in 2001, in which 110 food items were purchased from the same locations (Schecter et al. 2001). The study collected 12 different types of foods from 4 categories: meat, fish, dairy, and milk. Levels of CDDs ranged from below the detection limits to 59.2 pg/g for an OCDD in a sample of butter. For adult men aged 20–79 years, the estimated total TEQ intake per day was calculated as 2.4 pg/kg body weight. A survey of CDDs/CDFs in total diet food samples in Canada was conducted by Ryan et al. (1997). The study authors found, through analysis of more than 100 food samples collected from commercial outlets in 1992 and 1993, that the total TEQ

intake for CDDs/CDFs was about 0.8 pg TEQs/kg/day. If all dioxin-like PCBs were also included, this TEQ value rose to approximately 1.2 pg TEQs/kg/day.

Combustion processes are widely recognized as a source of CDDs/CDFs. Using a model, Hattemer-Frey and Travis (1989) estimated a total daily intake of CDDs/CDFs of $3x10^{-4}$ ng TEQs/day associated with exposure to a typical, state-of-the-art municipal solid-waste (MSW) incinerator, assuming a CDD/CDF emission rate based on the geometric mean from 11 proposed MSW facilities. Daily intakes of CDDs/CDFs in TEQs associated with exposure to a typical state-of-the-art municipal waste incinerator were estimated to be $1.3x10^{-4}$ ng/day from inhalation, $1.1x10^{-4}$ ng/day from total ingestion, $5.7x10^{-5}$ ng/day for mother's milk, and $2.2x10^{-6}$ ng/day from dermal absorption. This total daily intake value ($3x10^{-4}$ ng TEQs/day) was 160 times lower than the estimated total daily background intake from all sources of CDDs (0.047 ng/day) to which the general U.S. population is exposed. Thus, the study authors concluded that MSW incinerators will not substantially increase human exposure to CDDs/CDFs above normal background levels (Hattemer-Frey and Travis 1989). Table 5-26 shows estimated average daily intakes of CDD/CDF TEQs from various exposure pathways. Fries and Paustenbach (1990) evaluated the effects of 2,3,7,8-TCDD from incinerator emissions to humans. The study authors also concluded that airborne emissions of CDDs/CDFs from modern waste incinerators that are equipped with appropriate air pollution devices should not pose a significant health hazard via inhalation of CDD contaminated particles or via contamination of foods regardless of the incinerator location. Hattemer-Frey and Travis (1989) focused on ideal state-of-the-art incinerators. In a later analysis, Travis and Hattemer-Frey (1991) estimated that the total daily intake of CDDs/CDFs (TEQs) by a maximally exposed individual living near a modern municipal solid waste incinerator was 0.7 pg/day (0.9% of total daily intake), and 92.8 pg/day (99.1%of total daily intake) was from all other background exposures. These estimates are supported by data of Schecter et al. (1995) who found that workers who operate municipal waste incinerators have blood levels of TEQs that do not differ significantly from background levels.

Table 5-26. Estimated Average Daily Intake of TEQs Associated with Exposure to a Typical State-of-the-Art Municipal Waste Incinerator

Exposure pathway	Daily intake (ng/TEQ/day)	Percentage of total intake
Inhalation	$1.3x10^{-4}$	43
Total ingestion	$1.1x10^{-4}$	37
Mother's milk	$5.7x10^{-5}$	19

Table 5-26. Estimated Average Daily Intake of TEQs Associated with Exposure to a Typical State-of-the-Art Municipal Waste Incinerator

Exposure pathway	Daily intake (ng/TEQ/day)	Percentage of total intake
Dermal absorption	$2.2x10^{-6}$	1
Total intake	$3.0x10^{-4}$	100

TEQ = toxic equivalency

Source: Hattemer-Frey and Travis 1989

The presence of CDDs in cigarette smoke is also of importance with respect to inhalation exposure since cigarette smoke is inhaled directly into the lungs. Daily exposure to CDDs by smoking 20 cigarettes was estimated to be 18 TEQ pg/day equivalent to a daily intake of 0.26 pg/kg body weight/day (for a 70-kg adult) (Lofroth and Zebuhr 1992).

The presence of CDDs in a variety of consumer products ranging from plastic packaging to colored candle wax, and from textiles to air filters for home-heating systems suggests that CDDs are virtually ubiquitous in the environment (Beck et al. 1989c; Berry et al. 1993; Horstmann and McLachlan 1994; Malisch 1994; Ryan et al. 1992). 2,3,7,8-TCDD and 2,3,7,8-TCDF have been found in many paper products, including coffee-filter paper, although present-day paper products now contain <1 ng/kg TEQ and changes in the milling process have drastically reduced the levels of CDDs/CDFs in these products. The general population of the United States is continuously exposed to small amounts of CDDs, as exemplified by the fact that all human adipose tissue samples contain CDDs (EPA 1986a; Orban et al. 1994; Patterson et al. 1986a; Ryan et al. 1986; Schecter et al. 1986b; Stanley et al. 1986). Results of the NHATS conducted in 1982, which estimated the general population exposure to toxic organic chemicals, showed that 2,3,7,8-TCDD was detected in 35 of 46 (76%) composite samples, with an average lipid-adjusted concentration of 6.2±3.3 ppt (EPA 1986a; Stanley et al. 1986). The average concentration of the other CDD compounds ranged from 43.5 ppt for PeCDD (detected in 91% of the composites) to 694 ppt for OCDD (detected in 100% of the composites). The congener distributions found in adipose tissue are similar to those found in human milk (i.e., OCDD was the most abundant congener and 2,3,7,8-TCDD was the least abundant). The analysis of 46 composite adipose samples verified the prevalence of the 2,3,7,8-substituted tetra- through octaCDDs in the U.S. population (EPA 1986a; Stanley et al. 1986). The number of adipose samples in each composite was defined based on differences in age, gender, race, and regional affiliation of the individuals from whom the specimens were collected. The results also suggested that adipose tissue concentrations tended to increase with age for the congeners tested, with the exception of PeCDD. The NHATS study also showed regional differences in CDD concentrations in

adipose tissue, with the greatest exposure occurring in the East North Central region of the United States (i.e., Ohio, Michigan, Indiana, Illinois, and Wisconsin). Exposure was also relatively high in the mid-Atlantic and East South-Central regions (Phillips and Birchard 1991).

Results of the 1987 NHATS Study were summarized by Orban et al. (1994). Human adipose samples from autopsy cases were obtained through a network of pathologists to provide a representative sample of the general U.S. population. NHATS samples collected during 1987 were analyzed for 7 CDDs and 10 CDFs and the results are summarized in Table 5-27. Data were evaluated by census region, age group, sex, and racial group. The average concentration of 2,3,7,8-TCDD in adipose tissue in the U.S. population was estimated to be 5.38 pg/g (±6%). The 1987 survey data clearly show that nearly all of the CDD/CDF congeners increased with the age of the donor (i.e., the highest concentrations occur in the ≥45-year-old age group and the lowest concentrations occur in the 0–14-year-old age group). Orban et al. (1994) also compared NHATS 1987 data to the NHATS 1982 data. Because of slight differences in study design, the congeners that were most comparable between the two surveys were 2,3,7,8-TCDD and OCDD. Statistical analysis of the two survey data sets revealed no significant differences between the national average concentration of 2,3,7,8-TCDD determined in 1982 and 1987. There were also no significant differences in the profiles with respect to census region, sex, and race. With respect to age, however, there was a significant difference; the 1987 NHATS data demonstrated that the concentration of 2,3,7,8-TCDD consistently increased with the age of the donor. The average concentration of 2,3,7,8-TCDD in the 1987 survey increased from 1.98 pg/g in the 0–14-year-old group, to 4.37 pg/g in the 15–44-year-old group, to 9.4 pg/g in the ≥45-year-old group. The average concentration of OCDD in the 1982 survey was 768 pg/g (±79.7 standard error) as compared to 724 pg/g (± standard error 28.6 pg/g) in the 1987 study.

Table 5-27. Chlorinated Dioxins and Dibenzofurans in Adipose Tissue of the General U.S. Population

	Concentration (pg/g, lipid basis)[a]		
Compound	Minimum	Median	Maximum
2,3,7,8-TCDD	<0.980[b]	6.54	15.1
2,3,7,8-TCDF	0.893	1.89	3.88
1,2,3,7,8-PeCDD	<2.44	10.2	24.4
1,2,3,7,8,9-HxCDD	<3.86[b]	11.5	22.0
1,2,3,4,7,8/1,2,3,6,7,8-HxCDD	13.3	76.1	174.0

Table 5-27. Chlorinated Dioxins and Dibenzofurans in Adipose Tissue of the General U.S. Population

	Concentration (pg/g, lipid basis)[a]		
Compound	Minimum	Median	Maximum
1,2,3,4,6,7,8-HpCDD	20.9	110.0	230.0
OCDD	152.0	838.0	1,630.0

[a]Not detected concentrations were replaced by one-half the limit of detection.
[b]The minimum concentration is less than the minimum reported limit of detection.

HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; OCDD = octachlorodibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin

Source: Orban et al. 1994

Analysis of human adipose tissue from 35 autopsy cases from Georgia and Utah found 2,3,7,8-TCDD in all of the samples at a concentration range (whole-weight) of 2.7–19 ppt (Patterson et al. 1986b). The geometric mean value for 2,3,7,8-TCDD in these samples on a whole-weight basis was 7.1 ppt. The geometric mean value for 2,3,7,8-TCDD in 31 of these samples on a lipid basis was 9.6 ppt. The histories of exposure to 2,3,7,8-TCDD were not known for any of the autopsy cases (Patterson et al. 1986b).

The levels of select CDD congeners were measured in blood samples collected as part of the NHANES. 1,2,3,4,6,7,8-HpCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, OCDD, 1,2,3,7,8 PeCDD, and 2,3,7,8-TCDD levels for survey years 1999–2000, 2001–2002, and 2003–2004 are presented in the National Report on Human Exposures to Environmental Chemicals (CDC 2024a). These data are summarized in Tables 5-28–5-34. Weighted arithmetic means and unadjusted standard errors of pooled serum concentrations from 2005 to 2012 survey years are also available (CDC 2024b) (Tables 5-35–5-41).

Table 5-28. Serum 1,2,3,4,6,7,8-HpCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population

Survey years	Geometric mean (95% confidence limit)	Selected percentiles (95% confidence limit)			
		50th	75th	90th	95th
Total					
1999–2000	NC	<LOD	58.2 (<LOD–63.6)	86.0 (75.5–96.7)	112 (101–131)
2001–2002	39.0 (33.7–45.0)	40.2 (34.9–46.9)	68.7 (56.7–82.2)	115 (88.2–138)	147 (126–181)
2003–2004	25.3 (23.4–27.3)	24.9 (22.8–26.9)	42.5 (38.8–48.1)	70.4 (62.7–80.1)	91.3 (73.5–117)
Age group					
12–19 years					
1999–2000	NC	<LOD	<LOD	<LOD	63.6 (<LOD–75.6)
2001–2002	ND	ND	ND	ND	ND
2003–2004	16.7 (15.1–18.4)	16.4 (15.1–18.3)	23.6 (21.5–25.8)	33.4 (28.6–36.8)	46.7 (34.5–78.1)
≥20 years					
1999–2000	NC	<LOD	62.0 (57.1–66.7)	92.9 (81.2–101)	120 (102–139)
2001–2002	39.0 (33.7–45.0)	40.2 (34.9–46.9)	68.7 (56.7–82.2)	115 (88.2–138)	147 (126–181)
2003–2004	26.8 (24.6–29.2)	27.3 (24.6–29.0)	45.6 (41.3–53.2)	73.7 (64.1–88.6)	95.0 (76.1–126)
Gender					
Males					
1999–2000	NC	<LOD	<LOD	73.6 (69.0–80.8)	94.7 (83.1–103)
2001–2002	36.6 (31.7–42.3)	39.0 (33.3–42.6)	62.1 (49.7–75.0)	102 (75.8–132)	138 (103–169)
2003–2004	24.2 (21.7–27.0)	23.2 (21.1–25.6)	40.6 (35.3–46.9)	64.2 (58.8–73.7)	85.0 (65.8–113)
Females					
1999–2000	NC	<LOD	62.7 (<LOD–69.1)	102 (86.0–118)	131 (111–164)
2001–2002	41.2 (34.9–48.7)	43.6 (35.3–52.4)	76.0 (59.5–90.1)	125 (93.4–150)	158 (130–191)
2003–2004	26.3 (24.4–28.3)	26.8 (24.3–28.3)	44.4 (41.1–50.2)	76.1 (65.3–89.1)	95.7 (80.7–128)
Race/ethnicity					
Mexican Americans					
1999–2000	NC	<LOD	61.4 (<LOD–69.0)	97.7 (82.8–111)	132 (108–159)
2001–2002	39.6 (35.7–43.9)	39.7 (33.6–47.4)	64.0 (55.8–74.7)	107 (82.4–128)	149 (111–171)
2003–2004	25.8 (22.6–29.4)	26.1 (20.9–30.9)	41.9 (36.7–44.7)	61.0 (49.7–71.9)	80.1 (65.0–89.1)

Table 5-28. Serum 1,2,3,4,6,7,8-HpCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population

Survey years	Geometric mean (95% confidence limit)	Selected percentiles (95% confidence limit)			
		50th	75th	90th	95th
Non-Hispanic blacks					
1999–2000	NC	<LOD	58.1 (<LOD–71.1)	95.0 (75.1–110)	125 (102–183)
2001–2002	43.7 (35.4–54.0)	42.8 (32.2–59.8)	80.6 (60.9–106)	134 (101–166))	167 (130–230
2003–2004	25.8 (22.6–29.4)	23.7 (20.7–27.1)	41.2 (32.6–56.4)	69.2 (54.6–115)	115 (67.1–164)
Non-Hispanic whites					
1999–2000	NC	<LOD	59.0 (<LOD–64.8)	84.9 (72.0–97.0)	106 (96.7–122)
2001–2002	39.3 (33.0–46.8)	40.5 (34.0–50.1)	71.0 (56.3–87.5)	117 (87.1–147)	147 (125–186)
2003–2004	25.0 (22.6–27.7)	24.6 (22.3–27.4)	42.6 (39.4–48.5)	73.5 (60.4–86.7	93.7 (71.6–127)

HpCDD = heptachlorodibenzo-*p*-dioxin; LOD = limit of detection (LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 55.9, 10.3, and 13.0 pg/g lipid, respectively); NC = not calculated (proportion of results below LOD was too high to provide a valid result); ND = data not collected for this age group for survey years 2001–2002.

Source: CDC 2024a

Table 5-29. Serum 1,2,3,4,7,8-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population

Survey years	Geometric mean (95% confidence limit)	Selected percentiles (95% confidence limit)			
		50th	75th	90th	95th
Total					
2001–2002	NC	<LOD	<LOD	10.7 (<LOD–13.9)	14.9 (11.7–20.0)
2003–2004		<LOD	<LOD	<LOD	<LOD
Age group					
12–19 years					
2001–2002	ND	ND	ND	ND	ND
2003–2004	NC	<LOD	<LOD	<LOD	<LOD
≥20 years					
2001–2002	NC	<LOD	<LOD	10.7 (<LOD–13.9)	14.9 (11.7–20.0)
2003–2004	NC	<LOD	<LOD	<LOD	<LOD
Gender					
Males					
2001–2002	NC	<LOD	<LOD	10.9 (<LOD–14.3)	14.7 (11.5–17.6)
2003–2004	NC	<LOD	<LOD	<LOD	<LOD
Females					
2001–2002	NC	<LOD	<LOD	10.7 (<LOD–14.1)	15.6 (11.1–23.0)
2003–2004	NC	<LOD	<LOD	<LOD	<LOD
Race/ethnicity					
Mexican Americans					
2001–2002	NC	<LOD	<LOD	<LOD	9.20 (<LOD–11.8
2003–2004	NC	<LOD	<LOD	<LOD	<LOD
Non-Hispanic blacks					
2001–2002	NC	<LOD	<LOD	13.9 (<LOD–17.6)	18.3 (13.9–23.0)
2003–2004	NC	<LOD	<LOD	<LOD	<LOD

Table 5-29. Serum 1,2,3,4,7,8-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population

Survey years	Geometric mean (95% confidence limit)	Selected percentiles (95% confidence limit)			
		50th	75th	90th	95th
Non-Hispanic whites					
2001–2002	NC	<LOD	<LOD	11.3 (<LOD–14.4)	15.1 (12.0–20.5)
2003–2004	NC	<LOD	<LOD	<LOD	<LOD

HxCDD = hexachlorodibenzo-*p*-dioxin; LOD = limit of detection (LODs for survey years 2001–2002 and 2003–2004 were 9.0 and 11.9 pg/g lipid, respectively); NC = not calculated (proportion of results below LOD was too high to provide a valid result); ND = data not collected for this age group for survey years 2001–2002.

Source: CDC 2024a

Table 5-30. Serum 1,2,3,6,7,8-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population

Survey years	Geometric mean (95% confidence limit)	Selected percentiles (95% confidence limit)			
		50th	75th	90th	95th
Total					
1999–2000	NC	<LOD	32.6 (28.3–38.2)	56.9 (47.4–67.3)	74.0 (68.3–82.4)
2001–2002	34.6 (29.6–40.6)	39.2 (32.7–44.7)	60.8 (50.3–74.2)	95.2 (76.2–120)	128 (99.4–153)
2003–2004	17.2 (15.7–18.9)	20.0 (17.8–22.9)	36.5 (32.2–40.0)	53.0 (48.1–59.6)	68.5 (59.6–74.9)
Age group					
12–19 years					
1999–2000	NC	<LOD	<LOD	<LOD	26.7 (20.2–29.6)
2001–2002	ND	ND	ND	ND	ND
2003–2004	NC	<LOD	<LOD	16.1 (14.3–18.1)	19.4 (16.4–27.7)
≥20 years					
1999–2000	NC	<LOD	36.2 (31.5–40.7)	62.8 (53.6–69.1)	75.6 (70.5–84.2)
2001–2002	34.6 (29.6–40.6)	39.2 (32.7–44.7)	60.8 (50.3–74.2)	95.2 (76.2–120))	128 (99.4–153
2003–2004	19.7 (17.8–21.8)	23.8 (20.7–26.4)	39.3 (35.4–42.2)	56.6 (49.7–63.8)	70.8 (60.7–82.2)
Gender					
Males					
1999–2000	NC	<LOD	31.5 (23.7–38.2)	55.0 (45.7–64.2)	71.3 (59.4–79.4)
2001–2002	34.1 (28.3–41.1)	38.9 (32.1–44.7)	61.9 (50.0–79.5)	94.9 (70.8–131)	130 (88.5–181)
2003–2004	17.5 (15.5–19.8)	19.8 (17.8–21.6)	35.5 (29.8–40.3)	52.9 (45.4–63.2)	70.2 (57.5–88.7)
Females					
1999–2000	NC	<LOD	34.9 (29.1–39.7)	61.2 (51.0–69.2)	74.9 (68.4–92.2)
2001–2002	35.1 (29.9–41.2)	40.1 (32.4–46.3)	59.8 (49.8–72.3)	97.6 (77.1–114))	126 (108–142
2003–2004	16.9 (15.3–18.6)	20.5 (17.8–24.6)	36.9 (33.2–41.0)	53.6 (48.3–59.6)	65.6 (60.0–73.4)
Race/ethnicity					
Mexican Americans					
1999–2000	NC	<LOD	21.3 (<LOD–27.6)	43.3 (34.1–52.3)	58.0 (49.5–64.8)
2001–2002	18.3 (15.6–21.4)	21.2 (19.4–25.0)	31.9 (27.5–40.3)	51.5 (40.3–69.9)	68.3 (48.0–111)
2003–2004			21.1 (16.3–26.5)	32.2 (24.5–47.4)	43.0 (31.5–65.3)

Table 5-30. Serum 1,2,3,6,7,8-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population

Survey years	Geometric mean (95% confidence limit)	Selected percentiles (95% confidence limit)			
		50th	75th	90th	95th
Non-Hispanic blacks					
1999–2000	NC	<LOD	31.9 (26.6–41.2)	56.7 (44.9–74.6)	81.6 (72.2–91.7)
2001–2002	38.9 (33.6–45.0)	40.3 (33.5–47.3)	63.5 (54.6–76.9)	93.9 (78.7–133))	136 (92.6–185
2003–2004	16.2 (12.9–20.4)	18.1 (14.4–21.6)	34.9 (28.4–42.9)	54.5 (44.4–69.4)	74.0 (54.3–122)
Non-Hispanic whites					
1999–2000	NC	<LOD	35.5 (29.7–40.0)	60.9 (51.4–68.3)	74.3 (68.3–83.0)
2001–2002	37.8 (31.5–45.4)	42.8 (33.9–51.2)	65.0 (52.3–82.9)	99.6 (78.4–130)	131 (103–165)
2003–2004	18.7 (17.0–20.6)	22.9 (19.9–26.2)	38.0 (35.2–41.5)	56.6 (48.7–63.8)	69.0 (60.6–74.9)

HxCDD = hexachlorodibenzo-*p*-dioxin; LOD = limit of detection (LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 20.1, 9.1, and 12.3 pg/g lipid, respectively); NC = not calculated (proportion of results below LOD was too high to provide a valid result); ND = data not collected for this age group for survey years 2001–2002

Source: CDC 2024a

Table 5-31. Serum 1,2,3,7,8,9-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population

Survey years	Geometric mean (95% confidence limit)	Selected percentiles (95% confidence limit)			
		50th	75th	90th	95th
Total					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	12.5 (10.5–15.3)	17.0 (14.3–20.0)
2003–2004	NC	<LOD	<LOD	<LOD	<LOD
Age group					
12–19 years					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	ND	ND	ND	ND	ND
2003–2004	NC	<LOD	<LOD	<LOD	<LOD
≥20 years					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	12.5 (10.5–15.3)	17.0 (14.3–20.0)
2003–2004	NC	<LOD	<LOD	<LOD	<LOD
Gender					
Males					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002				12.1 (<LOD–14.8)	15.1 (12.9–18.5)
2003–2004	NC	<LOD	<LOD	<LOD	<LOD
Females					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002				13.0 (10.7–16.8)	18.3 (15.7–21.1)
2003–2004	NC	<LOD	<LOD	<LOD	<LOD
Race/ethnicity					
Mexican Americans					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	9.60 (<LOD–11.6)	12.2 (<LOD–20.6)
2003–2004	NC	<LOD	<LOD	<LOD	<LOD

Table 5-31. Serum 1,2,3,7,8,9-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population

Survey years	Geometric mean (95% confidence limit)	Selected percentiles (95% confidence limit)			
		50th	75th	90th	95th
Non-Hispanic blacks					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	14.6 (11.2–20.0)	19.9 (14.6–23.9)
2003–2004	NC	<LOD	<LOD	<LOD	<LOD
Non-Hispanic whites					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	12.9 (9.90–15.9)	17.3 (14.7–20.6)
2003–2004	NC	<LOD	<LOD	<LOD	<LOD

HxCDD = hexachlorodibenzo-*p*-dioxin; LOD = limit of detection (LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 20.3, 9.3, and 12.3 pg/g lipid, respectively); NC = not calculated (proportion of results below LOD was too high to provide a valid result); ND = data not collected for this age group for survey years 2001–2002

Source: CDC 2024a

Table 5-32. Serum 1,2,3,4,6,7,8,9-OCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population

Survey years	Geometric mean (95% confidence limit)	Selected percentiles (95% confidence limit)			
		50th	75th	90th	95th
Total					
1999–2000	NC	<LOD	406 (359–453)	674 (597–767)	913 (787–1,010)
2001–2002	346 (<LOD–394)	333 (<LOD–402)	573 (498–668)	944 (780–1,090)	1,260 (998–1,610)
2003–2004	NC	<LOD	336 (283–389)	582 (490–658)	767 (645–913)
Age group					
12–19 years					
1999–2000	NC	<LOD	<LOD	<LOD	421 (363–517)
2001–2002	ND	ND	ND	ND	ND
2003–2004	NC	<LOD	<LOD	244 (<LOD–330)	352 (264–458)
≥20 years					
1999–2000	NC	<LOD	445 (389–496)	710 (624–802))	948 (822–1,080
2001–2002	346 (<LOD–394)	333 (<LOD–402)	573 (498–668)	944 (780–1,090)	1260 (998–1,610)
2003–2004	220 (<LOD–244)	223 (<LOD–243)	358 (297–421)	597 (502–719)	794 (665–978)
Gender					
Males					
1999–2000	NC	<LOD	<LOD	517 (447–580)	704 (563–838)
2001–2002	NC	<LOD	442 (346–579)	767 (593–968)	1,030 (837–1,240)
2003–2004	NC	<LOD	270 (244–320)	457 (377–559)	668 (501–856)
Females					
1999–2000	NC	<LOD	504 (422–579)	802 (674–928)	1,010 (928–1,180)
2001–2002	410 (356–472)	405 (335–502)	647 (574–751)	1,020 (858–1,360)	1,450 (1,060–1,780)
2003–2004	235 (<LOD–256)	238 (225–248)	402 (321–486)	640 (551–749)	829 (675–1,020)
Race/ethnicity					
Mexican Americans					
1999–2000	NC	<LOD	418 (365–502)	703 (610–873)	940 (737–1,230)
2001–2002	NC	<LOD	432 (394–545)	755 (578–1,220)	1,150 (696–1,640)
2003–2004	NC	<LOD	296 (225–356)	452 (363–540)	588 (417–861)

Table 5-32. Serum 1,2,3,4,6,7,8,9-OCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population

Survey years	Geometric mean (95% confidence limit)	Selected percentiles (95% confidence limit)			
		50th	75th	90th	95th
Non-Hispanic blacks					
1999–2000	NC	<LOD	444 (371–519)	741 (566–983)	1,120 (799–1,560)
2001–2002	421 (352–503)	420 (339–509)	682 (537–907)	1,110 (956–1,520)	1,640 (1,130–1,900)
2003–2004	NC	<LOD	345 (276–455)	642 (513–883)	926 (636–1,310)
Non-Hispanic whites					
1999–2000	NC	<LOD	391 (333–452)	625 (562–754)	861 (676–1,010)
2001–2002	349 (<LOD–409)	335 (<LOD–421)	574 (496–679)	945 (764–1,170)	1,290 (972–1,660)
2003–2004	NC	<LOD	343 (282–403)	585 (464–674)	758 (635–922)

LODs = limit of detection (LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 329.0, 319.0, and 218.0 pg/g lipid, respectively); NC = not calculated (proportion of results below LOD was too high to provide a valid result); ND = data not collected for this age group for survey years 2001–2002; OCDD = octachlorodibenzo-*p*-dioxin

Source: CDC 2024a

Table 5-33. Serum 1,2,3,7,8-PeCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population

Survey years	Geometric mean (95% confidence limit)	Selected percentiles (95% confidence limit)			
		50th	75th	90th	95th
Total					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	11.3 (9.30–13.6)	15.8 (13.3–19.8)
2003–2004	NC	<LOD	6.10 (5.50–6.80)	9.00 (8.30–9.70)	11.0 (9.90–12.2)
Age group					
12–19 years					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	ND	ND	ND	ND	ND
2003–2004	NC	<LOD	<LOD	<LOD	4.80 (<LOD–5.90)
≥20 years					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	11.3 (9.30–13.6)	15.8 (13.3–19.8)
2003–2004	NC	<LOD	6.60 (5.90–7.20)	9.30 (8.60–10.1)	11.3 (10.1–12.7)
Gender					
Males					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	10.8 (9.10–13.3)	14.5 (11.7–19.4)
2003–2004	NC	<LOD	5.90 (5.30–6.40)	8.90 (7.90–9.60)	11.0 (9.60–12.7)
Females					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	6.10 (<LOD–7.80)	11.8 (9.40–14.3)	16.6 (13.7–20.8)
2003–2004	NC	<LOD	6.50 (5.70–7.20)	9.10 (8.30–10.1)	11.0 (10.0–12.2)
Race/ethnicity					
Mexican Americans					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	<LOD	8.70 (<LOD–12.7)
2003–2004	NC	<LOD	<LOD	6.50 (5.20–7.90)	7.80 (6.70–9.20)

Table 5-33. Serum 1,2,3,7,8-PeCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population

Survey years	Geometric mean (95% confidence limit)	Selected percentiles (95% confidence limit)			
		50th	75th	90th	95th
Non-Hispanic blacks					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	7.70 (<LOD–9.30)	13.9 (9.60–18.4)	18.4 (14.2–24.0)
2003–2004	NC	<LOD	6.40 (5.30–8.20)	9.90 (8.50–13.4)	14.4 (9.60–20.1)
Non-Hispanic whites					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	11.7 (9.50–14.3)	16.7 (13.6–20.2)
2003–2004	NC	<LOD	6.50 (5.80–7.10)	9.30 (8.60–10.0)	11.1 (10.1–12.2)

LOD = limit of detection (LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 14.2, 6.0, and 4.5 pg/g lipid, respectively); NC = not calculated (proportion of results below LOD was too high to provide a valid result); ND = data not collected for this age group for survey years 2001–2002; PeCDD = pentachlorodibenzo-*p*-dioxin

Source: CDC 2024a

Table 5-34. Serum 2,3,7,8-TCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population

Survey years	Geometric mean (95% confidence limit)	Selected percentiles (95% confidence limit)			
		50th	75th	90th	95th
Total					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	<LOD	<LOD
2003–2004	NC	<LOD	<LOD	4.10 (<LOD–4.40)	5.20 (4.30–5.80)
Age group					
12–19 years					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	ND	ND	ND	ND	ND
2003–2004	NC	<LOD	<LOD	<LOD	<LOD
≥20 years					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	<LOD	<LOD
2003–2004	NC	<LOD	<LOD	4.30 (3.90–4.60)	5.30 (4.50–6.10)
Gender					
Males					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	<LOD	<LOD
2003–2004	NC	<LOD	<LOD	<LOD	4.60 (3.80–5.30)
Females					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	<LOD	6.40 (<LOD–9.20)
2003–2004	NC	<LOD	<LOD	4.40 (4.00–4.90)	5.50 (4.50–6.60)
Race/ethnicity					
Mexican Americans					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	<LOD	<LOD
2003–2004	NC	<LOD	<LOD	<LOD	3.80 (<LOD–5.50)

Table 5-34. Serum 2,3,7,8-TCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population

Survey years	Geometric mean (95% confidence limit)	Selected percentiles (95% confidence limit)			
		50th	75th	90th	95th
Non-Hispanic blacks					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	<LOD	7.50 (<LOD–10.0)
2003–2004	NC	<LOD	<LOD	4.50 (<LOD–6.10)	6.20 (4.40–10.3)
Non-Hispanic whites					
1999–2000	NC	<LOD	<LOD	<LOD	<LOD
2001–2002	NC	<LOD	<LOD	<LOD	<LOD
2003–2004	NC	<LOD	<LOD	4.10 (<LOD–4.50)	5.20 (4.30–5.90)

LOD = limit of detection (LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 112.1, 5.8, and 3.8 pg/g lipid, respectively); NC = not calculated; (proportion of results below LOD was too high to provide a valid result); ND = data not collected for this age group for survey years 2001–2002; TCDD = tetrachlorodibenzo-*p*-dioxin

Source: CDC 2024a

Table 5-35. Serum 1,2,3,4,6,7,8-HpCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
Non-Hispanic whites	Male	12–19	2005–2006	19.2	1.6	9
			2007–2008	14.5	0.3	6
			2009–2010	13.2	0.5	10
			2011–2012	NC		6
		20–39	2005–2006	19.4	1.4	12
			2007–2008	16.9	1.6	15
			2009–2010	17.1	1	17
			2011–2012	24.3	3.6	12
		40–59	2005–2006	36.1	4.6	12
			2007–2008	21.0	1.7	15
			2009–2010	24.1	2.5	17
			2011–2012	23.0	2.7	12
		≥60	2005–2006	47.8	4.3	15
			2007–2008	36.5	2.1	23
			2009–2010	30.1	1.6	21
			2011–2012	37.1	1.4	12
	Female	12–19	2005–2006	15.0	1	10
			2007–2008	13.0	0.8	7
			2009–2010	9.94	0.9	8
			2011–2012	NC		5
		20–39	2005–2006	20.5	2.1	13
			2007–2008	17.3	0.8	12
			2009–2010	15.1	2.6	18
			2011–2012	15.8	1	13
		40–59	2005–2006	32.2	2.9	13
			2007–2008	22.2	1.8	17
			2009–2010	19.0	0.9	17
			2011–2012	25.0	2.3	11

Table 5-35. Serum 1,2,3,4,6,7,8-HpCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		≥60	2005–2006	49.8	3	17
			2007–2008	41.6	3.8	19
			2009–2010	30.8	2.8	14
			2011–2012	49.4	6.2	14
Non-Hispanic blacks	Male	12–19	2005–2006	17.2	0.7	13
			2007–2008	12.2	0.8	6
			2009–2010	8.75	0.59	6
			2011–2012	NC		7
		20–39	2005–2006	16.1	1	6
			2007–2008	16.0	1	6
			2009–2010	11.6	1.5	7
			2011–2012	15.7	1.3	9
		40–59	2005–2006	23.4	1.6	5
			2007–2008	20.8	1.3	6
			2009–2010	17.6	2.6	7
			2011–2012	21.7	3.2	7
		≥60	2005–2006	44.9	5.7	5
			2007–2008	28.9	4.7	8
			2009–2010	24.4	1.6	9
			2011–2012	30.1	3.3	9
	Female	12–19	2005–2006	15.9	1.7	14
			2007–2008	11.0	0.9	4
			2009–2010	8.67	0.72	6
			2011–2012	15.2	3.7	6
		20–39	2005–2006	20.8	1.6	7
			2007–2008	19.9	1.4	7
			2009–2010	13.6	1.9	7
			2011–2012	17.3	2.1	8

Table 5-35. Serum 1,2,3,4,6,7,8-HpCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		40–59	2005–2006	36.3	4.3	7
			2007–2008	28.1	1.8	6
			2009–2010	21.9	4.1	7
			2011–2012	33.2	3.7	8
		≥60	2005–2006	77.4	12.5	5
			2007–2008	55.1	5.3	6
			2009–2010	51.0	5.4	7
			2011–2012	50.9	5.6	7
Mexican-American	Male	12–19	2005–2006	15.3	1.1	11
			2007–2008	12.8	1	6
			2009–2010	12.5	0.9	8
			2011–2012	14.1	1.2	5
		20–39	2005–2006	26.0	2.6	9
			2007–2008	18.0	1.2	9
			2009–2010	19.9	2.1	8
			2011–2012	23.0	3.7	4
		40–59	2005–2006	34.5	3.6	4
			2007–2008	29.0	2	6
			2009–2010	29.5	2.2	7
			2011–2012	38.2	4	3
		≥60	2005–2006	40.3	5	4
			2007–2008	28.2	3.2	5
			2009–2010	46.0	7.2	5
			2011–2012	40.2	1.2	2
	Female	12–19	2005–2006	13.2	0.7	16
			2007–2008	11.2	2.3	5
			2009–2010	7.94	0.68	7
			2011–2012	NC		4

Table 5-35. Serum 1,2,3,4,6,7,8-HpCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		20–39	2005–2006	25.1	1.9	9
			2007–2008	23.0	2.6	7
			2009–2010	14.0	2.2	10
			2011–2012	17.0	1.9	3
		40–59	2005–2006	41.8	4.3	6
			2007–2008	30.9	3	5
			2009–2010	39.2	4.3	9
			2011–2012	29.9	1.6	3
		≥60	2005–2006	59.1	6.9	3
			2007–2008	53.6	2.3	5
			2009–2010	68.0	7.7	6
			2011–2012	46.5	8.3	3
All Hispanic	Male	12–19	2009–2010	12.4	0.8	11
			2011–2012	14.5	1.1	7
		20–39	2009–2010	16.9	1.9	13
			2011–2012	19.2	2.6	8
		40–59	2009–2010	2.3	2.3	12
			2011–2012	27.7	5.2	6
		≥60	2009–2010	6.3	6.3	8
			2011–2012	30.6	4.3	6
	Female	12–19	2009–2010	8.23	0.56	10
			2011–2012	13.1	1.7	7
		20–39	2009–2010	14.1	1.6	14
			2011–2012	15.6	1.2	7
		40–59	2009–2010	33.3	3.6	14
			2011–2012	24.4	2.3	7
		≥60	2009–2010	53.5	6.9	11
			2011–2012	43.7	4.4	7

Table 5-35. Serum 1,2,3,4,6,7,8-HpCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
Asians	Male	12–19	2011–2012	27.4	5.9	3
		20–39		30.1	3.9	6
		40–49		26.1	4.7	5
		≥60		37.4	3.4	4
	Female	12–19	2011–2012	19.5	4.3	3
		20–39		34.0	6.5	5
		40–49		50.9	7.5	6
		≥60		33.4	4.6	3

[a]Limits of detection for survey years 2005–2006, 2007–2008, 2009–2010, and 2011–2012 were 1.8, 0.62, 6.36, and 13.0 pg/g lipid, respectively.
[b]Weighted arithmetic means are not comparable to weighted geometric means; unadjusted standard errors do not incorporate survey design effects.
[c]Each pool was composed of serum from eight persons.

NC = not calculated (portion of results below limit of detection was too high to provide a valid result); HpCDD = heptachlorodibenzo-*p*-dioxin

Source: CDC 2024b

Table 5-36. Serum 1,2,3,4,7,8-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
Non-Hispanic whites	Male	12–19	2005–2006	NC	NC	9
			2007–2008	1.11	0.23	6
			2009–2010	1.08	0.06	10
			2011–2012	1.26	0.07	6
		20–39	2005–2006	1.44	0.35	12
			2007–2008	1.38	0.24	15
			2009–2010	1.79	0.1	17
			2011–2012	2.10	0.16	12
		40–59	2005–2006	4.47	0.42	12
			2007–2008	2.95	0.16	15
			2009–2010	2.84	0.2	17
			2011–2012	3.08	0.34	12
		≥60	2005–2006	7.15	0.76	15
			2007–2008	5.65	0.48	23
			2009–2010	4.51	0/19	20
			2011–2012	5.20	0.33	12
	Female	12–19	2005–2006	NC	NC	10
			2007–2008	NC	NC	7
			2009–2010	0.767	0.094	8
			2011–2012	0.79	0.064	5
		20–39	2005–2006	NC	NC	16
			2007–2008	1.10	0.18	12
			2009–2010	1.19	0.09	18
			2011–2012	1.49	0.13	12
		40–59	2005–2006	3.59	0.2	13
			2007–2008	2.45	0.21	17
			2009–2010	2.42	0.11	17
			2011–2012	2.86	0.21	11

Table 5-36. Serum 1,2,3,4,7,8-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		≥60	2005–2006	6.40	0.33	17
			2007–2008	5.71	0.43	20
			2009–2010	4.93	0.38	22
			2011–2012	6.44	0.61	14
Non-Hispanic blacks	Male	12–19	2005–2006	NC	NC	13
			2007–2008	NC	NC	6
			2009–2010	0.705	0.137	5
			2011–2012	1.37	0.26	7
		20–39	2005–2006	1.56	0.33	6
			2007–2008	1.06[d]	0.35	6
			2009–2010	1.17	0.15	7
			2011–2012	1.88	0.08	9
		40–59	2005–2006	2.78	0.37	5
			2007–2008	2.93	0.16	6
			2009–2010	2.34	0.22	7
			2011–2012	3.05	0.35	7
		≥60	2005–2006	6.65	0.19	5
			2007–2008	4.83	0.75	8
			2009–2010	3.85	0.34	9
			2011–2012	5.40	0.36	9
	Female	12–19	2005–2006	NC	NC	14
			2007–2008	NC	NC	4
			2009–2010	0.800	0.097	6
			2011–2012	0.81	0.159	5
		20–39	2005–2006	1.87	0.24	7
			2007–2008	0.972[d]	0.312	7
			2009–2010	1.23	0.13	7
			2011–2012	1.21	0.09	8

Table 5-36. Serum 1,2,3,4,7,8-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		40–59	2005–2006	3.83	0.44	7
			2007–2008	3.34	0.39	6
			2009–2010	2.49	0.36	7
			2011–2012	3.81	0.43	8
		≥60	2005–2006	12.7	1.7	5
			2007–2008	9.88	1.5	6
			2009–2010	6.79	0.82	7
			2011–2012	8.22	0.83	7
Mexican-American	Male	12–19	2005–2006	NC	NC	11
			2007–2008	NC	NC	6
			2009–2010	1.01	0.1	8
			2011–2012	1.08	0.07	5
		20–39	2005–2006	NC	NC	9
			2007–2008	1.44	0.19	9
			2009–2010	1.44	0.17	8
			2011–2012	2.08	0.14	4
		40–59	2005–2006	2.65[d]	0.93	4
			2007–2008	2.91	0.18	6
			2009–2010	2.66	0.13	7
			2011–2012	3.72	0.39	3
		≥60	2005–2006	4.96	0.17	4
			2007–2008	4.94	0.19	5
			2009–2010	5.68	0/82	5
			2011–2012	4.39	1.17	2
	Female	12–19	2005–2006	NC	NC	16
			2007–2008	NC	NC	5
			2009–2010	0.544	0.043	7
			2011–2012	NC		4

Table 5-36. Serum 1,2,3,4,7,8-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		20–39	2005–2006	NC	NC	9
			2007–2008	1.47	0.25	7
			2009–2010	0.944	0.133	10
			2011–2012	1.51	0.35	3
		40–59	2005–2006	3.64	0.8	6
			2007–2008	3.03	0.4	5
			2009–2010	2.76	0.18	9
			2011–2012	2.65	0.18	3
		≥60	2005–2006	7.30	0.67	3
			2007–2008	6.26	0.61	5
			2009–2010	6.95	0.96	6
			2011–2012	5.61	0.76	3
All Hispanics	Male	12–19	2009–2010	0.954	0.081	11
			2011–2012	1.03	0.007	7
		20–39	2009–2010	1.30	0.14	13
			2011–2012	1.80	0.15	8
		40–59	2009–2010	2.41	0.15	12
			2011–2012	2.78	0.5	6
		≥60	2009–2010	4.75	0.68	8
			2011–2012	3.90	0.47	6
	Female	12–19	2009–2010	0.573	0.036	10
			2011–2012	0.74	0.147	7
		20–39	2009–2010	0.979	0.096	14
			2011–2012	1.24	0.22	6
		40–59	2009–2010	2.46	0.19	14
			2011–2012	2.30	0.18	7
		≥60	2009–2010	5.85	0.71	11
			2011–2012	5.14	0.4	7

Table 5-36. Serum 1,2,3,4,7,8-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
Asians	Male	12–19	2011–2012	1.23	0.14	3
		20–39		1.72	0.2	6
		40–59		2.22	0.41	6
		≥60		2.46	0.57	4
	Female	12–19	2011–2012	0.70	0.21	2
		20–39		1.70	0.27	6
		40–59		2.33	0.24	6
		≥60		4.42[d]	1.41	3

[a]Limits of detection for survey years 2005–2006, 2007–2008, 2009–2010, and 2011–2012 were 0.14, 0.26, 0.4, and 0.4 pg/g lipid, respectively.
[b]Weighted arithmetic means are not comparable to weighted geometric means; unadjusted standard errors do not incorporate survey design effects.
[c]Each pool was composed of serum from eight persons.
[d]Unadjusted standard error of the mean estimate is >30%.

HxCDD = hexachlorodibenzo-*p*-dioxin; NC = not calculated (portion of results below limit of detection was too high to provide a valid result)

Source: CDC 2024b

Table 5-37. Serum 1,2,3,6,7,8-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
Non-Hispanic whites	Male	12–19	2005–2006	10.5	0.8	9
			2007–2008	9.78	0.47	6
			2009–2010	7.25	0.47	10
			2011–2012	7.52	0.76	6
		20–39	2005–2006	14.7	1.4	12
			2007–2008	14.2	0.6	15
			2009–2010	11.9	0.6	17
			2011–2012	13.2	1.1	12
		40–59	2005–2006	31.8	3.4	12
			2007–2008	23.0	1	15
			2009–2010	23.4	1.5	17
			2011–2012	19.9	2	11
		≥60	2005–2006	46.6	3.4	15
			2007–2008	40.5	2.6	23
			2009–2010	36.5	2.1	20
			2011–2012	41.8	2.5	11
	Female	12–19	2005–2006	6.76	0.95	10
			2007–2008	6.86	0.36	7
			2009–2010	5.69	0.61	8
			2011–2012	5.83	057	5
		20–39	2005–2006	13.1	1.4	16
			2007–2008	12.5	0.8	12
			2009–2010	10.8	1.1	18
			2011–2012	10.2	0.7	13
		40–59	2005–2006	25.6	1.2	13
			2007–2008	23.7	0.9	17
			2009–2010	19.5	0.9	17
			2011–2012	20.8	1.4	7

Table 5-37. Serum 1,2,3,6,7,8-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		≥60	2005–2006	47.4	3.5	17
			2007–2008	45.7	2.8	20
			2009–2010	40.8	2.8	22
			2011–2012	48.6	4.3	13
Non-Hispanic blacks	Male	12–19	2005–2006	9.16	0.4	13
			2007–2008	7.77	0.76	6
			2009–2010	6.71	0.71	6
			2011–2012	7.76	0.9	7
		20–39	2005–2006	12.7	0.8	6
			2007–2008	13.4	1.1	6
			2009–2010	8.65	1.1	7
			2011–2012	10.2	0.5	9
		40–59	2005–2006	20.4	1.3	5
			2007–2008	23.6	2.3	6
			2009–2010	18.2	1.8	7
			2011–2012	20.8	1.4	7
		≥60	2005–2006	45.5	6.1	5
			2007–2008	36.3	4.1	8
			2009–2010	31.0	2.1	9
			2011–2012	39.0	2.9	8
	Female	12–19	2005–2006	5.50	0.65	14
			2007–2008	6.07	0.32	4
			2009–2010	4.70	0.41	6
			2011–2012	NC		6
		20–39	2005–2006	12.2	0.8	7
			2007–2008	13.7	1.2	7
			2009–2010	9.23	0.94	7
			2011–2012	9.38	1.32	7

Table 5-37. Serum 1,2,3,6,7,8-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		40–59	2005–2006	25.1	2.6	7
			2007–2008	25.8	1.3	6
			2009–2010	19.8	1.8	7
			2011–2012	23.9	1.8	7
		≥60	2005–2006	69.4	8	5
			2007–2008	54.2	4.7	6
			2009–2010	49.8	5.3	7
			2011–2012	49.1	3.3	7
Mexican-American	Male	12–19	2005–2006	4.24	1.01	11
			2007–2008	7.12	0.78	6
			2009–2010	6.08	0.48	8
			2011–2012	6.46	1.38	4
		20–39	2005–2006	9.78	0.77	9
			2007–2008	10.4	0.4	9
			2009–2010	8.73	0.74	8
			2011–2012	10.2	0.9	4
		40–59	2005–2006	18.9	2.8	4
			2007–2008	19.4	1.2	6
			2009–2010	19.0	1.1	7
			2011–2012	20.8	1.7	3
		≥60	2005–2006	34.5	2.4	4
			2007–2008	32.0	1.7	5
			2009–2010	38.3	5.7	5
			2011–2012	39.0	2.9	8
	Female	12–19	2005–2006	3.62	0.73	16
			2007–2008	4.15	1.24	5
			2009–2010	3.95	0.2	7
			2011–2012	NC		4

Table 5-37. Serum 1,2,3,6,7,8-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		20–39	2005–2006	8.51	0.79	9
			2007–2008	9.61	0.78	7
			2009–2010	6.40	0.97	10
			2011–2012	8.84	1.97	3
		40–59	2005–2006	18.9	1.5	6
			2007–2008	19.5	1.7	5
			2009–2010	18.4	1.4	9
			2011–2012	19.0	1.1	2
		≥60	2005–2006	36.4	3.3	3
			2007–2008	37.0	3.9	5
			2009–2010	43.6	6.2	6
			2011–2012	41.5	3.2	3
All Hispanics	Male	12–19	2009–2010	6.11	0.38	11
			2011–2012	6.59	1.01	6
		20–39	2009–2010	8.06	0.83	13
			2011–2012	9.25	0.63	8
		40–59	2009–2010	16.8	1.1	12
			2011–2012	17.0	2	6
		≥60	2009–2010	32.9	4.4	8
			2011–2012	24.2	1.8	5
	Female	12–19	2009–2010	4.14	0.24	10
			2011–2012	NC		7
		20–39	2009–2010	6.82	0.69	14
			2011–2012	7.61	0.98	7
		40–59	2009–2010	17.3	1	14
			2011–2012	16.7	1.3	6
		≥60	2009–2010	37.9	4.1	11
			2011–2012	37.8	3.8	7

Table 5-37. Serum 1,2,3,6,7,8-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
Asians	Male	12–19	2011–2012	7.89	0.17	3
		20–39		10.2	1.3	6
		40–59		14.4	1.7	5
		≥60		17.4	1.2	4
	Female	12–19	2011–2012	NC		3
		20–39		9.95	1.24	6
		40–59		16.3	2.7	6
		≥60		25.9[d]	8.9	3

[a]Limits of detection for survey years 2005–2006, 2007–2008, 2009–2010, and 2011–2012 were 0.09, 0.09, 0.31, and 4.3 pg/g lipid, respectively.
[b]Weighted arithmetic means are not comparable to weighted geometric means; unadjusted standard errors do not incorporate survey design effects.
[c]Each pool was composed of serum from eight persons.
[d]Unadjusted standard error of the mean estimate is >30%

HxCDD = hexachlorodibenzo-*p*-dioxin; NC = not calculated (proportion of results below limit of detection was too high to provide valid result)

Source: CDC 2024b

Table 5-38. Serum 1,2,3,7,8,9-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
Non-Hispanic whites	Male	12–19	2005–2006	1.68	0.43	9
			2007–2008	2.18	0.1	6
			2009–2010	1.89	0.07	10
			2011–2012	1.77	0.16	5
		20–39	2005–2006	1.92	0.26	12
			2007–2008	2.33	0.28	15
			2009–2010	2.25	0.1	17
			2011–2012	2.80	0.26	9
		40–59	2005–2006	3.99	0.38	12
			2007–2008	2.99	0.15	15
			2009–2010	3.06	0.17	17
			2011–2012	2.93	.29	11
		≥60	2005–2006	5.48	0.47	15
			2007–2008	4.80	0.3	23
			2009–2010	4.56	0.25	21
			2011–2012	5.35	0.48	10
	Female	12–19	2005–2006	NC	NC	10
			2007–2008	1.64	0.37	7
			2009–2010	1.60	0.21	8
			2011–2012	1.71	0.28	4
		20–39	2005–2006	2.47	0.2	16
			2007–2008	2.29	0.27	12
			2009–2010	2.04	0.21	18
			2011–2012	2.22	0.1	9
		40–59	2005–2006	3.93	0.25	13
			2007–2008	3.29	0.24	17
			2009–2010	2.91	0.14	17
			2011–2012	3.47	0.44	11

Table 5-38. Serum 1,2,3,7,8,9-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		≥60	2005–2006	6.02	0.36	17
			2007–2008	6.23	0.4	20
			2009–2010	5.59	0.35	22
			2011–2012	6.75	0.65	13
Non-Hispanic blacks	Male	12–19	2005–2006	NC	NC	13
			2007–2008	1.73	0.28	6
			2009–2010	1.49	0.03	5
			2011–2012	2.18	0.31	6
		20–39	2005–2006	2.08	0.11	6
			2007–2008	1.37[d]	0.43	6
			2009–2010	1.52	0.18	7
			2011–2012	1.76	0.1	7
		40–59	2005–2006	2.57	0.18	5
			2007–2008	3.26	0.3	6
			2009–2010	2.36	0.25	7
			2011–2012	3.04	0.53	4
		≥60	2005–2006	5.18	0.91	5
			2007–2008	4.15	0.49	8
			2009–2010	3.46	0.33	9
			2011–2012	4.09	0.32	8
	Female	12–19	2005–2006	NC	NC	14
			2007–2008	NC	NC	4
			2009–2010	1.23	0.14	6
			2011–2012	1.32	0.18	4
		20–39	2005–2006	2.44	0.23	7
			2007–2008	1.92	0.57	7
			2009–2010	1.89	0.18	7
			2011–2012	2.37	0.2	6

Table 5-38. Serum 1,2,3,7,8,9-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		40–59	2005–2006	3.84	0.36	7
			2007–2008	3.97	0.26	6
			2009–2010	3.17	0.41	7
			2011–2012	5.47	1.04	4
		≥60	2005–2006	9.10	1.09	5
			2007–2008	8.05	0.79	6
			2009–2010	6.54	0.63	7
			2011–2012	6.76	0.74	6
Mexican-American	Male	12–19	2005–2006	NC	NC	11
			2007–2008	NC	NC	6
			2009–2010	1.67	0.09	7
			2011–2012	1.67	0.17	4
		20–39	2005–2006	2.20	0.29	9
			2007–2008	1.57	0.33	9
			2009–2010	1.67	0.15	8
			2011–2012	2.19	0.22	4
		40–59	2005–2006	3.37	0.53	4
			2007–2008	2.47	0.55	6
			2009–2010	2.73	0.18	7
			2011–2012	3.14	0.15	3
		≥60	2005–2006	4.52	0.22	4
			2007–2008	4.66	0.33	5
			2009–2010	5.43	0.74	5
			2011–2012	ND[e]		1
	Female	12–19	2005–2006	NC	NC	16
			2007–2008	1.46	0.43	5
			2009–2010	1.16	0.11	7
			2011–2012	1.09	0.27	4

Table 5-38. Serum 1,2,3,7,8,9-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		20–39	2005–2006	1.81	0.32	9
			2007–2008	NC	NC	7
			2009–2010	1.64	0.24	10
			2011–2012	1.97	0.45	3
		40–59	2005–2006	4.02	0.32	6
			2007–2008	3.94	0.29	5
			2009–2010	4.04	0.32	9
			2011–2012	3.88	0.34	2
		≥60	2005–2006	6.50	0.96	3
			2007–2008	7.48	0.57	5
			2009–2010	7.73	0.92	6
			2011–2012	7.23	0.57	3
All Hispanics	Male	12–19	2009–2010	1.77	0.12	10
			2011–2012	1.73	0.14	6
		20–39	2009–2010	1.74	0.12	13
			2011–2012	2.03	0.16	7
		40–59	2009–2010	2.50	0.14	12
			2011–2012	2.67	0.23	6
		≥60	2009–2010	4.67	0.6	8
			2011–2012	3.83	0.65	4
	Female	12–19	2009–2010	1.20	0.08	10
			2011–2012	1.21	0.2	6
		20–39	2009–2010	1.70	0.17	14
			2011–2012	2.03	0.22	6
		40–59	2009–2010	3.47	0.3	14
			2011–2012	3.24	0.36	5
		≥60	2009–2010	6.25	0.74	11
			2011–2012	6.26	0.75	7

Table 5-38. Serum 1,2,3,7,8,9-HxCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
Asians	Male	12–19	2011–2012	1.90	0.22	3
		20–39		2.32	0.22	6
		40–59		2.43	0.27	5
		≥60		2.67	0.18	4
	Female	12–19	2011–2012	1.35	0.1	2
		20–39		2.49	0.3	6
		40–59		3.34	0.37	6
		≥60		4.51	0.33	2

[a]Limits of detection for survey years 2005–2006, 2007–2008, 2009–2010, and 2011–2012 were 0.07, 0.1, 0.2, and 0.37 pg/g lipid, respectively.
[b]Weighted arithmetic means are not comparable to weighted geometric means; unadjusted standard errors do not incorporate survey design effects.
[c]Each pool was composed of serum from eight persons.
[d]Unadjusted standard error of the mean estimate is >30%.
[e]Weighted arithmetic means and their standard errors are not available for strata consisting of a single pool.

HxCDD = hexachlorodibenzo-*p*-dioxin; NC = not calculated (portion of results below limit of detection was too high to provide a valid result); ND = not determined

Source: CDC 2024b

Table 5-39. Serum 1,2,3,4,6,7,8,9-OCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
Non-Hispanic whites	Male	12–19	2005–2006	123	13	9
			2007–2008	114	7	6
			2009–2010	96.4	7.3	10
			2011–2012	NC		4
		20–39	2005–2006	129	8	12
			2007–2008	125	12	15
			2009–2010	109	5	17
			2011–2012	154	30	7
		40–59	2005–2006	238	25	12
			2007–2008	164	10	15
			2009–2010	172	16	17
			2011–2012	142	9	10
		≥60	2005–2006	379	38	15
			2007–2008	306	23	23
			2009–2010	284	18	21
			2011–2012	223	21	9
	Female	12–19	2005–2006	106	9	10
			2007–2008	104	5	7
			2009–2010	83.6	6.2	8
			2011–2012	NC		5
		20–39	2005–2006	179	19	16
			2007–2008	139	7	12
			2009–2010	126	11	18
			2011–2012	107	5	9
		40–59	2005–2006	304	22	13
			2007–2008	222	15	17
			2009–2010	198	10	17
			2011–2012	231	19	9

Table 5-39. Serum 1,2,3,4,6,7,8,9-OCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		≥60	2005–2006	546	66	17
			2007–2008	435	49	19
			2009–2010	407	31	22
			2011–2012	437	77	12
Non-Hispanic blacks	Male	12–19	2005–2006	142	12	13
			2007–2008	114	10	6
			2009–2010	90.2	4.3	5
			2011–2012	96.9	14.1	6
		20–39	2005–2006	127	9	6
			2007–2008	136	9	6
			2009–2010	102	6	7
			2011–2012	101	12	7
		40–59	2005–2006	200	32	5
			2007–2008	190	16	6
			2009–2010	161	14	7
			2011–2012	155	27	5
		≥60	2005–2006	420	82	5
			2007–2008	314	30	8
			2009–2010	265	11	9
			2011–2012	241	19	8
	Female	12–19	2005–2006	153	22	14
			2007–2008	100	9	4
			2009–2010	81.7	5.6	6
			2011–2012	NC		3
		20–39	2005–2006	188	18	7
			2007–2008	197	23	7
			2009–2010	139	15	7
			2011–2012	122	13	7

Table 5-39. Serum 1,2,3,4,6,7,8,9-OCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		40–59	2005–2006	381	43	7
			2007–2008	303	22	6
			2009–2010	239	29	7
			2011–2012	338	72	3
		≥60	2005–2006	927	135	5
			2007–2008	660	78	6
			2009–2010	672	133	7
			2011–2012	490	44	6
Mexican-American	Male	12–19	2005–2006	111	9	11
			2007–2008	117	9	6
			2009–2010	98.4	10.6	8
			2011–2012	NC		2
		20–39	2005–2006	180	21	9
			2007–2008	133	9	9
			2009–2010	130	12	8
			2011–2012	112	12	4
		40–59	2005–2006	220	19	4
			2007–2008	217	13	6
			2009–2010	231	32	7
			2011–2012	219	50	2
		≥60	2005–2006	350	46	4
			2007–2008	273	17	5
			2009–2010	413	78	5
			2011–2012	ND[d]		1
	Female	12–19	2005–2006	111	5	16
			2007–2008	110	13	5
			2009–2010	79.3	5.7	6
			2011–2012	NC		3

Table 5-39. Serum 1,2,3,4,6,7,8,9-OCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		20–39	2005–2006	184	12	9
			2007–2008	174	12	7
			2009–2010	123	19	10
			2011–2012	114	12	4
		40–59	2005–2006	410	60	6
			2007–2008	290	17	5
			2009–2010	336	34	9
			2011–2012	241	2	2
		≥60	2005–2006	540	65	3
			2007–2008	434	33	5
			2009–2010	552	52	6
			2011–2012	ND[d]		1
All Hispanics	Male	12–19	2009–2010	109	11	11
			2011–2012	NC		3
		20–39	2009–2010	128	13	13
			2011–2012	108	7	7
		40–59	2009–2010	200	22	12
			2011–2012	157	31	5
		≥60	2009–2010	361	68	7
			2011–2012	228	49	3
	Female	12–19	2009–2010	78.4	4.7	10
			2011–2012	NC		4
		20–39	2009–2010	121	14	14
			2011–2012	104	11	8
		40–59	2009–2010	286	29	14
			2011–2012	228	37	4
		≥60	2009–2010	458	48	11
			2011–2012	446	94	3

Table 5-39. Serum 1,2,3,4,6,7,8,9-OCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
Asians	Male	12–19	2011–2012	ND[d]		1
		20–39		174	13	6
		40–59		168	21	5
		≥60		253	22	3
	Female	12–19	2011–2012	135	30	3
		20–39		233	13	4
		40–59		313	20	4
		≥60		389	88	2

[a]Limits of detection for survey years 2005–2006, 2007–2008, 2009–2010, 2011–2012 were 8.88, 10.1, 33.9, and 92.0 pg/g lipid, respectively.
[b]Weighted arithmetic means are not comparable to weighted geometric means; unadjusted standard errors do not incorporate survey design effects.
[c]Each pool was composed of serum from eight persons.
[d]Weighted arithmetic means and their standard errors are not available for strata consisting of a single pool.

NC = not calculated (proportion of results below limit of detections was too high to provide a valid result); ND = not determined; OCDD = octachlorodibenzo-*p*-dioxin

Source: CDC 2024b

Table 5-40. Serum 1,2,3,7,8-PeCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
Non-Hispanic whites	Male	12–19	2005–2006	2.55	0.14	9
			2007–2008	2.31	0.29	6
			2009–2010	2.22	0.1	10
			2011–2012	1.69	0.24	6
		20–39	2005–2006	2.49	0.23	12
			2007–2008	2.93	0.28	15
			2009–2010	2.59	0.17	17
			2011–2012	2.36	0.18	12
		40–59	2005–2006	4.48	0.54	12
			2007–2008	3.96	0.13	15
			2009–2010	3.77	0.21	17
			2011–2012	3.36	0.28	12
		≥60	2005–2006	7.26	0.4	15
			2007–2008	7.08	0.76	23
			2009–2010	6.03	0.24	20
			2011–2012	5.77	0.35	12
	Female	12–19	2005–2006	1.55	0.22	10
			2007–2008	1.64	0.33	7
			2009–2010	1.70	0.24	8
			2011–2012	1.53	0.21	5
		20–39	2005–2006	2.57	0.23	16
			2007–2008	2.40	0.27	12
			2009–2010	2.06	0.12	17
			2011–2012	1.75	0.14	13
		40–59	2005–2006	4.25	0.2	13
			2007–2008	4.12	0.16	17
			2009–2010	3.65	0.17	17
			2011–2012	3.29	0.19	11

Table 5-40. Serum 1,2,3,7,8-PeCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		≥60	2005–2006	7.83	0.56	17
			2007–2008	8.09	0.41	20
			2009–2010	7.06	0.48	22
			2011–2012	5.77	0.35	12
Non-Hispanic blacks	Male	12–19	2005–2006	2.34	0.15	13
			2007–2008	2.21	0.42	6
			2009–2010	NC	NC	6
			2011–2012	1.69	0.27	7
		20–39	2005–2006	2.95	0.16	6
			2007–2008	2.94	0.26	6
			2009–2010	2.14	0.29	5
			2011–2012	1.87	0.23	9
		40–59	2005–2006	4.00	0.24	5
			2007–2008	4.41	0.34	6
			2009–2010	2.81	0.31	7
			2011–2012	3.17	0.62	7
		≥60	2005–2006	8.16	1.26	5
			2007–2008	6.56	0.8	8
			2009–2010	5.33	0.38	9
			2011–2012	5.79	0.37	9
	Female	12–19	2005–2006	NC	NC	14
			2007–2008	NC	NC	4
			2009–2010	NC	NC	5
			2011–2012	0.94	0.249	6
		20–39	2005–2006	2.52	0.1	7
			2007–2008	2.61	0.29	7
			2009–2010	2.17	0.19	7
			2011–2012	1.61	0.17	8

Table 5-40. Serum 1,2,3,7,8-PeCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		40–59	2005–2006	4.64	0.44	7
			2007–2008	4.40	0.44	6
			2009–2010	4.05	0.37	7
			2011–2012	3.70	0.4	8
		≥60	2005–2006	12.5	1.7	5
			2007–2008	11.4	1	6
			2009–2010	8.98	0.84	7
			2011–2012	8.50	0.78	7
Mexican-American	Male	12–19	2005–2006	NC	NC	11
			2007–2008	1.84	0.12	6
			2009–2010	1.87	0.31	8
			2011–2012	1.20	0.11	5
		20–39	2005–2006	2.13	0.26	9
			2007–2008	2.48	0.29	9
			2009–2010	2.09	0.17	8
			2011–2012	2.21	0.14	4
		40–59	2005–2006	3.61	0.63	4
			2007–2008	3.96	0.34	6
			2009–2010	3.45	0.19	7
			2011–2012	4.19	0.24	3
		≥60	2005–2006	5.59	0.16	4
			2007–2008	6.07	0.17	5
			2009–2010	6.57	1.05	5
			2011–2012	ND[d]		1
	Female	12–19	2005–2006	1.14	0.16	16
			2007–2008	1.53	0.28	5
			2009–2010	NC	NC	7
			2011–2012	0.74	0.185	4

Table 5-40. Serum 1,2,3,7,8-PeCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		20–39	2005–2006	1.65	0.23	9
			2007–2008	2.81	0.3	7
			2009–2010	NC	NC	10
			2011–2012	1.22[e]	0.58	4
		40–59	2005–2006	3.23	0.62	6
			2007–2008	4.15	0.68	5
			2009–2010	3.51	0.26	9
			2011–2012	3.07	0.52	3
		≥60	2005–2006	6.48	0.82	3
			2007–2008	6.43	0.64	5
			2009–2010	7.45	0.93	6
			2011–2012	6.68	0.44	3
All Hispanics	Male	12–19	2009–2010	1.78	0.25	11
			2011–2012	1.27	0.15	7
		20–39	2009–2010	1.83	0.18	13
			2011–2012	1.84	0.21	8
		40–59	2009–2010	3.06	0.21	11
			2011–2012	3.05	0.61	6
		≥60	2009–2010	6.07	0.84	7
			2011–2012	4.02	0.61	5
	Female	12–19	2009–2010	NC	NC	10
			2011–2012	0.97	0.164	7
		20–39	2009–2010	NC	NC	14
			2011–2012	1.22	0.32	7
		40–59	2009–2010	3.25	0.2	14
			2011–2012	2.61	0.28	7
		≥60	2009–2010	6.22	0.73	11
			2011–2012	6.58	0.5	7

Table 5-40. Serum 1,2,3,7,8-PeCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
Asians	Male	12–19	2011–2012	1.71	0.36	3
		20–39		2.58	0.29	6
		40–59		3.65	0.56	5
		>60		4.02	0.19	4
	Female	12–19	2011–2012	1.30	0.16	3
		20-39		1.63	0.34	6
		40–59		3.19	0.35	6
		>60		5.26	0.81	3

[a]Limits of detection for survey years 2005–2006, 2007–2008, 2009–2010, 2011–2012 were 0.51, 1.07, 1.56, and 0.43 pg/g lipid, respectively.
[b]Weighted arithmetic means are not comparable to weighted geometric means; unadjusted standard errors do not incorporate survey design effects.
[c]Each pool was composed of serum from eight persons.
[d]Weighted arithmetic means and their standard errors are not available for strata consisting of a single pool.
[e]Unadjusted standard error of the mean is >30%.

NC = not calculated (portion of results below limit of detection was too high to provide a valid result); ND = not determined; PeCDD = pentachlorodibenzo-*p*-dioxin

Source: CDC 2024b

Table 5-41. Serum 2,3,7,8-TCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
Non-Hispanic whites	Male	12–19	2005–2006	NC	NC	9
			2007–2008	NC	NC	6
			2009–2010	NC	NC	10
			2011–2012	NC	NC	6
		20–39	2005–2006	NC	NC	12
			2007–2008	NC	NC	15
			2009–2010	NC	NC	17
			2011–2012	NC	NC	12
		40–59	2005–2006	1.21	0.16	12
			2007–2008	0.931	0.086	15
			2009–2010	NC	NC	17
			2011–2012	0.88	0.101	12
		≥60	2005–2006	2.34	0.19	15
			2007–2008	2.13	0.22	23
			2009–2010	1.52	0.1	20
			2011–2012	1.54	0.09	12
	Female	12–19	2005–2006	NC	NC	10
			2007–2008	NC	NC	7
			2009–2010	NC	NC	8
			2011–2012	NC	NC	5
		20–39	2005–2006	NC	NC	16
			2007–2008	NC	NC	12
			2009–2010	NC	NC	18
			2011–2012	NC	NC	13
		40–59	2005–2006	1.31	0.19	13
			2007–2008	1.32	0.07	17
			2009–2010	NC	NC	17
			2011–2012	1.10	0.06	11

Table 5-41. Serum 2,3,7,8-TCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		≥60	2005–2006	2.86	0.21	17
			2007–2008	2.98	0.2	20
			2009–2010	2.07	0.19	22
			2011–2012	2.50	0.22	14
Non-Hispanic blacks	Male	12–19	2005–2006	NC	NC	13
			2007–2008	NC	NC	6
			2009–2010	NC	NC	5
			2011–2012	NC	NC	7
		20–39	2005–2006	NC	NC	6
			2007–2008	NC	NC	6
			2009–2010	NC	NC	7
			2011–2012	NC	NC	9
		40–59	2005–2006	1.26	0.18	5
			2007–2008	1.32	0.9	6
			2009–2010	NC	NC	7
			2011–2012	0.72	0.139	7
		≥60	2005–2006	3.47[d]	1.25	5
			2007–2008	2.04	0.42	8
			2009–2010	1.34	0.13	9
			2011–2012	1.50	0.12	9
	Female	12–19	2005–2006	NC	NC	14
			2007–2008	NC	NC	4
			2009–2010	NC	NC	5
			2011–2012	NC	NC	6
		20–39	2005–2006	0.712	0.117	7
			2007–2008	NC	NC	7
			2009–2010	NC	NC	7
			2011–2012	0.58	0.059	7

Table 5-41. Serum 2,3,7,8-TCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		40–59	2005–2006	1.81	0.21	7
			2007–2008	1.68	0.15	6
			2009–2010	1.17	0.22	7
			2011–2012	1.12	0.15	8
		≥60	2005–2006	6.40	1.64	5
			2007–2008	4.50	0.46	6
			2009–2010	3.54	0.37	7
			2011–2012	2.93	0.2	8
Mexican-American	Male	12–19	2005–2006	NC	NC	11
			2007–2008	NC	NC	6
			2009–2010	NC	NC	7
			2011–2012	NC	NC	5
		20–39	2005–2006	NC	NC	9
			2007–2008	NC	NC	9
			2009–2010	NC	NC	7
			2011–2012	0.62	0.108	4
		40–59	2005–2006	1.01	0.24	4
			2007–2008	0.984	0.188	6
			2009–2010	NC	NC	7
			2011–2012	1.01	0.09	3
		≥60	2005–2006	1.29	0.25	4
			2007–2008	1.80	0.21	5
			2009–2010	1.95	0.38	5
			2011–2012	ND[e]		1
	Female	12–19	2005–2006	NC	NC	16
			2007–2008	NC	NC	5
			2009–2010	NC	NC	7
			2011–2012	NC	NC	4

Table 5-41. Serum 2,3,7,8-TCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
		20–39	2005–2006	NC	NC	9
			2007–2008	0.925	0.121	7
			2009–2010	NC	NC	10
			2011–2012	NC	NC	3
		40–59	2005–2006	1.08	0.3	6
			2007–2008	1.03[d]	0.32	5
			2009–2010	NC	NC	9
			2011–2012	0.84	0.189	3
		≥60	2005–2006	2.34	0.3	3
			2007–2008	2.95	0.32	5
			2009–2010	2.30	0.29	6
			2011–2012	1.81	0.07	3
Mexican-American	Male	12–19	2009–2010	NC	NC	9
			2011–2012	NC	NC	7
		20–39	2009–2010	NC	NC	12
			2011–2012	0.54	0.07	8
		40–59	2009–2010	NC	NC	11
			2011–2012	0.83	0.097	6
		≥60	2009–2010	1.82	0.29	7
			2011–2012	1.25	0.2	5
	Female	12–19	2009–2010	NC	NC	10
			2011–2012	NC	NC	7
		20–39	2009–2010	NC	NC	14
			2011–2012	NC	NC	7
		40–59	2009–2010	NC	NC	14
			2011–2012	0.96	0.122	7
		≥60	2009–2010	2.30	0.2	11
			2011–2012	2.25	0.26	7

Table 5-41. Serum 2,3,7,8-TCDD (Lipid Adjusted) Concentrations (pg/g Lipid) for the U.S. Population[a]

Race/ethnicity	Gender	Age (years)	Survey (years)	Weighted arithmetic mean[b]	Unadjusted standard error	Number of pools[c]
Asians	Male	12–19	2011–2012	NC	NC	3
		20–39		0.71	0.081	6
		40–59		1.09	0.18	5
		≥60		1.27	0.09	4
	Female	12–19	2011–2012	NC	NC	3
		20–39		0.77	0.124	6
		40–59		1.07	0.08	6
		≥60		2.03	0.41	3

[a]Limits of detection for survey years 2005–2006, 2007–2008, 2009–2010, 2011–2012 were 0.39, 0.74, 1.1, and 0.45 pg/g lipid, respectively.
[b]Weighted arithmetic means are not comparable to weighted geometric means; unadjusted standard errors do not incorporate survey design effects.
[c]Each pool was composed of serum from eight persons.
[d]Unadjusted standard error of the mean estimate is >30%.
[e]Weighted arithmetic means and their standard errors are not available for strata consisting of a single pool.

NC = not calculated (portion of results below limit of detection was too high to provide a valid result); ND = not determined; TCDD = tetrachlorodibenzo-*p*-dioxin

Source: CDC 2024b

Patterson et al. (2008, 2009) reported the TEQs for dioxin-like compounds (CDDs, CDFs, coplanar PCBs, and mono-ortho-substituted PCBs) for survey years 2001–2002 and 2003–2004; these values are presented in Table 5-42. The blood TEQs of adults for the 2003–2004 monitoring period appear to be lower than levels in 2001–2002. LaKind et al. (2009) examined the temporal changes in serum CDD/CDF in adults for NHANES survey years 1999–2000, 2001–2002, and 2003–2004 (data summarized in Table 5-43) and found no significant change in median (50th percentile) serum CDD/CDF levels from 1999–2000 to 2001–2002; however, there was a significant decrease in CDD/CDF serum concentration in the 2003–2004 survey year. When the participants were divided by age, 56 and 38% decreases in serum CDD/CDF levels were observed for the 2003–2004 survey year in the 12–19 and 20–39-year-olds, respectively, as compared to the 1999–2000 survey year. A slight nonsignificant decrease (6%) was observed for 40–59-year-olds and a slight increase (12%) was observed for 60+-year-olds.

Table 5-42. Blood TEQ Levels[a] for Dioxin-Like Compounds (CDDs, CDFs, and select PCBs) Levels (pg/g Lipid) at 90th and 95th Percentiles by Age Group in NHANES 2001–2002 and 2003–2004 Survey Years

	TEQ for 2001–2002 survey years		TEQ for 2003–2004 survey years	
	90th percentile	95th percentile	90th percentile	95th percentile
Total, ≥12 years	No data[b]	No data	30.9 (28.2–33.9)[c]	37.8 (35.3–43.4)
Total, ≥20 years	41.0 (35.8–47.1)	56.1 (47.6–65.4)	32.5 (29.2–35.7	39.9 (36.6–45.7)
Age group				
12–29 years	No data	No data	12.1 (10.9–13.0)	14.0 (12.4–15.9)
20–39 years	23.0 (19.7–25.2)	26.2 (23.7–32.5)	16.2 (14.5–17.7)	18.7 (16.9–20.1)
40–49 years	35.4 (29.7–44.8)	46.9 (36.4–66.1)	28.2 (23.7–32.6)	32.0 (28.0–45.3)
≥60 years	67.7 (56.4–79.7)	79.7 (68.2–96.3)	49.7 (41.5–58.6)	63.2 (50.9–75.1)

[a]TEQs calculated using WHO 2005 toxic equivalency factors (TEFs).
[b]Data were not collected for this age group in the 2001–2002 survey.
[c]95% confidence interval.

CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; NHANES = National Health and Nutrition Examination Survey; PCB = polychlorinated biphenyl; TEQ = toxic equivalency; WHO = World Health Organization

Source: Patterson et al. 2008, 2009

Table 5-43. Serum CDD/CDF Concentrations for Mean and Selected Percentiles for the NHANES 1999–2000, 2001–2002, and 2003–2004 Survey Years

	Serum CDD/CDF concentrations (pg TEQ/g lipid)		
Percentile	1999–2000	2001–2002	2003–2004
10	8.36 (8.03–8.71)[a]	7.76 (7.07–8.07)	5.17 (4.92–5.50)
25	10.52 (10.17–10.99)	10.38 (10.17–10.80)	7.29 (6.95–7.68)

Table 5-43. Serum CDD/CDF Concentrations for Mean and Selected Percentiles for the NHANES 1999–2000, 2001–2002, and 2003–2004 Survey Years

	Serum CDD/CDF concentrations (pg TEQ/g lipid)		
Percentile	1999–2000	2001–2002	2003–2004
50	13.46 (12.92–13.81)	13.98 (13.42–14.59)	11.39 (10.60–12.15)
75	17.68 (17.04–18.30)	20.88 (19.57–22.12)	17.71 (16.61–18.65)
95	27.68 (24.90–29.65)	44.45 (40.11–48.79)	30.62 (28.51–32.34)
Arithmetic mean	15.4 (14.68–15.94)	18.05 (17.25–18.78)	13.90 (13.35–14.42)

[a]95% confidence interval.

CDD = chlorinated dibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; NHANES = National Health and Nutrition Examination Survey; TEQ = toxic equivalency

Source: LaKind et al. 2009b

A review of general population blood levels of CDDs, CDFs, and PCBs from published literature dating from 1989 to 2010 collected across the world is available (Consonni et al. 2012). The study authors reviewed 187 studies with 29,687 subjects from 26 different countries. The study authors noted that significant temporal decreases in TEQs were observed from the studies (1985–2008) for CDDs and CDFs; however, no significant decrease was found for non-ortho-PCBs, notably PCB 126.

Compared with background 2,3,7,8-TCDD levels (3.6 ppt), workers that were formerly involved in 2,4,5-TCP production had elevated 2,3,7,8-TCDD blood levels, with a mean concentration of 332 ppt (Päpke et al. 1992). PCP manufacturing resulted in the greatest increases for workers with respect to all congeners, with OCDD blood levels of approximately 300,000 ppt. Miniero et al. (2017) examined blood levels of professionally exposed and non-occupationally exposed individuals in metallurgical plants of Brescia, Italy. The lipid-based 2005 World Health Organization (WHO)-TEQ level of non-professionally exposed individuals was 7.94 pg/g lipid. The TEQs for professionally exposed individuals working in ferrous and non-ferrous metallurgic plants were 8.25 and 9.55 pg/g lipid, respectively. A U.S. domestic agricultural worker was exposed to 2,3,7,8-TCDD during spraying of 2,4,5-T herbicide on pastureland and hay ground. A sample of the herbicide that was used contained 7.7 ppb 2,3,7,8-TCDD. 2,3,7,8-TCDD levels measured in the worker's adipose tissue 5 years post-exposure were 72 ppt (whole weight) or 77 ppt (lipid basis) (Tong et al. 1989). Thirty-two years after an industrial accident in a chemical plant manufacturing trichlorophenol, the average lipid-adjusted concentration of 2,3,7,8-TCDD in the adipose tissue of exposed workers who developed symptoms (chloracne and other illnesses) was 49 ppt (range 11–141 ppt) (Schecter and Ryan 1988). Since 2,4,5-T and 2,4,5-TCP are no longer used in the United States, these are no longer occupational exposure routes for U.S. workers or workers in many

other nations. Additionally, the only PCP manufacturer in North America was scheduled to close a facility in Mexico that produces PCP, as well as a facility in Alabama that formulates and stores registered wood preservative products containing PCP in 2022 (EPA 2021). PCP is scheduled to have all active registrations phased out in the United States by 2027 (EPA 2021).

In a study by Tepper et al. (1997), serum levels of CDDs and CDFs were measured in pulp and paper mill workers in the United States. The study authors reported that serum levels of CDDs and CDFs among 46 long-term workers at a pulp and paper mill were not appreciably different among three exposure groups studied (community residents, low-exposure-potential worker group, and high-exposure-potential worker group). Serum CDD TEQs were 13.5 ppt (range, 9.5–19.1 ppt), 15.9 ppt (range, 6.5–31.8 ppt), and 13.3 ppt (range, 7.5–24.9 ppt), respectively. Total TEQ for both CDDs and CDFs were similar for the three groups at 19.1, 21.2, and 18.1 ppt, respectively. Serum levels of CDDs and CDFs in this study were within the range previously reported for persons with no known occupational exposure.

A series of adipose tissue samples collected from one exposed individual, as well as surgical and autopsy specimens from four control individuals, was analyzed for CDDs (TCDD, PeCDD, HxCDD, HpCDD, and OCDD) (Schecter et al. 1985a). All specimens were obtained from persons residing in urban or rural areas of upstate New York during 1983 or 1984. The worker who had been exposed to soot containing PCBs, CDFs, and small amounts of CDDs from the CDD-/CDF-contaminated Binghamton State Office Building in New York, had a total CDD concentration (whole-weight basis) of 1,015 ppt, whereas the average total CDD concentration for the controls was 765 ppt. Mean concentrations were highest for OCDD among all of the CDD congener groups in both the controls (585 ppt) and the exposed person (690 ppt). 2,3,7,8-TCDD concentrations were lowest in both groups, with averages of 6.3 ppt for the controls and 11.6 ppt for the exposed person. Intermediate levels were found for PeCDD (7.5–13.8 ppt), HxCDD (6.8–64.2 ppt), and HpCDD (2.6–119 ppt) in the control groups. Intermediate levels were also found in the exposed individual for PeCDD (15 ppt), HxCDD (7.3–72.6), and HpCDD (9.6–209 ppt) (Schecter et al. 1985a).

Workers who are involved with incineration operations may be exposed to levels of CDDs that are higher than background levels to which the general population is exposed. Schecter et al. (1991b) measured CDD and CDF blood levels on a lipid basis in pooled blood samples from a group of 56 New York City incinerator workers and 14 controls. The levels of 11 of the 18 CDD/CDF congeners measured were increased in the incinerator workers as compared to the controls. CDD levels in incinerator workers were 48, 17, 27, 30, and 31% higher for 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD,

1,2,3,4,6,7,8-HpCDD, and OCDD, respectively. Only 2,3,7,8-TCDD and 1,2,3,4,7,8-HxCDD were lower in incinerator workers' blood than in controls (5 and 15% lower, respectively). Overall, the total CDD/CDF level in workers' blood was, 1,007.2 ppt (lipid basis) as compared to 747.3 ppt for the controls (Schecter et al. 1991b)

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The recent train derailment and fire that followed in East Palestine Ohio, indicates that residents of this community and nearby may be potentially exposed to higher levels of CDDs and CDFs than other populations. Data collection is ongoing and will likely occur for years, so no long-term studies exist at this time; however, monitoring data show very high levels of CDDs in some environmental media such as soil (EPA 2023). Workers in industries that manufacture or use chemicals contaminated with CDDs such as PCP are one segment of the population at risk for higher exposure; however, PCP is being phased out by the EPA. Persons working in the hazardous waste industry or first responders to incidents where CDDs and CDFs may have been released (e.g., World Trade Center first responders) will be exposed to higher levels than the general population. Although production of PCBs ceased in the United States over 40 years ago, the use of PCBs is still authorized in transformers and other electrical equipment, and accidents involving PCB capacitors and transformers may entail high exposures to CDDs.

Military personnel near open burn pits were potentially exposed to higher levels of CDDs/CDFs than the general population. CDDs/CDFs and other substances were measured in air samples at Joint Base Balad in Iraq in 2007 (Masiol et al. 2016). The major source of CDDs/CDFs in the measured samples arose from the burn pit, which was the largest operating burn-pit on U.S. bases during the Iraq War. The average concentration of OCDD at all the sampling sites was 1.43 pg/m^3, with an average concentration as high as 6.68 pg/m^3 at one of the sampling sites. The next greatest average concentration was observed for 1,2,3,4,6,7,8- HpCDD (1.27 pg/m^3) for all the sampling sites. The average concentration of 2,3,7,8-TCDD at all 10 sampling sites was 0.06 pg/m^3.

A study of firefighters measured urinary CDDs levels before and after responding to a controlled residential fire. The levels of serum 1,2,3,7,8,9-HxCDD were significantly lower post-exposure, as compared to pre-exposure (Mayer et al. 2021a, 2021b). In comparisons to the general population, the serum levels of 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD in firefighters were significantly lower.

Historically, populations that have been exposed to higher-than-normal background levels of CDDs in the air, water, soil, and/or food have included those who were exposed to 2,3,7,8-TCDD as a result of industrial accidents (e.g., Nitro, West Virginia; and Seveso, Italy) and those exposed through environmental contamination (e.g., Times Beach, Missouri; Binghamton, New York; Love Canal, New York; Newark, New Jersey; and Vietnam) (Kahn et al. 1988; Schecter 1985; Schecter and Tiernan 1985; Schecter et al. 1987a, 1989a; Umbreit et al. 1986a, 1986b; Zook and Rappe 1994). Kahn et al. (2018) collected biomonitoring data from a set of adolescents in 2014–2016 who were exposed to debris from the World Trade Center collapse in 2001 and found that levels of CDDs/CDFs were approximately 7 times greater in these persons than from a control group of unexposed adolescents.

Very extensive residential contamination by 2,3,7,8-TCDD occurred in Seveso, Italy, when a 2,4,5-TCP reactor exploded in 1976 (Mocarelli et al. 1991). The contaminated area was divided into three zones based on the concentration of 2,3,7,8-TCDD in the soil. Families in zone A, the most heavily contaminated area based on soil 2,3,7,8-TCDD levels, were evacuated within 20 days of the explosion and measures were taken to minimize exposure of residents in nearby zones. An analysis of 20 blood samples from residents of zone A, which were collected and stored shortly after the accident, showed serum lipid levels of 828–56,000 ppt 2,3,7,8-TCDD. These serum lipid levels are among the highest ever reported for humans (Mocarelli et al. 1991).

2,3,7,8-TCDD has been detected at concentrations of 20–173 ppt in adipose tissue from three Vietnam veterans reported to have been heavily exposed to Agent Orange (Gross et al. 1984). Except for these few men, however, 2,3,7,8-TCDD concentrations in American Vietnam and non-Vietnam veterans were nearly identical with mean serum levels of approximately 4 ppt (CDC 1988). Concentrations of 2,3,7,8-TCDD in the controls (those who never served in Vietnam) ranged from not detected (4 ppt) to 20 ppt. The veterans had served in Vietnam in 1967 and 1968 in areas where Agent Orange had been heavily used (CDC 1988). In another study, 2,3,7,8-TCDD was detected in adipose tissue of 14 Vietnam veterans and 3 control patients at levels ranging from not detected (2–13 ppt) to 15 ppt. No significant differences in the tissue levels of Vietnam veterans and the controls were found in this study (Weerasinghe et al. 1986). Air Force personnel associated with Operation Ranch Hand (spraying of Agent Orange) in Vietnam from 1962 to 1971 had serum CDD levels up to 10 ppt (521 persons). A correlation was found between CDD concentrations and increased body fat (USAF 1991). The median half-life of 2,3,7,8-TCDD in 36 veterans was estimated to be 7.1 years (Pirkle et al. 1989). In 1987, many of the exposed Air Force personnel had serum CDD concentrations >50 ppt and several had

concentrations exceeding 300 ppt (CDC 1987). Wolfe et al. (1994) reported a half-life value of 11.3 years for Air Force personnel involved in Operation Ranch Hand.

It is possible that persons residing near emission sources such as hazardous waste incinerators may have the potential for greater exposure to CDDs than the general population; however, recent studies have suggested that the impact that these facilities create for local populations is low. Nadal et al. (2019) analyzed the temporal trends of total CDDs/CDFs in the plasma of residents living in the vicinity of a hazardous waste incinerator that was constructed in 1998 in Catalonia, Spain. Over a 2-decade period (1998–2018), they reported between a 59 and 80% decrease in plasma CDD/CDF levels for these residents depending upon age and gender. They concluded that these decreases were due to reduced dietary intakes of these substances and that the incinerator did not create measurable risk to the health of the population living in the vicinity of the facility. A comprehensive review of 82 studies regarding the biomonitoring of individuals residing near, or working at, hazardous waste incinerators suggested that there was only a low impact on the internal dose of CDD/CDF levels due to emissions from solid waste incinerators (Campo et al. 2019). Similarly, biomonitoring data of a population near a large waste incinerator located in Turin, Italy showed no significant differences in the serum levels of PCDD/PCDFs, and PCBs measured in the population group residing near the plant after 3 years of operation with respect to a control group (Iamiceli et al. 2021).

Children and adults may receive potentially higher oral exposures from ingestion of CDD-contaminated soils from their unwashed hands while playing or working in CDD-contaminated areas (Fries and Paustenbach 1990; Kimbrough et al. 1984; Paustenbach et al. 1992; Pohl et al. 1995). Bioavailability is an integral factor in the estimation of the internal dose (or dose at the target tissue) of the chemical. Like dermal absorption, gastrointestinal absorption of 2,3,7,8-TCDD and related compounds is variable, incomplete, and congener- and vehicle-specific. More lipid soluble congeners, such as 2,3,7,8-TCDF, are almost completely absorbed, while the extremely insoluble OCDD is poorly absorbed. However, laboratory data suggest that there are no major interspecific differences in the gastrointestinal absorption of CDDs and CDFs. Results from animal studies indicate that bioavailability of 2,3,7,8-TCDD from soil varies between sites because CDDs bind tightly to soil, and increasingly so with the passage of time and clay content of the soil (Gough 1991; Umbreit et al. 1986a;1986b). Therefore, 2,3,7,8-TCDD soil concentrations alone may not be indicative of the potential for human health hazard from contaminated soils, and site-specific evaluation may be essential. In their risk assessments, Kimbrough et al. (1984) assumed 30% bioavailability from ingestion of soil, but they point out that animal studies with contaminated Missouri soil indicated absorption as high as 30–50% (McConnell et al. 1984). Pohl et al.

(1995) assumed 40% bioavailability of 2,3,7,8-TCDD from soil. In contrast, Paustenbach et al. (1986) assumed only 10–30% bioavailability. However, unless toxicokinetic studies that use soil samples from the specific site are available, it is difficult to speculate on how much 2,3,7,8-TCDD as well as other CDDs will be bioavailable.

Anderson et al. (1998) completed a preliminary study of the levels of 8 CDDs, 10 CDFs, 36 PCBs, and 11 other persistent organochlorine pesticides in human serum samples from Great Lakes sport fish consumers. Overall, the 31 fishers on average consumed 49 Great Lakes sport fish meals per year, for a mean of 33 years. This is in contrast to the general population in the Great Lakes basin that typically consumes six meals of Great Lakes sport fish per year. A summary of the distribution of CDDs is provided in Table 5-44. CDD congeners detected most often were 1,2,3,4,6,7,8-HpCDD (31 detects), OCDD (31 detects), 1,2,3,6,7,8-HxCDD (30 detects), 2,3,7,8-TCDD (25 detects), and 1,2,3,7,8-PeCDD (20 detects). The overall mean concentration for 2,3,7,8-TCDD was 6.6 ppt. Total CDD concentrations were highest for Lake Huron fish consumers (1,259 ppt), intermediate for Lake Michigan consumers (1,087 ppt), and lowest for Lake Erie consumers (844 ppt). The comparison group serving as a control included individuals residing in Arkansas and had a total CDD serum concentration of 1,198 ppt. With respect to the TEQ values for CDDs, the pattern among Great Lakes fish consumers was similar to that for total CDD consumers with TEQs for Lake Huron fish consumers of 36 ppt, Lake Michigan consumers of 25.9 ppt, and Lake Erie consumers of 20.7 ppt. The TEQ values for the three Great Lakes sport fish consumer groups were statistically different ($p<0.03$). Although the comparison population had CDD concentrations within the range of the Lake Michigan and Lake Huron fish consumers, the TEQ value for CDDs for this population was the lowest of the four groups at 15.5 ppt. The study authors concluded that Great Lakes anglers who are life-long frequent consumers of sport fish represent a subpopulation with the potential for significant exposure to CDDs as well as CDFs and PCBs. The levels of CDDs, CDFs, and PCBs found in sportfish and human tissue residues were above those in the general population.

Table 5-44. Mean and Range (ppt) of Serum CDD (Lipid Adjusted)

Dioxin congener	All subjects (n=3)	Lake Michigan (n=9)	Lake Huron (n=11)	Lake Erie (n=11)	Comparison group[a]
2,3,7,8-TCDD[b]	6.6 (ND–17.2)	4.7 (ND–7.9)	10.5 (4.4–17.2)	4.3 (ND–9.0)	2.8 (0.3–8.9)
1,2,3,7,8-PeCDD[b]	10.4 (ND–31.5)	9.8 (ND–23.7)	16 (ND–31.5)	5.8 (ND–12.3)	6.6 (0.6–14.1)
1,2,3,4,7,8-HxCDD	8.4 (ND–22.7)	11.4 (ND–16.3)	8.4 (2.1–22.7)	6.6 (ND–16.6)	9.0 (0.9–121)

Table 5-44. Mean and Range (ppt) of Serum CDD (Lipid Adjusted)

Dioxin congener	All subjects (n=3)	Lake Michigan (n=9)	Lake Huron (n=11)	Lake Erie (n=11)	Comparison group[a]
1,2,3,6,7,8-HxCDD	126 (71.9–228)	120 (71.9–190)	142 (88.7–228)	115 (85.1–150)	70.8 (24.8–160)
1,2,3,7,8,9-HxCDD	7.0 (ND–22.8)	8.7 (ND–22.8)	6.5 (ND–16.1)	5.8 (ND–13)	9.4 (0.9–25.8)
1,2,3,4,6,7,8-HpCDD[b]	134 (34.9–314)	144 (72.5–204)	163 (86.7–314)	95.9 (34.9–179)	124 (29.1–358)
1,2,3,4,6,7,9-HpCDD[c]	[c]	ND	ND	[c]	4.4 (1.0–29.1)
OCDD	777 (297–1,869)	793 (409–1,587)	919 (371–1,869)	623 (297–981)	971 (286–2,710)
Dioxin total (ppt)	1,062 (453–2,410)	1,087 (615–2,017)	1,259 (729–2,410)	844 (453–1,286)	1,198[d]
Dioxin EPA TEQs[b]	27.5 (8.2–58.7)	25.9 (13.8–38.3)	36 (18.5–58.7)	20.7 (8.2–31.0)	15.5[d]

[a]Unexposed sample residing in Jacksonville, Arkansas (n=70).
[b]Three Great Lakes subgroups are statistically different (p<0.03).
[c]One observation detected.
[d]Range not available.

CDD = chlorinated dibenzo-*p*-dioxin; EPA = U.S. Environmental Protection Agency; HpCDD = heptachlorodibenzo-*p*-dioxin; HxCDD = hexachlorodibenzo-*p*-dioxin; ND = none detected; OCDD = octachlorinated dibenzo-*p*-dioxin; PeCDD = pentachlorodibenzo-*p*-dioxin; TCDD = tetrachlorodibenzo-*p*-dioxin; TEQ = toxic equivalency

Source: Anderson et al. 1998

Recent monitoring data in fish from the Great Lakes have shown a large decline in levels of CDDs and CDFs from decades ago, coinciding with declines of atmospheric emissions of dioxin-like substances (Gandhi et al. 2019). However, these monitoring results still show areas in which levels of CDDs and CDFs remain high due to past historical releases.

Ayotte et al. (1997) measured concentrations of CDDs/CDFs and PCBs in plasma of adult Inuits living in Arctic Quebec, Canada. The Inuit consume large amounts of fish and marine mammal tissue. The mean concentration of 2,3,7,8-TCDD was 8.4 ppt (range 2.5–36.0 ppt) in the Inuit population and <2 ppt (range <2) for the control population in Southern Quebec. The TEQ values for all CDDs/CDFs was 39.6 ppt (range 17.1–81.8 ppt) in the Inuit population and 14.6 ppt (range 11.5–18.9 ppt) for the control population. When PCBs and CDDs/CDFs are considered together, the mean TEQ values for all dioxin-like compounds were 184.2 ppt in the Inuit population (range 55.8–446.7 ppt) and 26.1 ppt (range 20.1–31.7 ppt) for the control population.

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of CDDs is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of CDDs.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 INFORMATION ON HEALTH EFFECTS

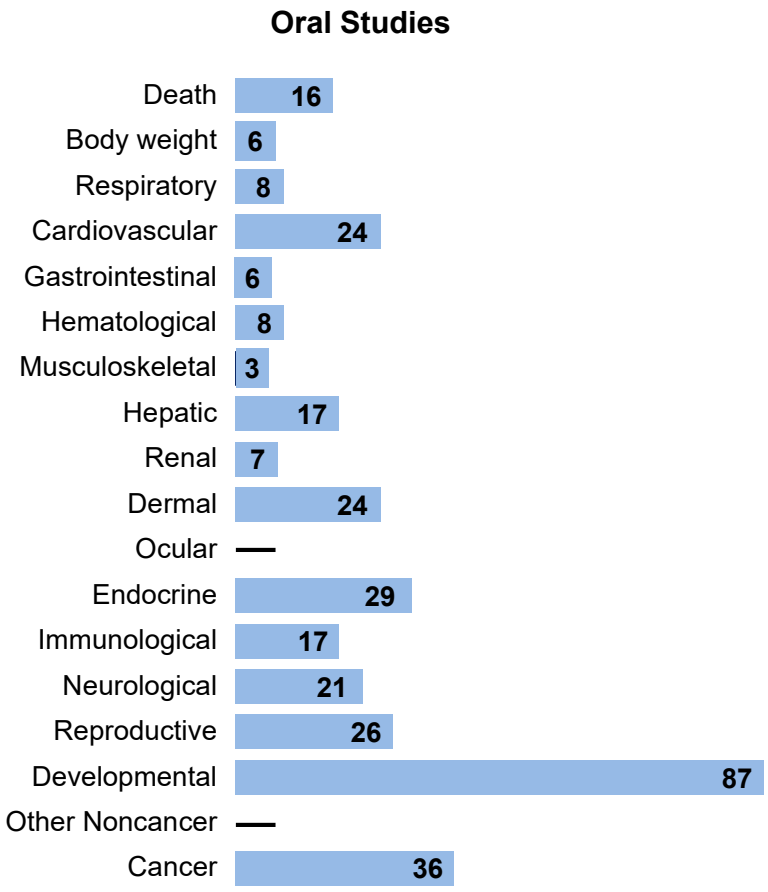
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to CDDs that are discussed in Chapter 2 are summarized in Figures 6-1, 6-2, and 6-3. The purpose of this figure is to illustrate the information concerning the health effects of CDDs. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figures 6-1, 6-2, and 6-3 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 6-1. Summary of Existing Human Health Effects Studies on Chlorinated Dibenzo-*p*-Dioxins (CDDs) by Route and Endpoint*

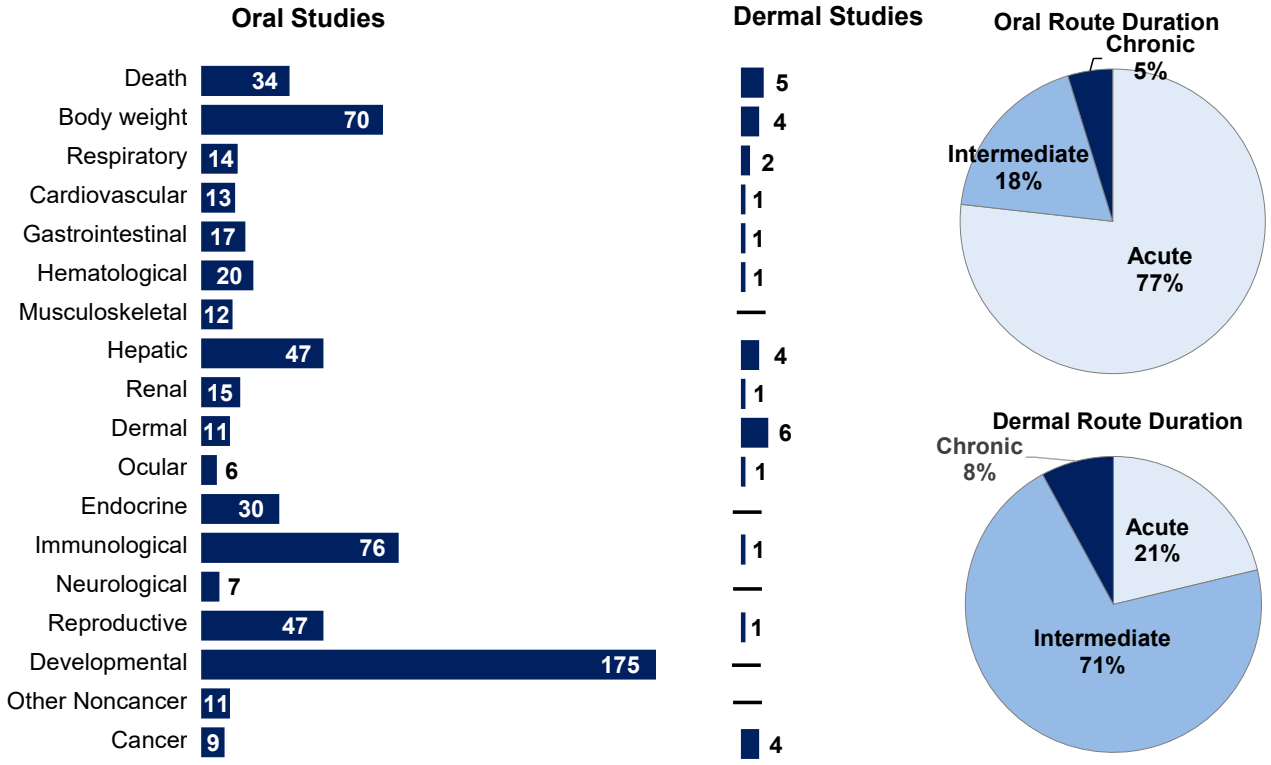
Potential body weight, liver, and kidney effects were the most studied endpoints
The majority of the studies examined oral exposure in **humans**



*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; studies may have examined more than one endpoint. No inhalation or dermal studies in humans were located.

Figure 6-2. Summary of Existing Animal Health Effects Studies on 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) by Route and Endpoint*

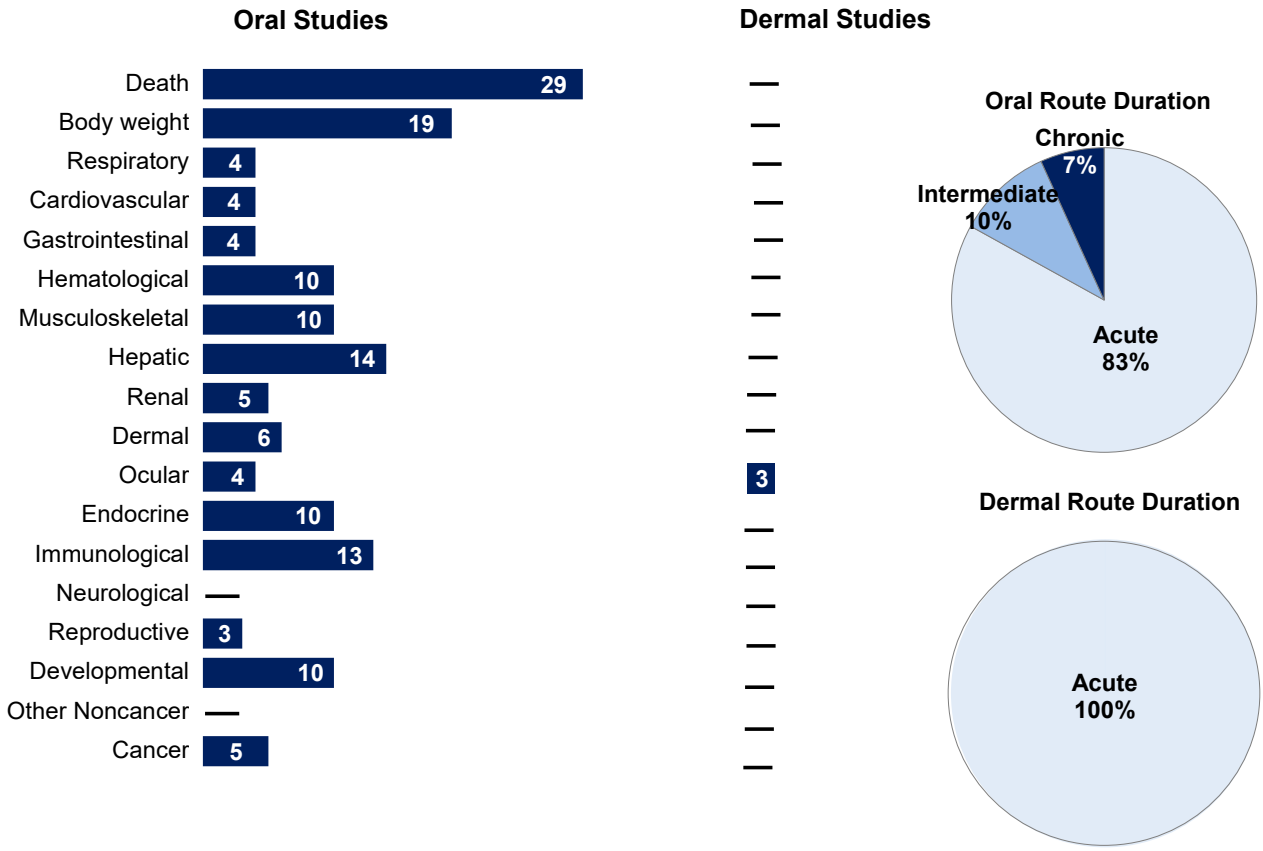
Potential body weight, liver, and kidney effects were the most studied endpoints
The majority of the studies examined oral exposure in animals



*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; studies may have examined more than one endpoint. No inhalation studies in animals were located.

Figure 6-3. Summary of Existing Health Effects Animal Studies on Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) by Route and Endpoint*

Potential body weight, liver, and kidney effects were the most studied endpoints
The majority of the studies examined oral exposure in animals



*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; studies may have examined more than one endpoint. No inhalation studies in animals were located.

Acute-Duration MRLs. Acute-duration exposure of humans to 2,3,7,8-TCDD can cause chloracne and hepatic effects (Goldman 1972; Reggiani 1980). Specifying the route of exposure in these human cases is difficult because the individuals were probably exposed by a combination of routes. Furthermore, human data did not provide any information regarding exposure levels, and co-exposure to other chemicals confound the results. Also, in most cases, the exposed subjects were examined long after exposure occurred. No inhalation studies were identified that could be used to derive inhalation MRLs for 2,3,7,8-TCDD or other CDD congeners. Since inhalation exposure is a relevant route for humans, additional studies are needed to evaluate dose-response relationships. The acute oral toxicity of 2,3,7,8-TCDD has been extensively studied in animals; the most sensitive targets of toxicity are developmental, immunological, reproductive, hepatic, and endocrine endpoints. The database was considered adequate for derivation of an acute-duration oral MRL for 2,3,7,8-TCDD.

No information was located regarding health effects of other congeners in humans, and limited data exist about effects caused by an acute-duration exposure to these congeners in animals. Although studies are available for several other CDD congeners—2-MCDD, 2,3,7-TrCDD, 1,2,3,4-TCDD, 1,2,3,7,8-PeCDD, 1,2,4,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD—the databases were not considered adequate for derivation of acute-duration oral MRLs. The information would be useful for populations living near hazardous waste sites that may be exposed to CDDs for acute durations.

Intermediate-Duration MRLs. Intermediate-duration exposure of humans to CDDs has occurred after industrial accidents or in population groups (e.g., Vietnam War veterans, Vietnamese communities, and pesticide production workers and applicators) exposed to CDD-contaminated herbicides. As stated above, the route of exposure and exposure levels cannot be exactly determined. The oral toxicity of 2,3,7,8-TCDD following oral exposure has been extensively evaluated in animals. The main adverse effects in animals following intermediate-duration oral exposure to 2,3,7,8-TCDD include developmental toxicity, immunotoxicity, reproductive toxicity, and hepatotoxicity. However, the database was not considered adequate for derivation of an intermediate-duration oral MRL for 2,3,7,8-TCDD because the lowest adverse effect level was for a serious health outcome (decreased pup survival). The intermediate-duration oral toxicity data for 2,3-DCDD, 2,7-DCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD have also been evaluated; however, the data were not considered adequate for derivation of MRLs. No data were located regarding toxicity or toxicokinetics in animals after intermediate-duration inhalation exposure to CDDs. Information obtained

from a 90-day inhalation exposure study would be relevant to people living near hazardous waste sites who may be exposed to CDDs for similar durations or much longer time periods.

Chronic-Duration MRLs. A number of epidemiology studies have examined the toxicity of CDDs following chronic-duration exposure to phenoxy herbicides and chlorophenols contaminated with 2,3,7,8-TCDD. Although a number of effects have been observed, interpretation of the results is confounded by a number of factors including lack of adequate exposure information, long postexposure periods, concomitant exposure to other chemicals, and small cohorts. Follow-up medical surveillance of subjects with known past high exposure to 2,3,7,8-TCDD would provide information on the possibility that adverse effects could manifest later in adult life when compounded by normal age-related changes. In addition, further research is needed in areas for which the animal data have demonstrated exposure related effects, but the human data are inconclusive. Chronic-duration oral studies of 2,3,7,8-TCDD in animals have identified several targets of toxicity; adverse developmental, reproductive, and immunological effects were observed at the lowest dose tested. These data were used to derive a chronic-duration oral MRL for 2,3,7,8-TCDD. The chronic-duration oral toxicity of 2,7-DCDD was also evaluated; however, the database was not considered adequate for derivation of an MRL because immunotoxicity has not been evaluated. Chronic-duration oral studies are not available for other congeners.

No studies were located regarding chronic effects of CDD exposure by the inhalation route. Toxicokinetic inhalation data and chronic-duration studies would be useful for assessing the risk levels for people living near municipal, medical, and industrial waste incinerators who can be exposed for chronic durations to CDDs by this route.

Health Effects.

Reproductive. Data from studies on reproductive effects in humans (Aschengrau and Monson 1989; Egeland et al. 1994; Forsberg and Nordstrom 1985; Henriksen et al. 1996; Phuong et al. 1989; Smith et al. 1982; USAF 1991; Wolfe et al. 1985, 1995) are inconclusive and are limited by confounding factors such as small cohorts, co-exposure to other chemicals, and inadequate exposure data. Better controlled epidemiological studies measuring 2,3,7,8-TCDD exposure levels or 2,3,7,8-TCDD body burdens would be useful to assess the human reproductive toxicity risk. Reproductive effects have been observed in oral animal studies. Increased incidences of pre- and post-implantation losses were observed in 2,3,7,8-TCDD-exposed rodents (Giavini et al. 1983; Neubert and Dillmann 1972; Smith et al. 1976; Sparschu et al. 1971a), rabbits (Giavini et

al. 1982), and monkeys (McNulty 1985). Adverse effects have also been observed in the reproductive organs (decreased weight), hormone levels, and gametes of male rats (Khera and Ruddick 1973; Moore et al. 1985) and nonpregnant female rats (Li et al. 1995a, 1995b). None of the acute-duration exposure studies assessed the potential of CDDs to impair fertility; data on fertility would be useful in assessing potential effects in humans exposed to CDDs for a short period of time. Reduced fertility (Bowman et al. 1989b; Hong et al. 1989; Murray et al. 1979; Schantz et al. 1992) and increased incidence of abortions (Bowman et al. 1989b; Hong et al. 1989; McNulty 1984; Schantz et al. 1992) were observed in animals exposed for intermediate or chronic durations. Reproductive effects have also been observed in animals exposed to mixed HxCDD (Schwetz et al. 1973), but not following exposure to 2-MCDD, 2,3-DCDD, 2,7-DCDD, 1,2,3,4-TCDD, or OCDD (Khera and Ruddick 1973). Data on the reproductive toxicity of CDD following dermal exposure are limited to a single animal study that found no adverse effects on reproductive organs of mice chronically exposed to 2,3,7,8-TCDD (NTP 1982a). No animal inhalation reproductive toxicity studies were located. Additional animal inhalation and dermal reproductive studies, particularly studies that assessed reproductive performance, would be useful to assess the possible risk in humans exposed to CDDs by these routes.

Developmental. Studies in humans and animals indicated that 2,3,7,8-TCDD can cross the placenta and is excreted in milk (Fürst et al. 1989; Schecter et al. 1989b, 1989d, 1990a). Studies on the developmental toxicity of 2,3,7,8-TCDD in humans are inconclusive. Some studies found significant increases in the risk of certain birth defects (Aschengrau and Monson 1990; Erickson et al. 1984; Hanify et al. 1981; Nelson et al. 1979; Phuong et al. 1989; Wolfe et al. 1985, 1995), while other studies found no significant alterations (Bisanti et al. 1980; Mastroiacovo et al. 1988; Townsend et al. 1982). However, a number of limitations (e.g., lack of exposure data, small sample sizes, and lack of reliable data for birth defects prior to 2,3,7,8-TCDD exposure) limit the interpretation of the results of these studies. Epidemiology studies that measure exposure concentrations or body burdens would be useful to determine if 2,3,7,8-TCDD and other CDD congeners are human developmental toxicants. Developmental toxicity has been observed in animals orally exposed to 2,3,7,8-TCDD (Abbott and Birnbaum 1989a; Abbott et al. 1992; Bjerke and Peterson 1994; Bjerke et al. 1994a, 1994b; Bowman et al. 1989a, 1989b; Brown et al. 1998; Courtney 1976; Couture-Haws et al. 1991b; Giavini et al. 1983; Gray and Ostby 1995; Gray et al. 1995; Håkansson et al. 1987; Huuskonen et al. 1994; McNulty 1985; Moore et al. 1973; Neubert and Dillmann 1972; Roman et al. 1998a, 1998b; Schantz et al. 1992; Silkworth et al. 1989b; Smith et al. 1976; Thomas and Hinsdill 1979; Weber et al. 1985), 2,7-DCDD (Khera and Ruddick

1973; Schwetz et al. 1973), mixed HxCDD (Schwetz et al. 1973), and OCDD (Schwetz et al. 1973). The most common effects were cleft palate, hydronephrosis, impaired development of the reproductive system, immunotoxicity, and death. No studies were located regarding developmental effects in animals after inhalation and dermal exposure. Such studies would be useful for extrapolating the possible risk to human populations exposed environmentally by these routes.

Immunotoxicity. Studies in humans did not provide conclusive evidence regarding immunotoxicity of CDDs (Ernst et al. 1998; Jansing and Korff 1994; Jennings et al. 1988; Jung et al. 1998; Mocarelli et al. 1986; Neubert et al. 1993, 1995; Reggiani 1980; Stehr et al. 1986; Svensson et al. 1994; Tonn et al. 1996; USAF 1991; Webb et al. 1989; Wolfe et al. 1985). Studies in animals indicated that CDDs are immunosuppressive (Kerkvliet 1995). 2,3,7,8-TCDD induced thymic atrophy or thymic weight changes after oral (Hanberg et al. 1989; McConnell et al. 1978b), dermal (Hebert et al. 1990), and parenteral exposure (Gorski et al. 1988; Olson et al. 1980a). Suppressed cell-mediated and humoral immunity was found in rodents after intermediate-duration exposure (Vos et al. 1973). Similarly, immunotoxic effects were found after oral exposure of rodents to 2,7-DCDD or to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD (Holsapple et al. 1986; NCI/NTP 1980). At least in mice, differences in responsiveness to CDDs' immunotoxicity *in vivo* segregated with the Ah locus (Nagayama et al. 1989; Vecchi et al. 1983).

Studies in animals aimed at identifying 2,3,7,8-TCDD-sensitive immune endpoints that can also be measured in humans would be valuable to determine correlative changes in the biomarker and immune function. However, this can be done only after establishing a database of normal values for the clinical immunology endpoints that may be used as biomarkers of immune function in immunotoxicity assessments. It is also important to determine in animals how well changes in lymphoid organs correlate with changes in the expression of lymphocyte subset/activation markers in peripheral blood. The role of the AhR in the immunotoxicity of 2,3,7,8-TCDD needs to be researched in species other than mice. In addition, the role of AhR-independent processes in 2,3,7,8-TCDD-induced immunotoxicity needs to be examined further. Such actions may include changes in intracellular calcium or in the activity of kinase/phosphatase systems, or interactions with hormone systems. A battery of immune function tests in human cohorts exposed to CDDs would be useful for detecting the immunotoxic responses in exposed individuals. The ability of CDD-exposed individuals to mount an integrated functional response

to a novel antigen, such as hepatitis B vaccine, would provide a broad measure of immune function in exposed human populations.

Neurotoxicity. Studies in Vietnam veterans could not conclusively demonstrate cognitive or other central nervous system deficits (Goetz et al. 1994). Neurological examinations revealed neurological effects in humans exposed to a CDD-contaminated environment (Pocchiari et al. 1979) and in occupational settings (Goldman 1972; Jirasek et al. 1976; Klawans 1987; Pazderova-Vejlupkova et al. 1981) shortly following exposure, but reports with comparison groups do not offer clear evidence that exposure to 2,3,7,8-TCDD is associated with chronic peripheral neuropathy (Suskind and Hertzberg 1984; Sweeney et al. 1993). No notable neurological effects were found in laboratory animals after oral or dermal exposure. The existing information suggests that in adults, no long-term neurologic affects were caused by high exposure to 2,3,7,8-TCDD-contaminated materials. However, the possibility exists that subtle central nervous system changes acquired in early adulthood could manifest later in adult life when compounded by normal age-related changes in the central nervous system (Goetz et al. 1994). Thus, it would be of interest to include tests of neurological function in ongoing prospective studies of 2,3,7,8-TCDD-exposed populations to determine if neurological effects occur as the exposed population ages.

Epidemiology and Human Dosimetry Studies. Epidemiology studies have investigated the toxicity of 2,3,7,8-TCDD in populations exposed in the workplace or in the contaminated environment (after industrial accidents or herbicide spraying) and in Vietnam veterans exposed to Agent Orange. The interpretation of the results of most of these studies is confounded by such factors as unknown levels of exposure, too short or too long postexposure periods, and small cohorts. Well-conducted epidemiological and occupational studies that quantify exposure levels would be useful to assess the risk for the main endpoints of concern (i.e., reproductive, developmental, immunotoxic effects, and cancer). Some studies have measured the levels of 2,3,7,8-TCDD and related compounds in serum lipid; these levels can then be used to estimate body burden at the time of exposure. There are a number of drawbacks associated with extrapolating body burdens back to the time of the original exposure using current serum 2,3,7,8-TCDD levels; these include uncertainty associated with 2,3,7,8-TCDD half-life in humans and having to use average serum 2,3,7,8-TCDD levels, average exposure durations, reference body weights, and percentage of body fat. There is a lack of consensus on the half-life of 2,3,7,8-TCDD in humans; half-lives of 5–12 years have been estimated (Pirkle et al. 1979; Schecter et al. 1994b; Wolfe et al. 1994). Additional human studies measuring 2,3,7,8-TCDD half-life would be useful in establishing dose-response

relationships for human effects. All the above limitations for assessing the body burden of 2,3,7,8-TCDD also apply to other CDDs where far less human toxicokinetic data are available. Thus, it would be useful to have congener-specific human toxicokinetic data on other CDDs and related compounds. Furthermore, human dosimetry studies would be useful in occupational settings to obtain results regarding levels of CDDs in the environment as opposed to levels in serum or adipose tissues.

Biomarkers of Exposure and Effect. Several studies reported results of measurements of CDD levels in the lipid fraction of adipose tissue, milk, and serum from members of the general population with unknown CDD exposure (Andrews et al. 1989; Ryan et al. 1985; Schecter et al. 1987b). The gas chromatography-mass spectrometry (GC/MS) tests used to detect CDD levels are sensitive and specific. Analytical testing for levels in biological fluids and tissues can be used for monitoring exposed populations. While chloracne is a known, readily identifiable effect of exposure to CDDs, it is not useful as a biomarker of exposure because of its variable expression in individuals with even very high levels of exposure to these agents. Further information on how aging and changes in body composition can influence the distribution of CDDs in tissues and body fluids would be valuable. A reverse transcriptase polymerase chain reaction method has been used to quantify CYP1A1 mRNA levels on total RNA extracts from human blood lymphocytes (Vanden Heuvel et al. 1993). This method was found to be much more sensitive than, for example, measuring EROD activity, and could potentially be used as a human exposure marker for CDDs and structurally related compounds. However, EROD activity measurements can be useful as a marker of exposure to the agents.

There are no specific biomarkers of effects for CDDs. Exposure to relatively high concentrations of CDDs can lead to the development of chloracne in humans. However, while the presence of chloracne indicates CDD or similar halogenated-chemical exposure, lack of chloracne does not indicate that exposure has not taken place, as evidenced in a cohort from the Seveso incident (Mocarelli et al. 1991). Additional studies could evaluate the feasibility of using body burden as a biomarker for predicting other effects of CDDs. Although the results of an earlier study suggested that 2,3,7,8-TCDD may form adducts with DNA, albeit at an extremely low rate (Poland and Glover 1979), later studies that have rigorously looked for 2,3,7,8-TCDD-DNA adducts have been negative (Randerath et al. 1988; Turteltaub et al. 1990). Expression of CYP1A1 mRNA, protein, and/or activity are sensitive biological responses in human tissues that can be observed following exposure to 2,3,7,8-TCDD and related compounds, and may be useful biomarkers of effects. Further studies to identify biomarkers of effects of CDDs would facilitate medical surveillance, leading to early detection of potentially adverse health effects and possible treatment.

Absorption, Distribution, Metabolism, and Excretion. There are no quantitative data regarding absorption in humans by the inhalation or dermal routes, but data from accidentally exposed individuals suggest that exposure by these routes may lead to a significant increase in body burden of CDDs (Patterson et al. 1994; Schecter et al. 1994b). Results from one human study indicated that >87% of an oral 2,3,7,8-TCDD dose in an oil vehicle was absorbed (Poiger and Schlatter 1986). Also, results from studies of absorption of CDDs from maternal milk by nursing infants showed that 90–95% of the dose of CDDs can be absorbed; hepta-substituted congeners and OCDD exhibited lower absorption rates (Abraham et al. 1994, 1996; Dahl et al. 1995; McLachlan 1993; Pluim et al. 1993b). The data indicate that 2,3,7,8-TCDD is effectively absorbed, and that absorption is vehicle-dependent (Fries and Marrow 1975; Lucier et al. 1986; Poiger and Schlatter 1980); oil vehicles were most effective (Olson et al. 1980b; Piper et al. 1973). Transpulmonary absorption of 2,3,7,8-TCDD also occurs in animals (Diliberto et al. 1996; Nessel et al. 1992). Dermal absorption of 2,3,7,8-TCDD in rats was found to be age-dependent (Anderson et al. 1993). In rats, following single equivalent intratracheal, oral, and dermal 2,3,7,8-TCDD doses, absorption was calculated as 95, 88, and 40% of the administered dose, respectively (Diliberto et al. 1996). The available information shows that absorption of 2,3,7,8-TCDD has been fairly well characterized in animals.

Based on analysis of CDDs in adipose tissue, milk, and blood, it appears that humans store exclusively 2,3,7,8-chlorine substituted congeners (Fürst et al. 1987; Van den Berg et al. 1986b). Data are available on tissue distribution of 2,3,7,8-TCDD in rats after inhalation, oral, and dermal exposure (Diliberto et al. 1996). The liver and adipose tissue are the major storage sites in animals. In general, distribution of CDDs is congener specific and depends on the dose and route of administration (Diliberto et al. 1996; Van den Berg et al. 1994). Age was also a factor in the distribution of 2,3,7,8-TCDD in mice (Pegram et al. 1995). The distribution of 2,3,7,8-TCDD-derived radioactivity in subcellular liver fractions has also been studied (Santostefano et al. 1996). 2,3,7,8-Chlorine substituted CDDs are the predominant congeners retained in tissue and body fluids from humans, rodents, and monkeys (Abraham et al. 1989; Van den Berg et al. 1983). Further dosimetry studies of various durations in which levels of 2,3,7,8-TCDD and related compounds are monitored in tissues suspected of being targets for 2,3,7,8-TCDD toxicity would provide valuable information. These data can be used to establish correlations between target-tissue doses and adverse effects.

Data regarding the biotransformation of CDDs in humans are limited to a self-dosing experiment that provided some evidence that 2,3,7,8-TCDD is partially excreted in the feces in the form of metabolites

(Wendling et al. 1990). The use of human cell systems in culture might be considered a useful addition to whole-animal studies for examining the metabolic fate of CDDs. Biotransformation of CDDs has been examined in several species, but the structure of metabolites has been elucidated only in the rat and dog (Poiger and Buser 1984). Although information regarding metabolism following inhalation or dermal exposure is lacking, there is no reason to believe that different pathways would operate after exposure by these routes.

Two studies were located that provided limited evidence of fecal excretion of 2,3,7,8-TCDD metabolites in adult humans (Sorg et al. 2009; Wendling et al. 1990). Several studies provided information regarding fecal excretion of CDDs in infants exposed through human milk (Abraham et al. 1994; McLachlan 1993; Pluim et al. 1993b). Elimination of CDDs through maternal milk is well documented (Fürst et al. 1994; Rappe et al. 1985; Schecter and Gasiewicz 1987a; Schecter et al. 1989d, 1989e). Fecal excretion is the main route of excretion of CDDs in animals after all routes of exposure (Diliberto et al. 1996). Estimates of 2,3,7,8-TCDD half-life in humans are available (Pirkle et al. 1989; Poiger and Schlatter 1986; Wolfe et al. 1994), but further information regarding the relationships between aging, fat redistribution, and half-lives in humans would be valuable.

Comparative Toxicokinetics. CDDs are efficiently absorbed from the gastrointestinal tract of mammals, but the vehicle plays an important role (Olson et al. 1980b; Piper et al. 1973; Poiger and Schlatter 1986; Van den Berg et al. 1987a). Distribution data in orally exposed rodents indicated that the highest postexposure levels were in the liver followed by the fat (Diliberto et al. 1996; Khera and Ruddick 1973; Olson 1986), but distribution is highly dose- and species-dependent. The studies to date suggest that compared with rodents, primates, including humans, accumulate significantly less CDDs in the liver than in adipose tissue (Neubert et al. 1990; Ryan et al. 1986; Van Miller et al. 1976). With the exception of the guinea pig, mammals retain only 2,3,7,8-substituted congeners. The high liver retention of 2,3,7,8-substituted congeners by rodents has been attributed to the presence of inducible storage sites, presumably CYP1A2 (Leung et al. 1990b). In all mammalian species studied, exposure by breastfeeding has a much greater contribution to the offspring 2,3,7,8-TCDD body burden than placental transfer. Metabolic capacities are species dependent. Rats, hamsters, and mice metabolize and eliminate CDDs much faster than the guinea pig. The metabolites were excreted predominantly via the bile and feces, with minor amounts excreted in the urine in all species (Diliberto et al. 1996; Fries and Marrow 1975; Weber and Birnbaum 1985). Whole-body half-lives ranged from 11 days in hamsters (Olson et al. 1980b) to >1 year in monkeys (Bowman et al. 1989b; McNulty et al. 1982) and were approximately 7–12 years in humans (Wolfe et al. 1994). The toxicity of CDDs has been associated with the parent compound and

not the metabolites (Mason and Safe 1986; Weber et al. 1982); therefore, metabolism and excretion represent a detoxification process. The data collected in later years indicate that differences in species susceptibility to CDDs cannot be explained by differences in toxicokinetics alone; it is likely that genetic factors have an important role. Based on this information, species-, congener-, and dose-specific toxicokinetic data need to be factored into human risk assessment for CDDs. Several models that describe the disposition of 2,3,7,8-TCDD in animals and humans were identified from the literature (Andersen et al. 1993, 1997a, 1997b; Carrier et al. 1995a, 1995b; Kissel and Robarge 1988; Kohn et al. 1993; Leung et al. 1988, 1990b). Although each new model that is published usually fills data gaps identified in earlier models, further research is necessary to increase their reliability for use in human risk assessment.

Children's Susceptibility. A limited number of human studies have examined health effects of CDDs in children. Data from the Seveso accident suggest that children may be more susceptible to the dermal toxicity of 2,3,7,8-TCDD (chloracne), but it is not known if this would be the case for other effects. Follow-up medical surveillance of the Seveso children (including measurement of serum 2,3,7,8-TCDD levels) would provide information on whether childhood exposure would pose a risk when the individual matures and ages. The available human and animal data provide evidence that 2,3,7,8-TCDD can cross the placenta and be transferred to an infant via human milk. Although information on the developmental toxicity of CDDs in humans is limited, there are extensive animal data that the developing organism is very sensitive to the toxicity of 2,3,7,8-TCDD. Several human studies have found significant alterations in markers of liver, thyroid, immune, and neurological function in young, breastfed infants of mothers with higher current background or general population CDD levels. Data suggest that the neurological effects are reversible; prospective studies of breastfed individuals would provide useful information on whether these children are at risk of developing additional effects as they age. Further data needs relating to developmental effects are discussed above under Developmental.

In general, the available toxicokinetic data did not examine potential differences between adults and children; toxicokinetic studies examining how aging and changes in body composition can influence distribution and turnover rates would be useful in assessing children's susceptibility to CDD toxicity. Most of the available mechanism-of-action data suggest that the toxicity of 2,3,7,8-TCDD is mediated through the AhR. It is not known whether there are any age-related differences in receptor binding or expression; studies in animals would be valuable to fill this information gap. No age-specific biomarkers of exposure or effect were identified for CDDs; the long half-life of 2,3,7,8-TCDD in humans suggests that there may not be a way to assess whether adults were exposed as children to 2,3,7,8-TCDD.

Additionally, there are no data to determine whether there are any interactions with other chemicals that would be specific for children. There is very little available information on methods for reducing 2,3,7,8-TCDD toxic effects or body burdens; it is likely that research in adults would also be applicable to children.

Physical and Chemical Properties. The physical and chemical properties of 2,3,7,8-TCDD are sufficiently characterized to predict the environmental fate of 2,3,7,8-TCDD (IARC 1977; Sax and Lewis 1987; Schroy et al. 1985; Shiu et al. 1988). Of all the CDDs, 2,3,7,8-TCDD has been the compound most studied. Not all isomers within each homologous class have been equally well studied for many of the physical and chemical properties. Information on physical and chemical properties of certain congeners (particularly 1,2,3,7,8,-PeCDD and 1,2,3,6,7,8-HxCDD) would be helpful in better understanding the different fate and transport pathways of the homologous groups.

Production, Import/Export, Use, Release, and Disposal. CDDs are not manufactured commercially in the United States except on a laboratory scale for use in chemical and toxicological research (CIL 1995). They are produced as undesired by-products during the manufacture of chlorophenols (e.g., PCP and 2,4,5-trichlorophenol) and during combustion processes (IARC 1977; NTP 1989; Podoll et al. 1986). CDDs are ubiquitous in the environment and have been found at low levels (ppt or lower) in air, water, soil, sediment, and foods. Continued monitoring of release data would provide useful information on trends. Current disposal methods are efficient and are subject to EPA and state regulations.

Environmental Fate. CDDs are subject to atmospheric transport and both wet and dry deposition (Kieatiwong et al. 1990). They are partitioned to air, water, sediment, and soil, and they accumulate in both aquatic and terrestrial biota. CDDs can volatilize to the atmosphere from water and soil surfaces; however, adsorption processes attenuate the rate of volatilization. They adsorb strongly to soils and are not likely to leach into groundwater (Eduljee 1987). In the aquatic environment, CDDs partition to sediment or suspended particulates. TCDD, HpCDD, and OCDD are subject to photolysis in air, water, and soil (Plimmer et al. 1973). 2,3,7,8-TCDD is biodegraded very slowly in soil and is thus likely to persist in the soil. A better understanding of environmental behavior of CDDs is needed with respect to the importance of vapor-phase versus particulate transport, the environmental behavior of different congeners, and the significance of processes that reintroduce CDDs into the atmosphere after deposition. Information regarding the degradation of other congeners, specifically OCDD, and their degradation

products in water, sediment, and soil would be useful in evaluating the various pathways of human exposure.

Bioavailability from Environmental Media. Toxicokinetic data in humans regarding absorption of CDDs following oral and dermal exposure are very limited (Poiger and Schlatter 1986). CDDs can be absorbed following oral exposure in both humans and animals (Birnbaum and Couture 1988; Fries and Marrow 1975; Koshakji et al. 1984; Norback et al. 1975; Olson et al. 1980b; Piper et al. 1973; Poiger and Schlatter 1980). The more highly chlorinated CDD congeners are absorbed to a lesser extent than 2,3,7,8-TCDD (Koshakji et al. 1984). Also, limited information is available on the bioavailability from fly ash (Van den Berg et al. 1983, 1985). 2,3,7,8-TCDD can be adsorbed following dermal contact (Banks and Birnbaum 1991; Poiger and Schlatter 1980; Shu et al. 1988); however, dermal absorption of 2,3,7,8-TCDD from soil is very low (Shu et al. 1988). More information is needed regarding oral and dermal exposure to determine the bioavailability of CDDs from food, water, and soil. Additional information is needed to examine the discrepancy noted in the mass balance from CDDs ingested from foods and eliminated in feces. For inhalation exposure, information on the bioavailability from fly ash and sediments would be useful. Information is also needed on the selective uptake of the 2,3,7,8-substituted CDD congeners.

Food Chain Bioaccumulation. CDDs are bioconcentrated in aquatic organisms, plants, and terrestrial animals. Shellfish (including crustaceans and bivalve mollusks) appear to accumulate CDDs nonselectively to relatively high concentrations in their tissues (Bopp et al. 1991; Brown et al. 1994; Cai et al. 1994; Conacher et al. 1993; Hauge et al. 1994; Rappe et al. 1991). In contrast, finfish appear to selectively accumulate primarily 2,3,7,8-TCDD and other 2,3,7,8-substituted isomers in their tissues (Rappe et al. 1991). Information from a larger number of species on the retention of 2,3,7,8-substituted CDD congeners and general information on retention and distribution of other CDDs would be useful in better understanding both aquatic and terrestrial food chains.

Exposure Levels in Environmental Media. CDDs have been detected in air, water, soil, sediment, plant material, and foods. Environmental monitoring studies show that the higher chlorinated CDDs are usually the ones most commonly found in environmental samples (Christmann et al. 1989; Clement et al. 1985, 1989; Pereira et al. 1985; Reed et al. 1990; Tashiro et al. 1989a; Tiernan et al. 1989). Current monitoring studies are needed to determine CDD levels in media surrounding hazardous waste sites. Using a model, the total average daily intake of 2,3,7,8-TCDD (by air, water, and food) for the general population was estimated to be 0.05 ng/day (range 0.008–0.3 ng/day) (FDA 2006; Travis and Hattemer-

Frey 1987). Dearfield et al. (2013), FDA (2006), Schecter et al. (1994a, 1994d, 1996a); and Schecter and Li (1997) have provided current information on CDD exposures from food. Food consumption accounts for >90% of background human exposure to 2,3,7,8-TCDD and other CDDs/CDFs in the general U.S. population (Dearfield et al. 2013; Hattemer-Frey and Travis 1989; Schaum et al. 1994). The average daily intake by nursing infants in the United States has been estimated to be 83 pg TEQs/kg (Schecter and Gasiewicz 1987a, 1987b). Since levels of CDDs and CDFs have declined in environmental media, including food items, as emissions have been reduced, these estimated intakes are likely higher than current intakes. A data need to estimate current daily intakes is identified. Dietary exposure studies should look at exposures for population sectors that have different diets (e.g., according to age, race/socioeconomic status, dietary preferences).

Exposure Levels in Humans. CDDs/CDFs have been found in blood (CDC 2024a, 2024b; Fingerhut et al. 1989; Needham et al. 1991; Päpke et al. 1989b, 1992, 1993), adipose tissue (EPA 1986a; Orban et al. 1994; Patterson et al. 1986a; Ryan et al. 1986; Schecter et al. 1986b; Stanley et al. 1986), and human milk of both the general population and workers exposed through industrial accidents or environmental contamination (Fürst et al. 1992; Pluim et al. 1993a; Ryan et al. 1993b; Schecter and Gasiewicz 1987b; Schecter and Tiernan 1985; Schecter et al. 1986a, 1986b, 1989e). Levels of 2,3,7,8-TCDD as well as other CDDs are generally higher in occupationally exposed individuals or those individuals exposed through industrial accidents or environmental contamination (Kahn et al. 1988; Schecter and Tiernan 1985; Schecter et al. 1986b, 1987a; Umbreit et al. 1986a, 1986b). CDDs have also been detected in human milk and blood of Canadian populations of native Inuit who consume large amounts of fish and marine mammals (Ayotte et al. 1997; Dewailly et al. 1992). Additional, recent biological monitoring data are needed, however, for those U.S. populations surrounding hazardous waste sites or municipal, medical, or industrial incinerators, for urban versus rural exposures, and for other potentially exposed populations including subsistence fishers and hunters (Liem et al. 1991; Startin et al. 1989; Wuthe et al. 1993). Recent information on tissue levels in the general population worldwide are for the most part lacking (Schecter et al. 1991a). As they are identified, exposed populations should be evaluated to characterize exposure levels and health effects. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Children in the general population are exposed to CDDs primarily through dietary exposures *in utero* via placental blood and in newborn infants via breastfeeding. Despite the fact that studies on the concentrations of CDDs in human milk have been conducted in various other countries, there is a need to determine the levels of CDDs in human milk in the United States. Additional

exposure studies also are needed to determine whether dietary modifications in mothers can reduce total CDD exposures in newborns and whether dietary modifications of the infant can also reduce lifetime exposure. For children in populations with potentially high exposure to CDDs, the primary exposure pathway is through their diet; however, additional exposure to CDDs via consumption of contaminated groundwater or soil, and dermal exposure to contaminated soil may increase their exposure levels. Studies of workers in various industrial settings that are exposed to CDDs (i.e., elevated CDD levels in adipose or blood serum) should be conducted to determine whether CDDs are routinely brought home by these workers on their clothing and shoes to assess whether this is an important exposure route for children.

Schecter and Li (1997) have calculated weight-adjusted intakes of CDDs derived from consumption of four types of fast foods for 6-year-old children. Additional information on dietary intake of CDDs from other types of foods should be conducted for various age groups of children to help identify the magnitude and sources of dietary exposure during childhood. Studies to verify these calculations would be helpful in assessing health risks to children.

The primary childhood specific means to decrease exposure to CDDs involves placing the infant on a cow's milk or soy-based baby formula and on maintenance of children on a long-term diet that is lower in animal fats (meat, dairy products, and fish) and higher in grains, fruits, and vegetables. It should be noted however, that because of the relatively short period of intake and the accepted benefits of breastfeeding, the maintenance of children on a long-term diet low in animal fat would likely be more beneficial in decreasing total lifetime CDD body burdens than cessation of breastfeeding. Additional means of reducing CDD exposures also should be investigated.

6.3 ONGOING STUDIES

Table 6-1 lists research studies identified in a search of the National Institutes of Health (NIH) Research Portfolio Online Reporting Tools Expenditures and Results (RePORTER 2022) that are currently being conducted that may fill some of the data needs discussed in Section 6.2.

Table 6-1. Ongoing Studies on Chlorinated Dibenzo-*p*-Dioxins (CDDs)

Investigator	Affiliation	Research description	Sponsor
Kaminiski NE	Michigan State University	Evaluate the mechanisms of IgM production suppression in response to dioxin-like compounds	NIEHS
Peterson PE	University of Wisconsin-Madison	Examining the relationship between *in utero* exposure to 2,3,7,8-TCDD and benign prostate hyperplasia in adults	NIEHS
Ko CI	University of Cincinnati	Examining the mechanisms of dioxin developmental toxicity	NIEHS

IgM = immunoglobulin M; NIEHS = National Institute of Environmental Health Sciences; 2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

Source: RePORTER 2022

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding CDDs in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for CDDs.

Table 7-1. Regulations and Guidelines Applicable to Chlorinated Dibenzo-*p*-Dioxins (CDDs)

Agency	Description	Information	Reference
	Air		
EPA	RfC	Not evaluated	IRIS 2012, IRIS 2002
WHO	Air quality guidelines	Not established[a]	WHO 2000
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	2,3,7,8-TCDD		
	1-Day health advisory (10-kg child)	$1x10^{-6}$ mg/L	
	10-Day health advisory (10-kg child)	$1x10^{-7}$ mg/L	
	DWEL	$4x10^{-8}$ mg/L	
	Lifetime health advisory	No data	
	10^{-4} Cancer risk	$2x10^{-8}$ mg/L	
	National primary drinking water regulations		EPA 2009
	2,3,7,8-TCDD		
	Maximum contaminant level	$3x10^{-8}$ mg/L	
	Public health goal	0 mg/L	
	RfD		
	2,3,7,8-TCDD	$7x10^{-10}$ mg/kg/day	IRIS 2012
WHO	Drinking water quality guidelines	No data	WHO 2022
	Provisional tolerable monthly intake		JECFA 2002
	PCDDs, PCDFs, and coplanar PCBs expressed as TEFs	70 pg/kg bw	
FDA	Substances added to food (formerly EAFUS)	Not listed	FDA 2023
	Allowable level in bottled water		FDA 2022
	2,3,7,8-TCDD	$3x10^{-8}$ mg/L	

Table 7-1. Regulations and Guidelines Applicable to Chlorinated Dibenzo-*p*-Dioxins (CDDs)

Agency	Description	Information	Reference
	Cancer		
HHS	Carcinogenicity classification		
	2,3,7,8-TCDD	Known to be a human carcinogen	NTP 2021
EPA	Carcinogenicity classification		
	HxCDD	B2[b]	IRIS 2002
	Inhalation unit risk		
	HxCDD	1.3 per µg/m^3	IRIS 2002
	Oral slope factor		
	HxCDD	6.2x10^3 per mg/kg/day	IRIS 2002
IARC	Carcinogenicity classification		
	2,3,7,8-TCDD	Group 1[c]	IARC 2012
	2,7-DCDD; 1,2,3,7,8-PeCDD; 1,2,3,6,7,8-HxCDD; 1,2,3,7,8,9-HxCDD; 1,2,3,4,6,7,8-HpCDD	Group 3[d]	IARC 1997
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	No data	OSHA 2021a, 2021b, 2021c
NIOSH	2,3,7,8-TCDD	Potential occupational carcinogen	NIOSH 2019
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2018b
DOE	PACs-air		DOE 2023a
	2,3,7,8-TCDD; 1,2,3,7,8-PeCDD		
	PAC-1[e]	0.00013 mg/m^3	
	PAC-2[e]	0.0014 mg/m^3	
	PAC-3[e]	0.0085 mg/m^3	
	1,2,3,8-TCDD		
	PAC-1[e]	0.003 mg/m^3	
	PAC-2[e]	0.033 mg/m^3	
	PAC-3[e]	0.2 mg/m^3	
	1,2,3,4,7,8-HxCDD; 1,2,3,6,7,8-HxCDD; 1,2,3,7,8,9-HxCDD		
	PAC-1[e]	0.0013 mg/m^3	
	PAC-2[e]	0.014 mg/m^3	
	PAC-3[e]	0.085 mg/m^3	
	1,2,3,4,6,7,8-HpCDD		
	PAC-1[e]	0.013 mg/m^3	
	PAC-2[e]	0.14 mg/m^3	
	PAC-3[e]	0.85 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Chlorinated Dibenzo-*p*-Dioxins (CDDs)

Agency	Description	Information	Reference
	1,2,3,4,6,7,8,9-OCDD		
	PAC-1[e]	0.43 mg/m^3	
	PAC-2[e]	4.7 mg/m^3	
	PAC-3[e]	28 mg/m^3	

[a]An air quality guideline for PCDDs and PCDFs was not proposed because direct inhalation exposures constitute only a small proportion of total exposure, but due to potential importance of the indirect contribution of PCDDs and PCDFs in air to the total human exposure through deposition and uptake in the food chain, measures should be undertaken to further reduce emissions to air from known sources.
[b]B2: probable human carcinogen.
[c]Group 1: carcinogenic to humans.
[d]Group 3: not classifiable as to carcinogenicity to humans.
[e]Definitions of PAC terminology are available from DOE (2023b).

AEGL = acute exposure guideline level; DCDD = dichlorodibenzo-*p*-dioxin; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = U.S. Environmental Protection Agency; FDA = Food and Drug Administration; HpCDD = heptachlorodibenzo-*p*-dioxin; HHS = Department of Health and Human Services; HxCDD = hexachlorodibenzo-*p*-dioxin; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OCDD = octachlorodibenzo-*p*-dioxin; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PCB = polychlorinated biphenyl; PCDD = polychlorinated dibenzo-*p*-dioxin; PCDF = polychlorinated dibenzofuran; PeCDD = pentachlorodibenzo-*p*-dioxin; PEL = permissible exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TCDD = tetrachlorodibenzo-*p*-dioxin; TEF = toxic equivalency factor; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)
CAS Numbers: 1746-01-6
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute, intermediate, and chronic

MRL Summary: There are insufficient data for the derivation of provisional acute-, intermediate-, or chronic-duration inhalation MRLs for 2,3,7,8-TCDD due to the lack of studies evaluating toxicity following inhalation exposure.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 2,3,7,8-TCDD following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)
CAS Numbers: 1746-01-6
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute
MRL: 0.0002 µg/kg/day ($2x10^{-4}$ µg/kg/day)
Critical Effect: Impaired immune function
Reference: Burleson et al. 1996
Point of Departure: NOAEL of 0.005 µg/kg/day
Uncertainty Factor: 30
Modifying Factor: 0.7
LSE Graph Key: 129
Species: Mouse

MRL Summary: A provisional acute-duration oral MRL of 0.0002 µg/kg/day ($2x10^{-4}$ µg/kg/day) was derived for 2,3,7,8-TCDD based on decreased host resistance in female B6C3F1 mice administered a single gavage dose of ≥0.01 µg/kg (Burleson et al. 1996). The MRL is based on a NOAEL of 0.005 µg/kg, a total uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability), and a modifying factor of 0.7 (to adjust for the higher bioavailability of 2,3,7,8-TCDD from an oil gavage vehicle than from food).

Selection of the Critical Effect: An extensive number of studies (>300) have evaluated the acute oral toxicity of 2,3,7,8-TCDD. The most sensitive endpoints were immunological, developmental, reproductive, hepatic, and endocrine (see Table A-1). The lowest LOAEL value was 0.01 µg/kg/day for immunological and developmental effects; the lowest LOAELs for the other endpoints were 5–10 times higher. As summarized in Tables A-2 and A-3, there is strong support for identifying immunological and developmental effects as sensitive targets of 2,3,7,8-TCDD toxicity.

Table A-1. Summary of NOAEL and LOAEL Values for Sensitive Targets of Acute-Duration Oral Exposure to 2,3,7,8-TCDD

Species, duration	Doses tested (µg/kg/day)	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Immunological					
B6C3F1 mouse, once	0, 0.001, 0.005, 0.01, 0.05, 0.1	Decreased influenza virus host resistance	0.005	0.01	Burleson et al. 1996
B6C3F1 mouse, 14 days	0, 0.01, 0.05, 0.1, 0.5, 1.0, 2.0	Suppressed serum total hemolytic complement activity	–	0.01	White et al. 1986
Developmental					
C3H/HeJ mouse, GD 13	0, 0.01, 0.1, 1	Altered mandible shape in offspring	–	0.01	Keller et al. 2008
Long-Evans rat, GD 15	0, 0.0125, 0.05, 0.2, 0.8	Decreased male/female sex ratio	–	0.0125	Yonemoto et al. 2005
Reproductive					

Table A-1. Summary of NOAEL and LOAEL Values for Sensitive Targets of Acute-Duration Oral Exposure to 2,3,7,8-TCDD

Species, duration	Doses tested (µg/kg/day)	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
NIH mouse, GDs 1–3, 4–8, or 1–8	0, 0.002, 0.05. 0.1	Preimplantation loss	0.002	0.05 (SLOAEL)	Li et al. 2006
Hepatic					
C57BL/6 mouse, once	0, 0.001, 0.01, 0.1, 1, 10, 100, 300	Cytoplasmic vacuolization	0.01	0.1	Boverhof et al. 2006
Hartley guinea pig, once	0, 0.1, 0.5, 2.5, 12.5, 20.0	Focal necrosis	–	0.1	Turner and Collins 1983
Endocrine					
Long-Evans rat, once	0, 0.0001–10	30% decrease in serum T4 levels	–	0.15	Crofton et al. 2005

[a]Doses adjusted for intermittent exposure.

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; SLOAEL = serious lowest-observed-adverse-effect level; T4 = thyroxine

Table A-2. Summary of Alterations in Immune Function Observed in Animals Following Acute-Duration Oral Exposure to 2,3,7,8-TCDD

Species	Effect	Range of LOAELs[a] (µg/kg/day)	Reference
Mouse	Suppressed host resistance	0.01–10	Burleson et al. 1996; Mitchell and Lawrence 2003; Vorderstrasse et al. 2003; Warren et al. 2000;
Rat	Suppressed host resistance	0.72–25	Huang and Koller 1998; Yang et al. 1994
Mouse	Suppressed serum total hemolytic complement activity	0.01–20	Lin and White 1993; White et al. 1986
Mouse	Impaired immune response to antigens	0.1–20	Ao et al. 2009; Chen et al. 2013; Frawley et al. 2014; Holsapple et al. 1986; Inouye et al. 2003, 2005; Ito et al. 2002; Luebke et al. 1999; Matuika et al. 1997; Smialowicz et al. 1997
Rat	Delayed-type hypersensitivity	10	Fan et al. 1996;

[a]Doses adjusted for intermittent exposure.

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; LOAEL = lowest-observed-adverse-effect level

Table A-3. Summary of Developmental Effects Observed in Animals Following Acute-Duration Oral Exposure to 2,3,7,8-TCDD[a]

Species	Effect	Range of LOAELs[b] (µg/kg/day)	Reference
Rat	Impaired development of skeletal system	1	Finnlä et al. 2010; Kattainen et al. 2001; Miettinen et al. 2002, 2005
Mouse	Impaired development of skeletal system	0.01–1	Keller et al. 2007, 2008
Rat	Impaired development and functional alterations of the reproductive system	0.064–10	Adamsson et al. 2008; Bell et al. 2007a; Bjerke and Peterson 1994; Bjerke et al. 1994a, 1994b; Brown et al. 1998; Dienhart et al. 2000; Fenton et al. 2002; Filgo et al. 2016; Flaws et al. 1997; Franczak et al. 2006; Gray and Ostby 1995; Gray et al. 1995, 1997a, 1997b; Haavisto et al. 2001, 2006; Hamm et al. 2000; Heimler et al. 1998; Hurst et al. 2002; Ikeda et al. 2005a; Kakeyama et al. 2008; Lewis et al. 2001; Mably et al. 1992a, 1992b, 1992c; Mai et al. 2020; Ohsako et al. 2002; Salisbury and Marcinkiewicz 2002; Sanabria et al. 2016; Simanainen et al. 2004b; Sommer et al. 1996; Taura et al. 2014; Yonemoto et al. 2005; Yu et al. 2019, 2020; Zhang et al. 2018b
Mouse	Impaired development and functional alterations of the reproductive system	1–10	Abbott et al. 2003; Allgeier et al. 2009; Bruner-Tran and Osteen 2010; Bruner-Tran et al. 2014; Cummings et al. 1999; Ding et al. 2011; Jin et al. 2010; Ko et al. 2002; Lin et al. 2002a, 2002b
Monkey	Impaired development and functional alterations of the nervous system	4	Moran et al. 2004
Rat	Impaired development and functional alterations of the nervous system	0.1–1	Fernández et al. 2010; Hojo et al. 2006, 2008; Hood et al. 2006; Kakeyama et al. 2007; Markowski et al. 2002; Nguyen et al. 2013a; Nishijo et al. 2007; Zhang et al. 2018b
Mouse	Impaired development and functional alterations of the nervous system	0.5–20	Endo et al. 2012; Haijima et al. 2010; Mitsuhashi et al. 2010; Safe and Luebke 2016
Rat	Effects on growth	0.1–1	Bjerke and Peterson 1994; Bjerke et al. 1994a; Hattori et al. 2014; Nayyar et al. 2002; Nishijo et al. 2007; Nishimura et al. 2006
Mouse	Effects on growth	1	Jin et al. 2010
Rat	Impaired thyroid function	0.1–1	Fenton et al. 2002; Nishimura et al. 2003; Seo et al. 1995

Table A-3. Summary of Developmental Effects Observed in Animals Following Acute-Duration Oral Exposure to 2,3,7,8-TCDD[a]

Species	Effect	Range of LOAELs[b] (µg/kg/day)	Reference
Rat	Gastrointestinal tract hemorrhage	0.125–10	Huuskonen et al. 1994; Khera and Ruddick 1973; Kransler et al. 2007; Shiverick and Muther 1983; Sparschu et al. 1971
Rat	Impaired development and functional alterations of the immune system	0.325–10	Faith and Moore 1977; Gehrs et al. 1997a, 1997b; Håkansson et al. 1987; Huuskonen et al. 19994; Thomas and Hinsdill 1979
Mouse	Impaired development and functional alterations of the immune system	0.2–10	Blaylock et al. 1992; Ding et al. 2018; Fine et al. 1989; Hogbaoam et al. 2008; Holladay et al. 1991; Mustafa et al. 2008;
Rat	Structural malformations and anomalies	1–18	Giavini et al. 1983; Huuskonen et al. 1994; Kransler et al. 2007; Nishimura et al. 2006
Mouse	Structural malformations and anomalies	0.5–50	Abbott and Birnbaum 1990; Abbott et al. 1987a, 1987b; Aragon et al. 2008a; Bryant et al. 2001; Courtney 1976; Couture-Haws et al. 1991b; Dasenbrock et al. 1992; Fujiwara et al. 2008; Li et al. 2010; Miettinen et al. 2004; Mimura et al. 1997; Moore et al. 1973; Neubert and Dillmann 1972; Silkworth et al. 1989b; Smith et al. 1976; Weber et al. 1985; Yamada et al. 2006; Yuan et al. 2017
Monkey	Fetal/infant mortality	1	Guo et al. 2000; McNulty 1984
Rat	Fetal/pup mortality	0.7–1	Bell et al. 2007a; Bjerke and Peterson 1994; Bjerke et al. 1994a; Ikeda et al. 2002; Ishimura et al. 2002; Kransler et al. 2009; Miettinen et al. 2006; Takeda et al. 2020; Tomasini et al. 2012

[a]Only includes developmental effects in which the lowest LOAEL was ≤1 µg/kg/day.
[b]Doses adjusted for intermittent exposure.

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; LOAEL = lowest-observed-adverse-effect level

Selection of the Principal Study: The Burleson et al. (1996), White et al. (1986), Keller et al. (2008), and Yonemoto et al. (2005) papers were considered candidate principal studies because they identified similar LOAEL values (0.01–0.0125 µg/kg/day); Burleson et al. (1996) was the only study that identified a NOAEL (0.005 µg/kg/day).

The Burleson et al. (1996) study was selected as the principal study because it identified the lowest LOAEL value and a NOAEL value.

Summary of the Principal Study:

Burleson GR, Lebrec H, Yang YG, et al. 1996. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on influenza virus host resistance in mice. Fundam Appl Toxicol 29:40-47.

Groups of 20 female B6C3F1 mice were administered a single gavage dose of 0, 0.001, 0.005, 0.01, 0.05, or 0.1 µg/kg 2,3,7,8-TCDD in corn oil. Seven days after 2,3,7,8-TCDD exposure, the mice were infected intranasally with influenza A/Hong Kong/8/68 (H3N2) virus. Immunotoxicity was evaluated based on mortality, as compared to controls.

Statistically significant increases in mortality were observed in the influenza A infected mice exposed to 0.01, 0.05, or 0.1 µg/kg 2,3,7,8-TCDD. The percent survival was 86, 84, 83, 72, 65, and 64% in the 0, 0.001, 0.005, 0.01, 0.05, and 0.1 µg/kg groups, respectively. The investigators also conducted additional studies designed to evaluate the mechanisms of action. These studies found no 2,3,7,8-TCDD-related increases in relative lung weight or thymus weights, which the investigators interpreted to indicate that the enhanced mortality was not due to severe pulmonary edema or thymic atrophy.

Selection of the Point of Departure for the MRL: The NOAEL of 0.005 µg/kg identified in the Burleson et al. (1996) study was selected as the POD for the MRL.

Benchmark dose (BMD) modeling was considered for the data from the four studies that identified the lowest LOAEL values in the acute oral database.

- Burleson et al. (1996): data were not amenable to modeling because incidence data for survival were not provided (only percent survival was reported).
- White et al. (1986): data were not amenable to modeling because the number of animals per group was not reported.
- Keller et al. (2008): data were not amenable to modeling because the number of male and female pups per group was not reported.
- Yonemoto et al. (2005): data (presented in Table A-4) were amenable to modeling.

Table A-4. Sex Ratio in Neonates of Rats Administered 2,3,7,8-TCDD on GD 15

	Dose (µg/kg)				
	0	0.0125	0.05	0.2	0.8
Male/female ratio[a]	101/85	69/90[b]	50/75[b]	87/73	95/80

[a]Data presented as the number of male/female live neonates.
[b]Significantly different from controls ($p<0.05$).

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; GD = gestation day

Source: Yonemoto et al. 2005

The incidence data (Table A-4) were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 3.3) with extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR), BMDL that is not 10 times lower than the lowest non-zero dose, and visual inspection of the dose-response curve. A BMR of 5% extra risk was used. Although several models provided adequate fit based on the first three criteria, the visual fit was poor at the low dose region. Additionally, the BMDL was 0.11 µg/kg/day, which is higher than the empirical LOAEL.

In the absence of adequate BMD modeling, a NOAEL/LOAEL approach was used to select the POD for the MRL.

Uncertainty Factor and Modifying Factor: The NOAEL of 0.005 µg/kg/day is divided by a total uncertainty factor (UF) of 30 and a modifying factor (MF) of 0.7:

- 3 UF for extrapolation from animals to humans
- 10 UF for human variability
- 0.7 MF to account for the higher bioavailability of 2,3,7,8-TCDD from an oil gavage vehicle than from food

The use of a partial uncertainty factor of 3 for extrapolation from animals to humans is supported by a comparison of species sensitivity, which suggests that even though there are wide ranges of sensitivity for some 2,3,7,8-TCDD-induced health effects, for most health effects, the LOAELs for the majority of animal species cluster within an order of magnitude. Based on the weight of evidence of animal species comparisons and human and animal mechanistic data, it is reasonable to assume that human sensitivity would fall within the range of animal sensitivity.

A modifying factor of 0.7 was applied to adjust for the difference in higher bioavailability of 2,3,7,8-TCDD from gavage with an oil vehicle than from food. Support for this modifying factor comes from toxicokinetic studies in Sprague-Dawley rats. In rats fed 0.35 or 1 µg/kg/day 2,3,7,8-TCDD in the diet for 42 days, approximately 60% of the administered dose was absorbed (Fries and Marrow 1975). In contrast, 70–84% of a single or repeated gavage dose of 0.01–50 µg/kg 2,3,7,8-TCDD in corn oil was absorbed in rats (Piper et al. 1973; Rose et al. 1976). Thus, the ratio of 2,3,7,8-TCDD absorption from the diet to gavage with an oil vehicle is 0.71–0.85.

MRL = NOAEL ÷ (UFs x MF)
0.005 µg/kg/day ÷ (30 x 0.7) = 0.0002 µg/kg/day ($2x10^{-4}$ µg/kg/day)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: As highlighted in Tables A-2 and A-3, there is strong support in the acute oral animal database for identifying immunological and developmental toxicity as the most sensitive targets of 2,3,7,8-TCDD toxicity. Human studies examining these endpoints following acute-duration oral exposure have not been identified. Epidemiological studies have investigated immunological and developmental outcomes in populations chronically exposed to CDDs. The immunological database provides some suggestive evidence of immunotoxicity, but the results are inconsistent. Epidemiological studies of populations with high exposures have reported developmental effects including increased neonatal TSH levels in children of women exposed to 2,3,7,8-TCDD in Seveso (Baccarelli et al. 2008) and impaired developmental of the reproductive system in boys of mothers living in Seveso (Mocarelli et al. 2011) and boys living in an area of Russia with high CDD soil levels (Korrick et al. 2011).

Agency Contacts (Chemical Managers): Hana R. Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)
CAS Numbers: 1746-01-6
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: The intermediate-duration oral database for 2,3,7,8-TCDD was not considered adequate for derivation of a provisional MRL. The lowest identified LOAEL in the intermediate database is 0.0009 µg/kg/day for liver effects (lymphocytic infiltration in mice) (Rasinger et al. 2018). At a slightly higher dose (0.001 µg/kg/day), decreased pup survival was observed, which is considered a serious LOAEL. An MRL based on the LOAEL for liver effects may not be protective of the serious developmental effects observed at a slightly higher dose.

Rationale for Not Deriving an MRL: The intermediate-duration database on 2,3,7,8-TCDD identifies several sensitive targets of toxicity: hepatic, reproductive, developmental, and immunological; the lowest LOAELs for these endpoints are summarized in Table A-5. The lowest LOAELs are 0.0009 µg/kg/day for lymphocytic infiltration in the liver of BALB/c mice (Rasinger et al. 2018) and 0.001 µg/kg/day for reduced epididymal sperm counts in Wistar rats (Latchoumycandane et al. 2002) and decreased postnatal survival in F1 pups (Murray et al. 1979). The decreased postnatal pup survival at 0.001 µg/kg/day is considered a serious LOAEL.

Table A-5. Summary of the Lowest NOAEL and LOAEL Values for Sensitive Targets of Intermediate-Duration Oral Exposure to 2,3,7,8-TCDD

Species, duration	Doses tested (µg/kg/day)	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Hepatic					
BALB/c mouse, 28 days	0, 0.0009 (F)	Lymphocytic infiltration in the liver	—	0.0009	Rasinger et al. 2018
Hartley guinea pig, 90 days	0, 0.0001, 0.0007, 0.005, 0.03 (F)	Hepatocellular inclusions and elevated serum triglyceride levels	0.0007	0.005	DeCaprio et al. 1986
Reproductive					
Wistar rat, 45 days	0, 0.001, 0.01, 0.1 (GO)	Reduced epididymal sperm count (8.6%)	—	0.001	Latchoumy-candane et al. 2002
Sprague-Dawley rat, 60 days	0, 0.05, 0.1, 0.2 (GO)	Decreased sperm counts and motility; increased sperm mortality and abnormalities	—	0.05	El-Tawil and Elsaieed 2005

Table A-5. Summary of the Lowest NOAEL and LOAEL Values for Sensitive Targets of Intermediate-Duration Oral Exposure to 2,3,7,8-TCDD

Species, duration	Doses tested (µg/kg/day)	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Developmental					
Sprague-Dawley rat, 90 days premating and during gestation and lactation periods	0, 0.001, 0.01, 0.1 (F)	Decreased pup survival to PND 21	—	0.001 (SLOAEL)	Murray et al. 1979
Wistar rat, 12 weeks premating and during gestation and lactation periods	0, 0.0024, 0.008, 0.046 (F)	Delayed puberty in male offspring	—	0.0024	Bell et al. 2007b
Standard dark mink, 35 days premating and during gestation and lactation (132 days total)	0.00003 (control), 0.003, 0.007 (F)	Reduced kit survival in first 3 weeks	—	0.003	Hochstein et al. 2001
Lewis Furth rat, GDs 14 and 21, PNDs 7 and 14, and PNDs 21–240	0, 0.007 (GO)	Accelerated onset of acyclicity in female offspring	—	0.007	Jablonska et al. 2010
Immunological					
B6C3F1 mouse, 13 weeks	0, 0.0011, 0.011, 0.11, 0.32	Decreased antibody response to sheep red blood cells	—	0.0011	Smialowicz et al. 2008
Hartley guinea pig, 90 days	0, 0.0001, 0.0007, 0.005, 0.03	Decreased thymus weight	0.0007	0.005	DeCaprio et al. 1986
Hartley guinea pig, 8 weeks, 1 day/week	0, 0.001, 0.006, 0.03, 0.14 (GO)	Impaired delayed hypersensitivity response to tuberculin and decreased thymus weight	0.001	0.006	Vos et al. 1973

[a]Doses adjusted for intermittent exposure.

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; (F) = 2,3,7,8-TCDD administered in feed; GD = gestation day; (GO) = 2,3,7,8-TCDD administered via gavage with an oil vehicle; PND = postnatal day

As illustrated in Tables A-6, A-7, A-8, and A-9, there is strong support for identifying the liver, sperm, developing organism, and immunological system, respectively, as sensitive targets of 2,3,7,8-TCDD following intermediate-duration oral exposure.

Table A-6. Summary of Hepatic Effects in Animals Following Intermediate-Duration Oral Exposure to 2,3,7,8-TCDD

Species, duration	Effect	NOAEL (µg/kg/day)[a]	LOAEL (µg/kg/day)[a]	Reference
BALB/c mouse, 28 days	Lymphocytic infiltration in the liver	—	0.0009	Rasinger et al. 2018
Rhesus monkey, 9 months	Biliary hyperplasia	—	0.011	Allen et al. 1977
Sprague-Dawley rat, 4 weeks (19 doses)	Hepatocellular hypertrophy	0.003	0.022	Harrill et al. 2015
Sprague-Dawley rat, 14 weeks, 5 days/week	Hepatocellular hypertrophy	0.0071	0.016	NTP 2006
Sprague-Dawley rat, 31weeks, 5 days/week	Hepatocellular hypertrophy	0.007	0.016	NTP 2006
BALB/c mouse, 28 days	Hepatocytes with pyknotic nuclei and tissue congestion	—	0.09	Maranghi et al. 2013
Rhesus monkey, 3 weeks, 3 days/week	Biliary hyperplasia in mothers	0.02	0.1	McNulty 1984
C57BL/6 mouse, 28 days (once every 4 days)	Cytoplasmic vacuolization	0.08	0.3	Fader et al. 2017
C57BL/6 mouse, 28 days (once every 4 days)	Cytoplasmic vacuolization	0.3	0.8	Fader et al. 2015

[a]Doses adjusted for intermittent exposure.

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Table A-7. Summary of Alterations in Sperm Parameters in Animals Following Intermediate-Duration Oral Exposure to 2,3,7,8-TCDD

Species, duration	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Wistar rat, 45 days	Reduced epididymal sperm count	—	0.001	Latchoumycandane et al. 2002
Sprague-Dawley rat, 60 days	Decreased sperm counts and motility; increased sperm mortality and abnormalities	—	0.05	El-Tawil and Elsaieed 2005

Table A-7. Summary of Alterations in Sperm Parameters in Animals Following Intermediate-Duration Oral Exposure to 2,3,7,8-TCDD

Species, duration	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Sprague-Dawley rat, 29 weeks, 1 day/week	Decreased sperm count	0.02	0.05	Ma et al. 2010
Wistar/NIN rat, 15 days	Decreased epididymal sperm count, sperm viability, and sperm motility	—	0.1	Dhanabalan et al. 2010
Wistar/NIN rat, 15 days	Decreased epididymal sperm count, sperm viability, sperm motility, and testicular sperm production	—	0.1	Dhanabalan et al. 2011

[a]Doses adjusted for intermittent exposure.

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Table A-8. Summary of Developmental Effects in Animals Following Intermediate-Duration Oral Exposure to 2,3,7,8-TCDD

Species, duration	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Sprague-Dawley rat, 90 days premating and during gestation and lactation periods	Decreased pup survival to PND 21 in F1a generation; increased pup survival in F1b generation; and no alterations in F2 or F3 generations	—	0.001	Murray et al. 1979
Wistar rat, 12 weeks premating and during gestation and lactation periods	Delayed puberty in males	—	0.0024	Bell et al. 2007b
Standard dark mink, 35 days premating and during gestation and lactation (132 days total)	Reduced kit survival in first 3 weeks	—	0.003	Hochstein et al. 2001
Lewis Furth rat, GDs 14 and 21, PNDs 7 and 14, and PNDs 21–240	Accelerated onset of acyclicity in female offspring	—	0.007	Jablonski et al. 2010
C57BL/6NCji mouse, LDs 0–17	Altered immune function	0.001	0.011	Sugita-Konishi et al. 2003

Table A-8. Summary of Developmental Effects in Animals Following Intermediate-Duration Oral Exposure to 2,3,7,8-TCDD

Species, duration	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Holtzman rat, 2 weeks premating and during gestation and lactation periods (1 day/week)	Reduced male/female ratio Decreased pup body weight Decreased ventral prostate weight	—	0.02	Ikeda et al. 2005b
C57BL/6J mouse, GDs 0, 7, and14 and LD 2	Decreased pup survival Altered immune function	0.04	0.1	Vorderstrasse et al. 2006
C57BL/6 mouse, GDs 0, 7, and14 and LD 2	Altered immune function	—	0.17	Hogaboam et al. 2008
Wistar rat, GD 1–LD 30	Altered thyroid hormone levels	—	0.2	Ahmed 2011

[a]Doses adjusted for intermittent exposure.

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; GD = gestation day; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PND = postnatal day

Table A-9. Summary of Immunological Effects in Animals Following Intermediate-Duration Oral Exposure to 2,3,7,8-TCDD

Species, duration	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
B6C3F1 mouse, 13 weeks, 5 days/week	Decreased antibody response to sRBC	–	0.0011	Smialowicz et al. 2008
Hartley guinea pig, 90 days	Decreased thymus weight	0.0007	0.005	DeCaprio et al. 1986
Hartley guinea pigs, 8 weeks, 1 day/week	Impaired delayed hypersensitivity response to tuberculin and decreased thymus weight	–	0.006	Vos et al. 1973
Sprague-Dawley rat, 13 weeks	Decreased thymus weight	–	0.014	Van Birgelen et al. 1995
Sprague-Dawley rat, 14 weeks, 5 days/week	Thymic atrophy	0.0071	0.016	NTP 2006
Sprague-Dawley rats, 31 weeks, 5 days/week	Thymic atrophy	0.016	0.032	NTP 2006
C57BL/6 mouse, 5—8 weeks, 1 day/week	Decreased response to sRBC	–	0.07	Vecchi et al. 1983a

Table A-9. Summary of Immunological Effects in Animals Following Intermediate-Duration Oral Exposure to 2,3,7,8-TCDD

Species, duration	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Sprague-Dawley rat, 4 weeks, 4–5 days/week	Decreased thymus weight	0.022	0.1	Harrill et al. 2016
C57BL/6jfh mouse, 4 weeks, 1 day/week	Increased mortality after infection	0.07	0.14	Thigpen et al. 1975
Sprague-Dawley rat, 4 weeks, 4–5 days/week	Decreased thymus weight and thymic atrophy	0.1	0.3	Harrill et al. 2015
B6D2F1 mouse, 4 weeks, 1 day/week	Suppressed response in graft versus host test	0.14	0.71	Vos et al. 1973
CD rat, 6 weeks, 1 day/week	Decreased thymus weight and thymic atrophy	0.14	0.71	Vos et al. 1973
Sprague-Dawley rat, 13 weeks, 10 doses	Decreased thymus weight	–	0.8	Viluksela et al. 1994

[a]Doses adjusted for intermittent exposure.

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; sRBC = sheep red blood cell

To identify potential PODs for deriving an MRL, BMD modeling was evaluated for the Latchoumycandane et al. (2002), Murray et al. (1979), and DeCaprio et al. (1986) studies; Rasinger et al. (2018) is a single-dose study. The sperm count data from the Latchoumycandane et al. (2002) study (Table A-10), the postnatal survival incidence data for the F1a offspring from the Murray et al. (1979) study (Table A-11), and the serum triglyceride and relative thymus weight data from DeCaprio et al. (1986) (Table A-12) were fit to all available continuous and dichotomous models, respectively, in EPA's BMDS (version 3.3). A BMR of 1 standard deviation was used for the sperm count, serum triglyceride, and relative thymus weight data and 5% extra risk was used for the postnatal survival data. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residual at the data point (except the control) closest to the predefined BMR, BMDL that is not 10 times lower than the lowest non-zero dose, and visual inspection of the dose-response curve. None of the models provided adequate fit to the sperm count data from Latchoumycandane et al. (2002), the postnatal survival data in the F1a pups from Murray et al. (1979), or the serum triglyceride and relative thymus weight data from DeCaprio et al. (1986). Thus, a NOAEL/LOAEL approach was used to identify potential PODs.

Table A-10. Epididymal Sperm Counts in Wistar Rats Administered 2,3,7,8-TCDD for 45 Days

	Dose (µg/kg/day)			
	0	0.001	0.01	0.1
Sperm count[a]	8.2±0.13	7.52±0.15[b]	6.33±0.15[b]	5.29±0.19[b]

[a]Mean±standard deviation.
[b]Significantly different from controls ($p<0.05$).

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

Source: Latchoumycandane et al. 2002

Table A-11. Postnatal Survival in the Offspring of Sprague-Dawley Rats Administered 2,3,7,8-TCDD[a]

	Dose (µg/kg/day)			
Postnatal survival[b]	0	0.001	0.01	0.1
F1a offspring	99/106	73/87[c]	63/93[c]	–[d]
F1b offspring	160/215	110/120[c]	93/138	4/5
F2 offspring	205/235	126/148	51/87[c]	
F3 offspring	235/296	163/208	64/83	

[a]F_0 rats were exposed for 90 days prior to mating and during gestation and lactation.
[b]Number of liveborn pups surviving to PND 21/number of liveborn pups.
[c]Significantly different from controls ($p<0.05$).
[d]No liveborn pups.

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

Source: Murray et al. 1979

Table A-12. Serum Triglyceride Levels and Relative Thymus Weight in Male Hartley Guinea Pigs Exposed to 2,3,7,8-TCDD

	Dose (µg/kg/day)[a]				
	0	0.0001	0.0007	0.005	0.03
Serum triglyceride levels[b] (mg triolein equivalent/dL)	148±63	145±51	159±35	226±57[c]	–
Relative thymus weight[b] (g/body weight x100)	0.078±0.019	0.066±0.0095	0.068±0.013	0.059±0.0095[c]	–

[a]Doses adjusted for intermittent exposure.
[b]mean±standard deviation.
[c]Significantly different from controls ($p<0.05$).

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

Source: DeCaprio et al. 1986

The intermediate-duration oral database for 2,3,7,8-TCDD was not considered adequate for derivation of an MRL. Basing an MRL on the lowest LOAEL of 0.0009 µg/kg/day for liver effects (Rasinger et al. 2018) may not be protective of the developmental toxicity of 2,3,7,8-TCDD; the lowest LOAEL for developmental effects is 0.001 µg/kg/day for decreased pup survival (Murray et al. 1979). Basing an MRL on the NOAEL 0.0007 µg/kg/day for immune and liver effects (DeCaprio et al. 1986) may not be protective for developmental effects since it is only slightly lower than the serious LOAEL value.

Agency Contacts (Chemical Managers): Hana R. Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)
CAS Numbers: 1746-01-6
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic
MRL: $4x10^{-7}$ µg/kg/day
Critical Effect: Neurodevelopmental and immunological
Reference: Bowman et al. 1989a, 1989b; Hong et al. 1989; Rier et al. 2001a; Schantz et al. 1986, 1992; Schantz and Bowman 1989
Point of Departure: LOAEL of 0.00012 µg/kg/day
Uncertainty Factor: 300
LSE Graph Key: 244, 246
Species: Monkey

MRL Summary: A provisional chronic-duration oral MRL of $4x10^{-7}$ µg/kg/day was derived for 2,3,7,8-TCDD based on neurodevelopmental effects in the offspring of monkeys exposed to 2,3,7,8-TCDD in the diet for up to 3.5–4 years (Bowman et al. 1989a, 1989b; Hong et al. 1989; Schantz and Bowman 1989; Schantz et al. 1986, 1992) and immunological effects in the mothers (Rier et al. 2001a). The MRL is a based on a LOAEL of 0.00012 µg/kg/day and a total uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: Several studies have evaluated the chronic toxicity of 2,3,7,8-TCDD in laboratory animals. The most sensitive effects include developmental, reproductive, immunological, dermal, hepatic, respiratory, and gastrointestinal endpoints (see Table A-13). The lowest LOAEL is 0.00012 µg/kg/day for neurodevelopmental and immunological effects in monkeys (Bowman et al. 1989a, 1989b; Hong et al. 1989; Rier et al. 2001a; Schantz and Bowman 1989; Schantz et al. 1986, 1992). The next lowest LOAELs are 10-fold higher. Thus, neurodevelopmental effects and impaired immune function were selected as co-critical effects. In addition to these data, endometriosis was also observed in monkeys at 0.00012 µg/kg/day (Rier et al. 1993). However, a follow-up analysis conducted by Rier et al. (2001b) suggests that 3,3′,4 4′-tetrachlorobiphenyl may have been the causative agent rather than 2,3,7,8-TCDD; thus, endometriosis was not considered a critical effect.

Table A-13. Summary of NOAEL and LOAEL Values for Sensitive Targets of Chronic-Duration Oral Exposure to 2,3,7,8-TCDD

Species, duration	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Developmental				
Rhesus monkey, 16.2 or 27 months	Increased close, social contact between mother and infant, impaired learning, and altered peer group social behavior and self-directed behaviors	–	0.00012	Bowman et al. 1989a, 1989b; Hong et al. 1989; Schantz and Bowman 1989;Schantz et al. 1986, 1992

Table A-13. Summary of NOAEL and LOAEL Values for Sensitive Targets of Chronic-Duration Oral Exposure to 2,3,7,8-TCDD

Species, duration	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Immunological				
Rhesus monkey, 3.5–4 years	Impaired immune function	–	0.00012	Rier et al. 2001a
Dermal				
Swiss mouse, 1 year (1 day/week)	Skin lesions and generalized amyloidosis	–	0.001	Toth et al. 1979
Hepatic				
Sprague-Dawley rat, 105 weeks (5 days/week)	Hepatocyte hypertrophy and inflammation	–	0.002	NTP 2006
Respiratory				
Sprague-Dawley rat, 105 weeks (5 days/week)	Bronchiolar metaplasia of alveolar epithelium	–	0.002	NTP 2006
Gastrointestinal				
Sprague-Dawley rat, 105 weeks (5 days/week)	Squamous hyperplasia of gingival mucosa	–	0.002	NTP 2006

[a]Doses adjusted for intermittent exposure.

2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: The lowest LOAELs for developmental and immunological effects were identified in a 3.5–4-year study in monkeys; the results were published in several papers (Bowman et al. 1989a, 1989b; Hong et al. 1989; Rier et al. 2001a; Schantz and Bowman 1989; Schantz et al. 1986, 1992).

Summary of the Principal Study:

Bowman RE, Schantz SL, Gross ML, et al. 1989a. Behavioral effects in monkeys exposed to 2,3,7,8-TCDD transmitted maternally during gestation and for four months of nursing. Chemosphere 18:235-242.

Bowman RE, Schantz SL, Weerasinghe NCA, et al. 1989b. Chronic dietary intake of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at 5 or 25 parts per trillion in the monkey: TCDD kinetics and dose-effect estimate of reproductive toxicity. Chemosphere 18:243-252.

Hong R, Taylor K, Abonour R. 1989. Immune abnormalities associated with chronic TCDD exposure in Rhesus. Chemosphere 18:313-320.

Schantz S, Bowman RE. 1989. Learning in monkeys exposed perinatally to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Neurotoxicol Teratol 11:13-19.

Schantz SL, Laughlin NK, Van Valkenberg HC, et al. 1986. Maternal care by rhesus monkeys of infant monkey exposed to either lead or 2,3,7,8-tetrachlorodibenzo-p-dioxin. Neurotoxicol 2:637-650.

Schantz SL, Ferguson SA, Bowman RE. 1992. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on behavior of monkey in peer groups. Neurotoxicol Teratol 14:433-446.

This series of studies evaluated the developmental toxicity of 2,3,7,8-TCDD in Rhesus monkeys exposed in the diet for up to 3.5–4 years. The results of the studies have been published in several papers. Groups of eight female Rhesus monkeys were exposed to 0, 5, or 25 ppt 2,3,7,8-TCDD in the diet. Maternal intakes were estimated (Schantz et al. 1992) as 59.6 ng/kg at 16.2 months in the 5 ppt group, 163 ng/kg at 3.5 years in the 5 ppt group, and 938 ng/kg at 4 years in the 25 ppt group. Given the similarity of the estimated doses in the 5 ppt group at 16.2 months and 3.5 years, it was assumed that the estimated intake for the 25 ppt group at 4 years could also be used for the 16.2-month time point. The estimated daily intakes were 0.00012 and 0.00064 μg/kg/day for the 5 and 25 ppt dietary groups, respectively. PCBs (average concentration of 7.6 ppb) and dichlorodiphenyl dichloroethane (DDE) (average concentration of 1.0 ppb) were detected in feed samples analyzed for contaminants (Schantz and Bowman 1989). The monkeys were mated 3 times: cohort I—mating started after 7 months of exposure with an average of 16.2 months of exposure prior to the infants' birth; cohort II—mating began after 27 months of exposure and the offspring were delivered at 36 months of maternal exposure; and cohort III—females were exposed for 3.5 years (5 ppt group) or 4 years (25 ppt group) and were mated beginning 10 months post-exposure and infants were born about 18 months post-exposure. In cohorts I and II, the females were mated with unexposed males or males exposed to PCBs; unexposed males were used for cohort III.

Reproductive toxicity was assessed using an ordinal scale of offspring survival time, Index of Overall Reproductive Success (IORS); the scoring was 0 if mother failed to get pregnant, 1 if animal was pregnant but aborted, 2 if delivered a stillborn, 3 if delivered a live birth, 4 if offspring survived to weaning, and 5 if offspring survived to 1 year of age. Immunotoxicity was evaluated in the mothers 4 years post-exposure and in infants in cohorts I, II, and III combined. Immune tests included lymphocyte counts, measurement of proliferative responses to three mitogens (phytohemagglutinin, pokeweed, and concanavalin A) and allo- and xeno-transplantation antigens, and measurement of antibodies following inoculation with tetanus toxoid. A neonatal assessment consisting of tests of sensory responsivity, neuromotor development, and temperament was conducted on postpartum days 1, 7, 8, 14, 21, and 28. Other neurobehavioral tests included Piagetian concept formation for object permanence was tested 1 time/week between 0.5 and 3.5 months of age; mother-infant social testing was conducted 2 times/week for 2–4 months postpartum; visual exploration; locomotor activity, peer group social behavior were also evaluated. When the offspring were 8.6 months of age, they were placed in peer groups of four monkeys (two controls and two 5 ppt monkeys) for 1.5 hours/day, 5 days/week to evaluate socialization (social interactions and other behaviors). At 18 months of age, the monkeys were assigned new peer groups containing monkeys from the same treatment groups. Cognitive tests of discrimination reversal learning, color discrimination, and shape discrimination were conducted when the offspring were 14 months of age. At 20 months of age, the offspring were tested for delayed spatial alternation. Locomotor activity was evaluated at 5.5, 12, 24, and 36 months of age.

No alterations in birth weight or growth were observed in the offspring.

Bowman et al. 1989b (cohorts I and II): A significant decrease in the index of overall reproductive success (ordinal scale of offspring survival time) was observed in the 0.00064 μg/kg/day group. Significant alterations in the offspring were limited to an increased response to tetanus toxoid

immunization, which correlated with TCDD body burdens; data were not analyzed on a dose-basis and thus, a LOAEL cannot be defined.

Hong et al. 1989 (cohorts I, II, and III combined): An increase in total T-lymphocytes were observed in the mothers exposed to 0.00064 μg/kg/day; there were no alterations in the antigen response to tetanus toxoid. An impaired mixed lymphocyte response to reduced macrophages was observed in the 0.00012 and 0.00064 μg/kg/day mothers; the investigators were unsure of the clinical significance of the alteration. Significant alterations in the offspring were limited to an increased response to tetanus toxoid immunization, which correlated with TCDD body burdens. Increased (50%) abortions, stillbirths, and infant deaths were observed at 0.00064 μg/kg/day, as compared to 12% in the control group and 8% in the 0.00012 μg/kg/day group.

Schantz et al. 1986 (cohort III): In the social interactions of mother-infant dyads, increased and prolonged maternal care was observed in the TCDD-exposed groups, as evidenced by the increased time spent in close, social contact (mutual ventral contact and nipple contact). Ventral contact was longer in the 0.00012 μg/kg/day group, as compared to the 0.00064 μg/kg/day group and mothers in the 0.00064 μg/kg/day group approached and retrieved their infants more often than in the 0.00012 μg/kg/day group.

Schantz and Bowman 1989 (cohorts I and II): Impaired performance on learning a shape reverse learning problem was observed at 0.00012 μg/kg/day; no effect on spatial or color reverse learning problems were observed. There were no significant alterations in delayed spatial alternation performance.

Bowman et al. 1989a (cohort I): Locomotor hyperactivity was observed in 0.00012 μg/kg/day at 5.5 months of age, but not at other times. Peer group social behavior was altered at 0.00012 μg/kg/day; significant effects were observed in social play behaviors (increased rough-tumble play, decreased play retreats, and decreased yield to displacement) and self-directed behaviors and environmental exploration. There were no significant alterations in fine motor control, Hamilton search task, or delayed spatial alternation test. In a re-evaluation of the discrimination alterations in reversal learning tests from Schantz and Bowman (1989), significant alterations were found in tests of spatial, color, and shape problems (analyzed as within-group regression as related to TCDD levels in fat).

Bowman et al. 1989a (cohort III): Infants were more passive at neonatal assessment; there were no alterations on Piagetian Concept Formation. Significant alterations in peer group social behavior were observed at 0.00012 μg/kg/day: social play behaviors (increased rough-tumble play and decreased yield to displacement) and self-directed behaviors. There were no significant alterations in fine motor control, Hamilton search task, or delayed spatial alternation test.

Schantz et al. 1992 (cohort I): Offspring of the 0.00012 μg/kg/day group spent more time in self-initiated rough-tumble play and retreated less often during play than controls. Other effects included less frequent retreats during play, less often displacement from positions, and more frequent self-directed behavior. No significant relationship between TCDD concentrations in fat and play behaviors were observed; the investigators suggested that this may be partially due to the small number.

Schantz et al. 1992 (cohort III): When monkeys were socialized in groups only containing monkeys from the same treatment group, the monkeys in the 0.00064 μg/kg/day group engaged in virtually no rough-tumble play during the first 2 weeks, which is in contrast to the controls and 0.00012 μg/kg/day group. There were alterations in displacement. In later testing, the TCDD-exposed group failed to show increases in playface and yield to displacement. An increase in self-directed behavior was also observed at 0.00064 μg/kg/day.

Rier SE, Coe CL, Lemieux AM, et al. 2001a. Increased tumor necrosis factor-α production by peripheral blood leukocytes from TCDD-exposed Rhesus monkeys. Toxicol Sci 60:327-337.

Groups of eight female Rhesus monkeys were fed a diet containing 0, 5, or 25 ppt 2,3,7,8-TCDD for 3.5–4 years, equivalent to doses of 0, 0.00012, and 0.00064 µg/kg/day. The monkeys were mated 3 times: after 7 months of exposure, after 27 months of exposure, and 10 months post-exposure. Potential immunological effects were evaluated 13 years after exposure termination. The following immunological endpoints were examined: phenotypic distribution of peripheral blood leukocytes and cytokine production in response to phytohemagglutinin (PHA).

A significant increase In the production of the cytokine, tumor necrosis factor-α was observed at both TCDD doses in response to PHA. An increase in the production of interferon-gamma was also observed in response to PHA in TCDD-exposed monkeys (both dose groups combined), as compared to controls. No significant alterations in peripheral blood leukocyte phenotypes were observed in the combined TCDD group.

Selection of the Point of Departure for the MRL: The LOAEL of 0.00012 µg/kg/day for neurodevelopmental effects and immunological effects was selected as the POD for the MRL.

BMD modeling was not conducted for the neurodevelopmental endpoints because quantitative data were not available for both TCDD groups for all endpoints. The altered immune response data were modeled. The tumor necrosis factor-α levels (Table A-14) were fit to all continuous models of EPA's BMDS (version 3.3). A BMR of 1 standard deviation was used for the immune response data. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), scaled residual at the data point (except the control) closest to the predefined BMR, BMDL that is not 10 times lower than the lowest non-zero dose, and visual inspection of the dose-response curve. None of the models provided adequate fit to the tumor necrosis factor-α level data. In the absence of adequate BMD modeling, a NOAEL/LOAEL approach was used to identify the POD.

Table A-14. Altered Immune Response in Monkeys Exposed to 2,3,7,8-TCDD in the Diet for 3.5–4 Years

	Dose (µg/kg/day)		
Effect	0	0.00012	0.00064
Tumor necrosis factor-α[a]	38.7±59.1	133.9±103.6	375.1±350.0

[a]Data reported as mean±standard deviation, n=10, 6, and 3 in the 0, 0.00012, and 0.00064 µg/kg/day groups, respectively.

Source: Rier et al. 2001a

Calculations

Uncertainty Factor: A total uncertainty factor of 300 was used:

- 10 for use of a LOAEL
- 3 for extrapolation from animals to humans
- 10 for human variability

The use of a partial uncertainty factor of 3 for extrapolation from animals to humans is supported by a comparison of species sensitivity, which suggests that even though there are wide ranges of sensitivity for some 2,3,7,8-TCDD-induced health effects, for most health effects, the LOAELs for the majority of animal species cluster within an order of magnitude. Based on the weight of evidence of animal species comparisons and human and animal mechanistic data, it is reasonable to assume that human sensitivity would fall within the range of animal sensitivity.

MRL = LOAEL x UF
MRL = 0.00012 μg/kg/day x 1/300 = $4x10^{-7}$ μg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: There is strong support in the acute- and intermediate-duration oral 2,3,7,8-TCDD database to support identifying immunological (see Tables A-2 and A-9) and developmental (see Tables A-3 and A-8) toxicity as the most sensitive targets of 2,3,7,8-TCDD toxicity. Epidemiological studies have investigated immunological and developmental outcomes in populations chronically exposed to CDDs. The immunological database provides some suggestive evidence of immunotoxicity, but the results are inconsistent. Epidemiological studies of populations with high exposures have reported developmental effects including increased neonatal TSH levels in children of women exposed to 2,3,7,8-TCDD in Seveso (Baccarelli et al. 2008) and impaired developmental of the reproductive system in boys of mothers living in Seveso (Mocarelli et al. 2011) and boys living in an area of Russia with high CDD soil levels (Korrick et al. 2011).

Agency Contacts (Chemical Managers): Hana R. Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Monochlorodibenzo-*p*-dioxin (2-MCDD)
CAS Numbers: 39227-54-8
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute, intermediate, chronic

MRL Summary: There are insufficient data for the derivation of provisional acute-, intermediate-, or chronic-duration inhalation MRLs for 2-MCDD due to the lack of studies evaluating toxicity following inhalation exposure.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 2-MCDD following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Monochlorodibenzo-*p*-dioxin (2-MCDD)
CAS Numbers: 39227-54-8
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of a provisional acute-duration oral MRL for 2-MCDD due to the lack of studies reporting adverse health effects.

Rationale for Not Deriving an MRL: The available data on the acute oral toxicity of 2-MCDD is limited to a developmental toxicity study that did not find any adverse effects at the highest dose tested (2,000 µg/kg/day) in the offspring of rats exposed to 2-MCDD on GDs 6–15 (Khera and Ruddick 1973).

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Monochlorodibenzo-*p*-dioxin (2-MCDD)
CAS Numbers: 39227-54-8
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of a provisional intermediate-duration oral MRL for 2-MCDD due to the lack of studies evaluating toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 2-MCDD following intermediate-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2-Monochlorodibenzo-*p*-dioxin (2-MCDD)
CAS Numbers: 39227-54-8
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a provisional chronic-duration oral MRL for 2-MCDD due to the lack of studies evaluating toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 2-MCDD following chronic-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3-Dichlorodibenzo-*p*-dioxin (2,3-DCDD)
CAS Numbers: 29446-15-9
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of provisional acute-, intermediate-, or chronic-duration inhalation MRLs for 2,3-DCDD due to the lack of studies evaluating toxicity following inhalation exposure.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 2,3-DCDD following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3-Dichlorodibenzo-*p*-dioxin (2,3-DCDD)
CAS Numbers: 29446-15-9
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of a provisional acute-duration oral MRL for 2,3-DCDD due to the lack of studies reporting adverse health effects.

Rationale for Not Deriving an MRL: The available data on the acute oral toxicity of 2,3-DCDD are limited to a developmental toxicity study that did not find any adverse effects at the highest dose tested (2,000 µg/kg/day) in the offspring of rats exposed to 2,3-DCDD on GDs 6–15 (Khera and Ruddick 1973).

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3-Dichlorodibenzo-*p*-dioxin (2,3-DCDD)
CAS Numbers: 29446-15-9
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of a provisional intermediate-duration oral MRL for 2,3-DCDD due to the lack of studies evaluating toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 2,3-DCDD following intermediate-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3-Dichlorodibenzo-*p*-dioxin (2,3-DCDD)
CAS Numbers: 29446-15-9
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a provisional chronic-duration oral MRL for 2,3-DCDD due to the lack of studies evaluating toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 2,3-DCDD following chronic-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,7-Dichlorodibenzo-*p*-dioxin (2,7-DCDD)
CAS Numbers: 33857-26-0
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of provisional acute-, intermediate-, or chronic-duration inhalation MRLs for 2,7-DCDD due to the lack of studies evaluating toxicity following inhalation exposure.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 2,7-DCDD following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,7-Dichlorodibenzo-*p*-dioxin (2,7-DCDD)
CAS Numbers: 33857-26-0
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of an acute-duration oral MRL for 2,7-DCDD due to the limited number of potential endpoints examined in the three available acute-duration toxicity studies.

Rationale for Not Deriving an MRL: There are limited available data on the acute oral toxicity of 2,7-DCDD. A suppressed antibody response to sheep red blood cells were observed in B6C3F1 mice administered ≥0.1 µg/kg/day 2,7-DCDD for 14 days (Holsapple et al. 1986); no hepatic effects were observed at doses as high as 10 µg/kg/day. No developmental effects were observed in Wistar rats administered ≤2,000 µg/kg/day on GDs 6–15 (Khera and Ruddick 1973) or Sprague-Dawley rats administered ≤100,000 µg/kg/day on GDs 6–15 (Schwetz et al. 1973). Although immunotoxicity is a known sensitive endpoint of CDDs, particularly 2,3,7,8-TCDD, toxicity, the database was not considered adequate for derivation of an MRL because the available studies have not examined a wide range of endpoints and the low LOAEL value for immunological effects has not been replicated.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,7-Dichlorodibenzo-*p*-dioxin (2,7-DCDD)
CAS Numbers: 33857-26-0
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of a provisional intermediate-duration oral MRL for 2,7-DCDD due to the lack of studies evaluating toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 2,7-DCDD following intermediate-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,7-Dichlorodibenzo-*p*-dioxin (2,7-DCDD)
CAS Numbers: 33857-26-0
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a provisional chronic-duration oral MRL for 2,7-DCDD due to the lack of chronic-duration studies evaluating immunotoxicity, a known sensitive target of toxicity.

Rationale for Not Deriving an MRL: The chronic-duration oral toxicity of 2,7-DCDD has been investigated in rats and mice exposed via the diet. Osborne-Mendel rats exposed to 250,000 µg/kg/day for 110 weeks had a 17% decrease in body weight gain and fatty liver changes (NCI/NTP 1979). A 16% decrease in body weight gain and toxic hepatitis were observed in B6C3F1 mice exposed to 650,000 µg/kg/day for 90 weeks (NCI/NTP 1979). The data were considered inadequate for derivation of a provisional MRL because no chronic-duration studies evaluated potential immunological effects. An acute-duration oral study by Holsapple et al. (1986) observed impaired immune function at doses at least 100 times lower than liver effects.

Agency Contacts (Chemical Managers): Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,7-Trichlorodibenzo-*p*-dioxin (2,3,7-TrCDD)
CAS Numbers: 33857-28-2
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of provisional acute-, intermediate-, or chronic-duration inhalation MRLs for 2,3,7-TrCDD due to the lack of studies evaluating toxicity following inhalation exposure.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 2,3,7-TrCDD following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,7-Trichlorodibenzo-*p*-dioxin (2,3,7-TrCDD)
CAS Numbers: 33857-28-2
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of a provisional acute-duration oral MRL for 2,3,7-TrCDD due to the lack of data on non-lethality endpoints.

Rationale for Not Deriving an MRL: Available data on the acute oral toxicity of 2,3,7-TrCDD is limited to a study that calculated an LD_{50} of 29,444 µg/kg in Hartley guinea pigs (McConnell et al. 1978b).

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,7-Trichlorodibenzo-*p*-dioxin (2,3,7-TrCDD)
CAS Numbers: 33857-28-2
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of a provisional intermediate-duration oral MRL for 2,3,7-TrCDD due to the lack of studies evaluating toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 2,3,7-TrCDD following intermediate-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,7-Trichlorodibenzo-*p*-dioxin (2,3,7-TrCDD)
CAS Numbers: 33857-28-2
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a provisional chronic-duration oral MRL for 2,3,7-TrCDD due to the lack of studies evaluating toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 2,3,7-TrCDD following chronic-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4-Tetrachlorodibenzo-*p*-dioxin (1,2,3,4-TCDD)
CAS Numbers: 30746-58-8
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of provisional acute-, intermediate-, or chronic-duration inhalation MRLs for 1,2,3,4-TCDD due to the lack of studies evaluating toxicity following inhalation exposure.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,4-TCDD following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4-Tetrachlorodibenzo-*p*-dioxin (1,2,3,4-TCDD)
CAS Numbers: 30746-58-8
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of a provisional acute-duration oral MRL for 1,2,3,4-TCDD due to the lack of studies identifying adverse health effects.

Rationale for Not Deriving an MRL: Available data on the acute oral toxicity of 1,2,3,4-TCDD is limited to two developmental toxicity studies that reported no developmental effects in Wistar rats administered 800 µg/kg/day on GDs 6–15 (Khera and Ruddick 1973) or CD-1 mice administered 1,000 µg/kg/day on GDs 7–16 (Courtney 1976).

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4-Tetrachlorodibenzo-*p*-dioxin (1,2,3,4-TCDD)
CAS Numbers: 30746-58-8
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of a provisional intermediate-duration oral MRL for 1,2,3,4-TCDD due to the lack of studies evaluating toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,4-TCDD following intermediate-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4-Tetrachlorodibenzo-*p*-dioxin (1,2,3,4-TCDD)
CAS Numbers: 30746-58-8
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a provisional chronic-duration oral MRL for 1,2,3,4-TCDD due to the lack of studies evaluating toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,4-TCDD following chronic-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin (1,2,3,7,8-PeCDD)
CAS Numbers: 40321-76-4
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of provisional acute-, intermediate-, or chronic-duration inhalation MRLs for 1,2,3,7,8-PeCDD due to the lack of studies evaluating toxicity following inhalation exposure.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,7,8-PeCDD following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin (1,2,3,7,8-PeCDD)
CAS Numbers: 40321-76-4
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of a provisional acute-duration oral MRL for 1,2,3,7,8-PeCDD. Although two studies have examined potentially sensitive targets (i.e., developmental toxicity and immunotoxicity), the study examining developmental toxicity (Madsen and Larsen 1989) is poorly reported and there is uncertainty regarding the adversity of the immunological effect observed in the immunotoxicity study (Ao et al. 2009).

Rationale for Not Deriving an MRL: A small number of studies have evaluated the acute oral toxicity of 1,2,3,7,8-PeCDD in animals; see Table A-15 for a summary of NOAEL and LOAEL values. The lowest LOAEL is 0.5 µg/kg for a decreased thymus weight in the offspring of Wistar rats administered 1,2,3,7,8-PeCDD on GD 16 (Madsen and Larsen 1989). At doses of 1–1.5 µg/kg/day, there was suppressed IL-5 production in response to ovalbumin exposure in mice (Ao et al. 2009) and decreases in serum T4 levels in rats (Crofton et al. 2005; Simanainen et al. 2002). At higher doses, decreases in thymus weight, increases in incisor tooth defects, decreases in body weight, and death have been observed. The available data have identified developmental toxicity and immunotoxicity as the most sensitive targets of 1,2,3,7,8-PeCDD toxicity.

The database was not considered suitable for derivation of an acute-duration oral MRL for 1,2,3,7,8-PeCDD. The Madsen and Larsen (1989) study identified the lowest LOAEL; however, the study methods and results are poorly reported. The study description lacks information such as the vehicle, purity of the test compound, and body weights of the dams; it is also unclear whether a concurrent control group was used. The Ao et al. (2009) study was not considered as the basis for an MRL because there is some uncertainty regarding the adversity of the suppressed IL-5 production in the absence of a change in IgM levels.

Table A-15. Summary of NOAEL and LOAEL Values for in Animals Following Acute-Duration Oral Exposure to 1,2,3,7,8-PeCDD

Species, duration	Doses tested (µg/kg/day)	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Wistar rat, GD 16	0, 0.5, 2, 10	Decreased thymus weight in offspring		0.5	Madsen and Larsen 1989
C57BL/6J mouse, once	0, 1.0, 3.0, 10, 50	Suppressed IL-5 production in response to ovalbumin exposure		1.0	Ao et al. 2009
Hans/Wistar rat, once	0, 0.1–300	50% decreased serum T4 levels		1.4	Simanainen et al. 2002
Long-Evans rat, once	0, 0.003–10	30% decreased serum T4 levels		1.51	Crofton et al. 2005
Hartley guinea pig	NS	LD_{50}		3.1 (SLOAEL)	McConnell et al. 1978b

Table A-15. Summary of NOAEL and LOAEL Values for in Animals Following Acute-Duration Oral Exposure to 1,2,3,7,8-PeCDD

Species, duration	Doses tested (µg/kg/day)	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Long-Evans rat, once	0, 0.1–300	50% decreased serum T4 levels		3.6	Simanainen et al. 2002
Long-Evans rat, once	0, 0.1–300	50% decreased relative thymus weight		7.2	Simanainen et al. 2002
Hans/Wistar rat, once	0, 0.1–300	50% decreased relative thymus weight		10	Simanainen et al. 2002
Long-Evans rat, once	0, 0.1–300	50% decreased body weight		14	Simanainen et al. 2002
Hans/Wistar rat, once	0, 0.1–300	50% increase in incisor tooth defects		24	Simanainen et al. 2002
Long-Evans rat, once	0, 0.1–300	50% increase in incisor tooth defects		24	Simanainen et al. 2002
Hans/Wistar rat, once	0, 0.1–300	50% decreased body weight		32	Simanainen et al. 2002
Sprague-Dawley rat, once	0, 100, 150, 200, 300	LD_{50}		206	Stahl et al. 1992
C57Bl/6 mouse	NS	LD_{50}		337.5	McConnell et al. 1978b

[a]Doses adjusted for intermittent exposure.

1,2,3,7,8-PeCDD = 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin; LD_{50} = median lethal dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; SLOAEL = serious lowest-observed-adverse-effect level; T4 = thyroxine

Agency Contacts (Chemical Managers): Hana R. Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin (1,2,3,7,8-PeCDD)
CAS Numbers: 40321-76-4
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of a provisional intermediate-duration oral MRL for 1,2,3,7,8-PeCDD; the lowest dose tested (2.6 µg/kg/day) in the only study evaluating intermediate-duration toxicity is a serious LOAEL for increased mortality.

Rationale for Not Deriving an MRL: The toxicity of 1,2,3,7,8-PeCDD has been examined in one study in which Sprague-Dawley rats were administered 10 gavage doses in a 13-week period (Viluksela et al. 1998a, 1998b). A 75% mortality rate was observed at 2.6 µg/kg/day; other effects observed at this dose included decreased body weight gain; occasional hair loss; sores in the ears, nose, tail, and feet; and decreased hematocrit and platelet levels. Because the lowest dose tested is a serious LOAEL, this study is not suitable for derivation of an MRL.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin (1,2,3,7,8-PeCDD)
CAS Numbers: 40321-76-4
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a provisional chronic-duration oral MRL for 1,2,3,7,8-PeCDD due to the lack of studies evaluating toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,7,8-PeCDD following chronic-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,4,7,8-Pentachlorodibenzo-*p*-dioxin (1,2,4,7,8-PeCDD)
CAS Numbers: 58802-08-7
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of provisional acute-, intermediate-, or chronic-duration inhalation MRLs for 1,2,4,7,8-PeCDD due to the lack of studies evaluating toxicity following inhalation exposure.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,4,7,8-PeCDD following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,4,7,8-Pentachlorodibenzo-*p*-dioxin (1,2,4,7,8-PeCDD)
CAS Numbers: 58802-08-7
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of a provisional acute-duration oral MRL for 1,2,4,7,8-PeCDD due to the lack of studies evaluating non-lethality endpoints.

Rationale for Not Deriving an MRL: One study evaluated the acute-oral toxicity of 1,2,4,7,8-PeCDD in animals (McConnell et al. 1978b). This study reported an LD_{50} of 1,125 µg/kg in Hartley guinea pigs following administration of a single dose; the LD_{50} in C57BL/6 mice was >5,000 µg/kg.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,4,7,8-Pentachlorodibenzo-*p*-dioxin (1,2,4,7,8-PeCDD)
CAS Numbers: 58802-08-7
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of a provisional intermediate-duration oral MRL for 1,2,4,7,8-PeCDD due to the lack of studies evaluating toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,4,7,8-PeCDD following intermediate-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,4,7,8-Pentachlorodibenzo-*p*-dioxin (1,2,4,7,8-PeCDD)
CAS Numbers: 58802-08-7
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a provisional chronic-duration oral MRL for 1,2,4,7,8-PeCDD due to the lack of studies evaluating toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,4,7,8-PeCDD following chronic-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin (1,2,3,4,7,8-HxCDD)
CAS Numbers: 39227-28-6
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of provisional acute-, intermediate-, or chronic-duration inhalation MRLs for 1,2,3,4,7,8-HxCDD due to the lack of studies evaluating toxicity following inhalation exposure.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,4,7,8-HxCDD following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin (1,2,3,4,7,8-HxCDD)
CAS Numbers: 39227-28-6
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of a provisional acute-duration oral MRL for 1,2,3,4,7,8-HxCDD due to the lack of studies evaluating two potentially sensitive endpoints (immune function and developmental toxicity).

Rationale for Not Deriving an MRL: Several studies have evaluated the acute oral toxicity of 1,2,3,4,7,8-HxCDD in animals; the NOAEL and LOAEL values are summarized in Table A-16. The lowest LOAEL is 5.1 µg/kg for a 50% decrease in serum T4 levels in Hans/Wistar rats (Simanainen et al. 2002). At higher doses, decreases in relative thymus weight, increases in incisor tooth defects, decreased body weight gain, and death have been reported. The available studies have examined a limited number of potential endpoints and did not examine immune function and developmental outcomes, which are the most sensitive targets of toxicity following acute-duration oral exposure to 2,3,7,8-TCDD.

Table A-16. Summary of NOAEL and LOAEL Values in Animals Following Acute-Duration Oral Exposure to 1,2,3,4,7,8-HxCDD

Species, duration	Doses tested (µg/kg/day)	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Hans/Wistar rat, once	0, 0.3–300	50% decreased serum T4 levels	–	5.1	Simanainen et al. 2002
Hans/Wistar rat, once	0, 0.3–300	50% decreased relative thymus weight	–	14	Simanainen et al. 2002
Long-Evans rat, once	0, 0.3–300	50% decreased serum T4 levels	–	21	Simanainen et al. 2002
Long-Evans rat, once	0, 0.3–300	50% decreased relative thymus weight	–	37	Simanainen et al. 2002
Hans/Wistar rat, once	0, 0.3–300	50% increase in incisor tooth defects	–	64	Simanainen et al. 2002
Hartley guinea pig, once	NS	LD_{50}	–	72.5 (SLOAEL)	McConnell et al. 1978b
Long-Evans rat, once	0, 0.3–300	50% increase in incisor tooth defects	–	130	Simanainen et al. 2002
Long-Evans rat, once	0, 0.3–300	50% decreased body weight	–	140 (SLOAEL)	Simanainen et al. 2002
Hans/Wistar rat, once	0, 0.3–300	50% decreased body weight	–	390 (SLOAEL)	Simanainen et al. 2002
C57BL/6 mouse, once	NS	LD_{50}	–	825 (SLOAEL)	McConnell et al. 1978b

Table A-16. Summary of NOAEL and LOAEL Values in Animals Following Acute-Duration Oral Exposure to 1,2,3,4,7,8-HxCDD

Species, duration	Doses tested (µg/kg/day)	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Sprague-Dawley rat, once	0, 20, 30, 40, 60	LD_{50}	–	887 (SLOAEL)	Stahl et al. 1992

[a]Doses adjusted for intermittent exposure.

1,2,3,7,8-HxCDD = 1,2,3,7,8-hexachlorodibenzo-*p*-dioxin; LD_{50} = median lethal dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; SLOAEL = serious lowest-observed-adverse-effect level; T4 = thyroxine

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin (1,2,3,4,7,8-HxCDD)
CAS Numbers: 39227-28-6
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of a provisional intermediate-duration oral MRL for 1,2,3,4,7,8-HxCDD because the lowest dose resulted in increases in mortality.

Rationale for Not Deriving an MRL: One study (Viluksela et al. 1998a, 1998b) evaluated the toxicity of 1,2,3,4,7,8-HxCDD in Sprague-Dawley rats administered 10 gavage doses in a 13-week period. At the lowest dose tested (10.3 µg/kg/day), observed effects included 25% mortality; decreased hematocrit and platelet count, occasional hair loss; and sores in ears, nose, tail, and feet. At 15.4 µg/kg/day, decreased body weight gain and decreased serum total T4 levels were also observed. The database was not considered adequate for derivation of an MRL because the lowest exposure level is a serious LOAEL.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin (1,2,3,4,7,8-HxCDD)
CAS Numbers: 39227-28-6
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a provisional chronic-duration oral MRL for 1,2,3,4,7,8-HxCDD due to the lack of studies evaluating chronic oral toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the chronic-duration oral toxicity of 1,2,3,4,7,8-HxCDD.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin (1,2,3,6,7,8-HxCDD)
CAS Numbers: 57653-85-7
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of provisional acute-, intermediate-, or chronic-duration inhalation MRLs for 1,2,3,6,7,8-HxCDD due to the lack of studies evaluating toxicity following inhalation exposure.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,6,7,8-HxCDD following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin (1,2,3,6,7,8-HxCDD)
CAS Numbers: 57653-85-7
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of a provisional acute-duration oral MRL for 1,2,3,6,7,8-HxCDD due to the lack of studies evaluating potentially sensitive endpoints, such developmental toxicity.

Rationale for Not Deriving an MRL: Two studies have evaluated the acute-duration oral toxicity of 1,2,3,6,7,8-HxCDD in animals. Suppression of serum complement activity was observed in B6C3F1 mice administered 1 µg/kg/day for 14 days (White et al. 1986); no effects were observed at 0.1 µg/kg/day. At 10 µg/kg/day, there was an increased susceptibility to *Streptococcus pneumoniae* infection. The second study reported LD_{50} values of 70 and 1,250 µg/kg in Hartley guinea pigs and C57BL/6 mice, respectively (McConnell et al. 1978b). The database was not considered adequate for derivation of an MRL due to the lack of studies evaluating potential developmental toxicity endpoints (a sensitive target of 2,3,7,8-TCDD toxicity) and studies evaluating a wide range of potential endpoints.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin (1,2,3,6,7,8-HxCDD)
CAS Numbers: 57653-85-7
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of a provisional intermediate-duration oral MRL for 1,2,3,6,7,8-HxCDD due to the lack of studies evaluating intermediate-duration oral toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the intermediate-duration oral toxicity of 1,2,3,6,7,8-HxCDD.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin (1,2,3,6,7,8-HxCDD)
CAS Numbers: 57653-85-7
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a provisional chronic-duration oral MRL for 1,2,3,6,7,8-HxCDD due to the lack of studies evaluating chronic-duration oral toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the chronic-duration oral toxicity of 1,2,3,6,7,8-HxCDD.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin (1,2,3,4,6,7,8-HpCDD)
CAS Numbers: 35822-46-9
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of provisional acute-, intermediate-, or chronic-duration inhalation MRLs for 1,2,3,4,6,7,8-HpCDD due to the lack of studies evaluating toxicity following inhalation exposure.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,4,6,7,8-HpCDD following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin (1,2,3,4,6,7,8-HpCDD)
CAS Numbers: 35822-46-9
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of a provisional acute-duration oral MRL for 1,2,3,4,6,7,8-HpCDD due to the lack of studies evaluating potentially sensitive endpoints, such as developmental toxicity.

Rationale for Not Deriving an MRL: Two studies have evaluated the acute-oral toxicity of 1,2,3,4,6,7,8-HpCDD in animals; the results are summarized in Table A-17. The lowest LOAEL is 20 µg/kg for a decreased splenic antibody response to sheep red blood cells in C57BL/6 mice administered a single dose of 1,2,3,4,6,7,8-HpCDD (Kerkvliet and Brauner 1987). Higher doses were associated with decreases in serum T4 levels, decreased relative thymus weight, increased incisor tooth defects, and decreased body weight (Simanainen et al. 2002). The database was not considered adequate for derivation of an MRL due to the lack of studies evaluating potential developmental toxicity endpoints (a sensitive target of 2,3,7,8-TCDD toxicity) and studies evaluating a wide range of potential endpoints.

Table A-17. Summary of NOAEL and LOAEL Values in Animals Following Acute-Duration Oral Exposure to 1,2,3,4,6,7,8-HpCDD

Species, duration	Doses tested (µg/kg/day)	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
C57BL/6 mouse, once	0, 20, 100, 500	Decreased splenic antibody response to sRBC		20	Kerkvliet and Brauner 1987
Long-Evans rat, once	0, 0.3–3,000	50% decreased serum T4 levels		47	Simanainen et al. 2002
Hans/Wistar rat, once	0, 0.3–3,000	50% decreased serum T4 levels		99	Simanainen et al. 2002
Long-Evans rat, once	0, 0.3–3,000	50% decreased relative thymus weight		150	Simanainen et al. 2002
Hans/Wistar rat, once	0 0.3–3,000	50% decreased relative thymus weight		610	Simanainen et al. 2002
Long-Evans rat, once	0, 0.3–3,000	50% increase in incisor tooth defects		630	Simanainen et al. 2002
Hans/Wistar rat, once	0, 0.3–3,000	50% increase in incisor tooth defects		760	Simanainen et al. 2002
Long-Evans rat, once	0, 0.3–3,000	50% decreased body weight		980 (SLOAEL)	Simanainen et al. 2002

Table A-17. Summary of NOAEL and LOAEL Values in Animals Following Acute-Duration Oral Exposure to 1,2,3,4,6,7,8-HpCDD

Species, duration	Doses tested (µg/kg/day)	Effect	NOAEL[a] (µg/kg/day)	LOAEL[a] (µg/kg/day)	Reference
Hans/Wistar rat, once	0, 0.3–3,000	50% decreased body weight		2500 (SLOAEL)	Simanainen et al. 2002

[a]Doses adjusted for intermittent exposure.

1,2,3,4,6,7,8-HpCDD = 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; SLOAEL = serious lowest-observed adverse-effect level; sRBC = sheep red blood cell; T4 = thyroxine

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin (1,2,3,4,6,7,8-HpCDD)
CAS Numbers: 35822-46-9
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of a provisional intermediate-duration oral MRL for 1,2,3,4,6,7,8-HpCDD due to the lack of studies evaluating potentially sensitive endpoints, such immune function and developmental toxicity.

Rationale for Not Deriving an MRL: One study evaluated the toxicity of 1,2,3,4,6,7,8-HpCDD in Sprague-Dawley rats administered 10 doses in a 13-week period (Viluksela et al. 1994). The lowest LOAEL was 4 µg/kg/day for increased relative liver weight and decreased relative thymus weight. Decreased serum total T4 levels and decreased platelet counts were observed at 24 and 73 µg/kg/day, respectively, and decreased body weight gain (48%) and mortality (50%) were observed at 110 µg/kg/day. No effects were observed at 0.3 µg/kg/day. The database was not considered adequate for derivation of an MRL due to the lack of studies evaluating potential immune function and developmental toxicity endpoints (a sensitive target of 2,3,7,8-TCDD toxicity).

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin (1,2,3,4,6,7,8-HpCDD)
CAS Numbers: 35822-46-9
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a provisional chronic-duration oral MRL for 1,2,3,4,6,7,8-HpCDD due to the lack of studies evaluating chronic-duration oral toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the chronic-duration oral toxicity of 1,2,3,4,6,7,8-HpCDD.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Octachlorodibenzo-*p*-dioxin (OCDD)
CAS Numbers: 3268-87-9
Date: October 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of provisional acute-, intermediate-, or chronic-duration inhalation MRLs for OCDD due to the lack of studies evaluating toxicity following inhalation exposure.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of OCDD following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Octachlorodibenzo-*p*-dioxin (OCDD)
CAS Numbers: 3268-87-9
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of an acute-duration oral MRL for OCDD due to the lack of studies evaluating a wide range of potential endpoints.

Rationale for Not Deriving an MRL: Three studies have evaluated the acute-duration oral toxicity of OCDD in animals. An increase in the incidence of subcutaneous edema was observed in the offspring of Sprague-Dawley rats administered 500,000 µg/kg/day on GDs 6–15 (Schwetz et al. 1973). No developmental effects were observed in CD-1 mice administered 20 µg/kg/day on GDs 7–16 (Courtney 1976) and no significant alterations in the immune response to sheep red blood cells in B6C3F1 mice administered 10 µg/kg/day for 14 days (Holsapple et al. 1986). The database was not considered adequate for derivation of an MRL due to the lack of studies evaluating a wide range of potential endpoints, which is needed to identify the most sensitive target of toxicity.

Agency Contacts (Chemical Managers): Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Octachlorodibenzo-*p*-dioxin (OCDD)
CAS Numbers: 3268-87-9
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of an intermediate-duration oral MRL for OCDD due to the lack of studies evaluating potentially sensitive endpoints, such immune function and developmental toxicity.

Rationale for Not Deriving an MRL: One study evaluated the toxicity of OCDD in Fisher 344 rats administered 36 µg/kg/day OCDD 5 day/week for 4–13 weeks (Couture et al. 1988). The observed effects included hepatocellular vacuolization, increased lymphocyte levels, and decreased hematocrit. The database was not considered adequate for derivation of an MRL due to the lack of studies evaluating potential immune function and developmental toxicity endpoints (a sensitive target of 2,3,7,8-TCDD toxicity).

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Octachlorodibenzo-*p*-dioxin (OCDD)
CAS Numbers: 3268-87-9
Date: October 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for OCDD due to the lack of studies evaluating chronic-duration oral toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the chronic-duration oral toxicity of OCDD.

Agency Contacts (Chemical Managers): Hana Pohl

APPENDIX B. UPDATE TO THE ATSDR POLICY GUIDELINE FOR DIOXINS AND DIOXIN-LIKE COMPOUNDS IN RESIDENTIAL SOIL

Purpose

The Agency for Toxic Substances and Disease Registry (ATSDR) is updating its *Policy Guideline for Dioxins and Dioxin-Like Compounds in Residential Soil*.

The objective of this update is to ensure that ATSDR health assessors evaluate dioxin levels that exceed the ATSDR established screening level of 0.05 ppb as described in the ATSDR Public Health Assessment Guidance Manual (PHAGM) (ATSDR 2005). The 0.05 ppb value should be used as the comparison value when following the PHAGM. The comparison value is not a threshold for toxicity and should not be used to predict adverse health effects (ATSDR 2005).

This update replaces Appendix B in the Toxicological Profile for Chlorinated Dibenzo-p-dioxins (CDDs) (December, 1998). It does not reflect a change in ATSDR's scientific assessment on dioxin toxicity or the ATSDR Minimal Risk Level (MRL). This update does not impact the EPA guidance which continues to identify 1 ppb as the preliminary remediation goal for residential exposure scenarios. (EPA 1998).

History of the Dioxin Policy Guideline

In the 1998 version of the profile, ATSDR adopted a Policy Guideline for Dioxin and Dioxin-like Compounds. The policy was developed to guide health assessors in evaluating the public health implications of dioxin and dioxin-like compounds (including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and other structurally related halogenated aromatic hydrocarbons) in residential soils near or on hazardous waste sites. The 1998 guideline established three levels as criteria for comparing dioxin levels in residential soil:

- a **screening level**,
- an **evaluation level**, and
- an **action level**.

The 1998 guideline also recommended specific considerations for public health actions within each of these levels.

Since the release of the Policy Guideline in 1998, ATSDR issued the PHAGM. By issuing this update to the guideline, ATSDR is ensuring that health assessors will use the screening level as the appropriate comparison value for following the PHAGM, rather than the "action level" described in the earlier version of this policy guidance. This does not reflect a change in dioxin science; it is simply a reiteration to ensure that the appropriate value is used as a starting point when following the procedures described in the PHAGM.

If health assessors follow the PHAGM, the evaluation and action levels values, as set in 1998, are no longer necessary.

Changes Being Made to the ATSDR Policy Guideline for Dioxins and Dioxin-Like Compounds in Residential Soil

The specific changes to the policy guideline, the reason for those changes, and the expected impact of those changes are summarized in the following table:

Change	Reason for Change	Impact of Change
Elimination of the "evaluation level" and the "action level"	Confusion about interpretation of the evaluation and action levels was a barrier to a more consistent evaluation of exposure to dioxin in residential soils.	This change brings the guidelines up-to-date with ATSDR's PHAGM which uses only screening levels. The public health actions described in the 1998 policy guideline remain options that may be applied as appropriate rather than being triggered by a prescribed soil concentration. The minimal risk level (MRL) for dioxin exposure described in the 1998 Toxicological Profile remains the same.
Ensure consistency with ATSDR PHAGM	PHAGM was not referenced in the previous policy.	Consistency with 2005 PHAGM will ensure more comprehensive evaluation, for instance assessing both direct and indirect exposure pathways should result in a more comprehensive evaluation of exposure conditions at sites with dioxin contamination.

Summary

This policy update replaces Appendix B in the Toxicological Profile for Chlorinated Dibenzo-p-dioxins (CDDs) (December, 1998). ATSDR will no longer refer to an Action Level for dioxin in these evaluations. The 0.05 ppb screening level is retained as an initial comparison value for health assessments. The update does not change the assessment of health hazards associated with dioxin exposure, as summarized in the 1998 ATSDR Toxicological Profile and in the derivation of the Minimal Risk Level (MRL). The policy update impacts site-specific health assessments evaluating exposure to dioxin directly from residential soils. The update ensures consistency in the methodology ATSDR uses for site-specific evaluations of health risks for all chemicals.

EPA's preliminary remediation goal for dioxin in soil has not changed and remains at 1 ppb. ATSDR does not establish clean-up goals or preliminary remediation goals, but ATSDR believes that health risks associated with levels of dioxins in soil below 1 ppb would be low under most scenarios where the primary exposure pathway is incidental ingestion through direct exposure to soil. In such instances, ATSDR public health recommendations may include community health education or limiting access to contaminated areas. Consistency with 2005 PHAGM also ensures that a comprehensive evaluation of dioxins from contaminated soils includes the consideration of scenarios where dioxins may enter the food chain pathway.

APPENDIX C. LITERATURE SEARCH FRAMEWORK FOR CDDs

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to CDDs.

C.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for CDDs. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of CDDs have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of CDDs are presented in Table C-1.

Table C-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects

Table C-1. Inclusion Criteria for the Literature Search and Screen

Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

C.1.1 Literature Search

The current literature search was intended to update the 1998 toxicological profile for CDDs; thus, the literature search was restricted to studies published between January 1996 and December 2021. The following main databases were searched in January 2011 and December 2021:

- PubMed
- Scientific and Technical Information Network's TOXCENTER
- National Technical Reports Library (NTRL)
- Toxline

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for CDDs. The query strings used for the literature search are presented in Table C-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table C-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to CDDs were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table C-2. Database Query Strings

Database search date	Query string
PubMed	
12/2021	((((("Polychlorinated Dibenzodioxins/toxicity"[mh] OR "Polychlorinated Dibenzodioxins/adverse effects"[mh] OR "Polychlorinated Dibenzodioxins/poisoning"[mh] OR "Polychlorinated Dibenzodioxins/pharmacokinetics"[mh]) OR ("Polychlorinated Dibenzodioxins"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Polychlorinated Dibenzodioxins"[mh] AND toxicokinetics[mh:noexp]) OR ("Polychlorinated Dibenzodioxins/blood"[mh] OR "Polychlorinated Dibenzodioxins/cerebrospinal fluid"[mh] OR "Polychlorinated Dibenzodioxins/urine"[mh]) OR ("Polychlorinated Dibenzodioxins"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Polychlorinated Dibenzodioxins"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Polychlorinated Dibenzodioxins/antagonists and inhibitors"[mh]) OR ("Polychlorinated Dibenzodioxins/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Polychlorinated Dibenzodioxins"[mh] AND cancer[sb]) OR ("Polychlorinated Dibenzodioxins/pharmacology"[majr])) OR ((("Dioxins"[mh] AND (39227-53-7[rn] OR 39227-54-8[rn] OR 50585-39-2[rn] OR 38178-38-0[rn] OR 29446-15-9[rn] OR 33857-26-0[rn] OR 38964-22-6[rn] OR 39227-58-2[rn] OR 33857-28-2[rn] OR 30746-58-8[rn] OR 53555-02-5[rn] OR 34816-53-0[rn] OR 33423-92-6[rn] OR 50585-46-1[rn] OR 1746-01-6[rn] OR 41903-57-5[rn] OR 39227-61-7[rn] OR 40321-76-4[rn] OR 58802-08-7[rn] OR 36088-22-9[rn] OR 57653-85-7[rn] OR 64461-98-9[rn] OR 19408-74-3[rn] OR 39227-62-8[rn] OR 34465-46-8[rn] OR 39227-28-6[rn] OR 35822-46-9[rn] OR 58200-70-7[rn] OR 37871-00-4[rn] OR 3268-87-9[rn])) OR ("Dioxins"[mh] AND (monochlorodibenzodioxin* OR chlorodibenzodioxin* OR dichlorodibenzodioxin* OR trichlorodibenzodioxin* OR tetrachlorodibenzodioxin* OR pentachlorodibenzodioxin* OR hexachlorodibenzodioxin* OR heptachlorodibenzodioxin* OR octachlorodibenzodioxin* OR Chlorooxanthrene OR Dichlorooxanthrene OR Heptachlorooxanthrene OR Hexachlorooxanthrene OR Octachlorooxanthrene OR Pentachlorooxanthrene OR

Table C-2. Database Query Strings

Database search date	Query string
	Tetrachlorooxanthrene OR Trichlorooxanthrene OR "Tetradioxin"[tw] OR "polychlorinated dibenzo-p-dioxin"[tw] OR "polychlorinated dibenzo-p-dioxins"[tw] OR "chlorinated dibenzo-p-dioxin"[tw] OR "chlorinated dibenzo-p-dioxins"[tw] OR "polychlorinated dioxins"[tw] OR "chlorinated dioxins"[tw] OR "polychloro dibenzo-p-dioxins"[tw] OR "chloro dibenzo-p-dioxins"[tw] OR "tetrachloro dibenzo-p-dioxin"[tw] OR "chlorodibenzo-p-dioxin"[tw] OR "chlorodibenzo-para-dioxin"[tw] OR "chlorodibenzo-4-dioxin"[tw] OR "chlorodibenzo(b,e)(1,4)dioxin"[tw] OR "chlorodibenzo-1,4-dioxin"[tw] OR "monochlorodibenzo-p-dioxin"[tw] OR "monochlorodibenzo-para-dioxin"[tw] OR "monochlorodibenzo-4-dioxin"[tw] OR "monochlorodibenzo(b,e)(1,4)dioxin"[tw] OR "monochlorodibenzo-1,4-dioxin"[tw] OR "Dichlorodibenzo-p-dioxin"[tw] OR "Dichlorodibenzo-para-dioxin"[tw] OR "Dichlorodibenzo-4-dioxin"[tw] OR "Dichlorodibenzo(b,e)(1,4)dioxin"[tw] OR "dichlorodibenzo-1,4-dioxin"[tw] OR "trichlorodibenzo-p-dioxin"[tw] OR "trichlorodibenzo-para-dioxin"[tw] OR "trichlorodibenzo-4-dioxin"[tw] OR "trichlorodibenzo(b,e)(1,4)dioxin"[tw] OR "trichlorodibenzo-1,4-dioxin"[tw] OR "tetrachlorodibenzo-p-dioxin"[tw] OR "tetrachlorodibenzo-para-dioxin"[tw] OR "tetrachlorodibenzo-4-dioxin"[tw] OR "tetrachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "tetrachlorodibenzo-1,4-dioxin"[tw] OR "pentachlorodibenzo-p-dioxin"[tw] OR "pentachlorodibenzo-para-dioxin"[tw] OR "pentachlorodibenzo-4-dioxin"[tw] OR "pentachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "pentachlorodibenzo-1,4-dioxin"[tw] OR "hexachlorodibenzo-p-dioxin"[tw] OR "hexachlorodibenzo-para-dioxin"[tw] OR "hexachlorodibenzo-4-dioxin"[tw] OR "hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "hexachlorodibenzo-1,4-dioxin"[tw] OR "heptachlorodibenzo-p-dioxin"[tw] OR "heptachlorodibenzo-para-dioxin"[tw] OR "heptachlorodibenzo-4-dioxin"[tw] OR "heptachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "heptachlorodibenzo-1,4-dioxin"[tw] OR "octachlorodibenzo-p-dioxin"[tw] OR "octachlorodibenzo-para-dioxin"[tw] OR "octachlorodibenzo-4-dioxin"[tw] OR "octachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "octachlorodibenzo-1,4-dioxin"[tw] OR "Polychlorinated Dibenzodioxin"[tw] OR "Polychlorinated Dibenzodioxins"[tiab] OR "Chlorinated Dibenzodioxin"[tw] OR "Chlorinated Dibenzodioxins"[tw] OR "HpCDD"[tw] OR "HxCDD"[tw] OR "OCDD"[tw] OR "PCDD"[tw] OR "PCDDs"[tw] OR "PeCDD"[tw] OR "PnCDD"[tw] OR "TCDBD"[tw] OR "TCDD"[tw] OR "TCDDs"[tw] OR "TeCDD"[tw] OR "1,2,3,4,6,7,8,9-dibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8,9-OCTACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachorodibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8-HEPTACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,6,7,8-heptachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorooxanthrene"[tw] OR "1,2,3,4,6,7,8-Heptapolychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8-HpCDD"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorooxanthrene"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,7,8-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzodioxin"[tw] OR "1,2,3,4,7,8-Hexachlorooxanthrene"[tw] OR "1,2,3,4,7,8-HxCDD"[tw] OR "1,2,3,4,7-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzodioxin"[tw] OR

Table C-2. Database Query Strings

Database search date	Query string
	"1,2,3,4,7-Pentachlorooxanthrene"[tw] OR "1,2,3,4-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzodioxin"[tw] OR "1,2,3,4-tetrachlorodibenzodioxine"[tw] OR "1,2,3,4-Tetrachlorooxanthrene"[tw] OR "1,2,3,6,7,8-Hcdd/1,2,3,7,8,9-hcdd"[tw] OR "1,2,3,6,7,8-Hexa polychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzodioxin"[tw] OR "1,2,3,6,7,8-Hexachlorooxanthrene"[tw] OR "1,2,3,6,7,8-HXCDD"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo-p-dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzodioxin"[tw] OR "1,2,3,6,7,9-Hexachlorooxanthrene"[tw] OR "1,2,3,6,7,9-HxCDD"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,7,8,9-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzodioxin"[tw] OR "1,2,3,7,8,9-Hexachlorooxanthrene"[tw] OR "1,2,3,7,8,9-HxCDD"[tw] OR "1,2,3,7,8-PeCDD"[tw] OR "1,2,3,7,8-Penta polychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzodioxin"[tw] OR "1,2,3,7,8-Pentachlorooxanthrene"[tw] OR "1,2,3,7,8-PnCDD"[tw] OR "1,2,3,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,3,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,2,3,8-Tetrachlorodibenzodioxin"[tw] OR "1,2,3,8-Tetrachlorooxanthrene"[tw] OR "1,2,4,6,7,9-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzodioxin"[tw] OR "1,2,4,6,7,9-Hexachlorooxanthrene"[tw] OR "1,2,4,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,4,7,8-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4,7,8-Pentachlorooxanthrene"[tw] OR "1,2,4-Trichlorodibenzo-1,4-dioxin"[tw] OR "1,2,4-Trichlorodibenzo-p-dioxin"[tw] OR "1,2,4-Trichlorodibenzo-para-dioxin"[tw] OR "1,2,4-Trichlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4-Trichlorodibenzodioxin"[tw] OR "1,2,4-Trichlorooxanthrene"[tw] OR "1,2,7,8,-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,7,8-Tetrachlorooxanthrene"[tw] OR "1,3,6,8-TCDD"[tw] OR "1,3,6,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,3,6,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,3,6,8-Tetrachlorodibenzodioxin"[tw] OR "1,3,6,8-Tetrachlorooxanthrene"[tw] OR "1,3,7,8-TCDD"[tw] OR "1,3,7,8-TeCDD"[tw] OR "1,3,7,8-Tetrachlorodibenzo-4-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo[1,4]dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzodioxin"[tw] OR "1,3,7,8-Tetrachlorooxanthrene"[tw] OR "1,3-Dichlorodibenzo-p-dioxin"[tw] OR "1,3-Dichlorodibenzo-para-dioxin"[tw] OR "1,3-Dichlorooxanthrene"[tw] OR "1,6-Dichlorodibenzo-p-dioxin"[tw] OR "1,6-Dichlorodibenzo-para-dioxin"[tw] OR "1,6-Dichlorooxanthrene"[tw] OR "1-CHLORODIBENZO-P-DIOXIN"[tw] OR "1-Chlorodibenzo[b,e][1,4]dioxin"[tw] OR "1-Chlorodibenzodioxin"[tw] OR "1-Chlorooxanthrene"[tw] OR "1-Monochlorodibenzo-p-dioxin"[tw] OR "1-Monochlorodibenzodioxin"[tw] OR "1234678-HpCDD"[tw] OR "2,3,4,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "2,3,4,7,8-Pentachlorodibenzodioxin"[tw] OR "2,3,6,7-Tetrachlorodibenzo-p-dioxin"[tw] OR "2,3,6,7-Tetrachlorodibenzodioxin"[tw] OR "2,3,7,8-TCDD"[tw] OR "2,3,7,8-Tetra polychlorinated dibenzo-p-dioxin"[tw] OR "2,3,7,8-

Table C-2. Database Query Strings

Database search date	Query string
	Tetrachlordibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7,8-Tetrachloro-1,4-dioxin"[tw] OR "2,3,7,8-Tetrachloro-dibenzo-p-dioxin"[tw] OR "2,3,7,8-Tetrachloro-p-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo-1,4-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzodioxin"[tw] OR "2,3,7,8-tetrachlorodibenzodioxine"[tw] OR "2,3,7,8-Tetrachlorooxanthrene"[tw] OR "2,3,7,8-tetraclorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7-TRICHLORODIBENZO-P-DIOXIN"[tw] OR "2,3,7-Trichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7-Trichlorooxanthrene"[tw] OR "2,3-Dichlorodibenzo-4-dioxin"[tw] OR "2,3-Dichlorodibenzo-p-dioxin"[tw] OR "2,3-Dichlorodibenzo-para-dioxin"[tw] OR "2,3-Dichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3-Dichlorodibenzodioxin"[tw] OR "2,3-Dichlorooxanthrene"[tw] OR "2,7-Dichlorodibenzo(b,e)(1,4)dioxin"[tw] OR "2,7-Dichlorodibenzo-4-dioxin"[tw] OR "2,7-DICHLORODIBENZO-P-DIOXIN"[tw] OR "2,7-Dichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,7-Dichlorodibenzodioxin"[tw] OR "2,7-Dichlorooxanthrene"[tw] OR "2,8-Dichlorodibenzo-4-dioxin"[tw] OR "2,8-Dichlorodibenzo-para-dioxin"[tw] OR "2,8-Dichlorodibenzodioxin"[tw] OR "2,8-Dichlorooxanthrene"[tw] OR "2-Chlorodibenzo-4-dioxin"[tw] OR "2-Chlorodibenzo-p-dioxin"[tw] OR "2-Chlorodibenzo-para-dioxin"[tw] OR "2-Chlorooxanthrene"[tw] OR "2-Monochlorodibenzo-p-dioxin"[tw] OR "Dichlorodibenzo-p-dioxin"[tw] OR "Hcdd mixture"[tw] OR "Heptachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Heptachlorodibenzo-p-dioxin"[tw] OR "Heptachlorodibenzo-p-dioxins"[tw] OR "Heptachlorodibenzo[b,e][1,4]dioxin"[tw] OR "Heptachlorodibenzodioxin"[tw] OR "Hexachlorodibenzo-4-dioxin"[tw] OR "Hexachlorodibenzo-p-dioxin"[tw] OR "Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "Hexachlorodibenzodioxin"[tw] OR "HpCDD"[tw] OR "HxCDD"[tw] OR "Markush_benzodioxin"[tw] OR "OCDD"[tw] OR "Octa polychlorinated dibenzo-p-dioxin"[tw] OR "Octachloro-para-dibenzodioxin"[tw] OR "Octachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Octachlorodibenzo-4-dioxin"[tw] OR "Octachlorodibenzo-p-dioxin"[tw] OR "Octachlorodibenzo[b,e][1,4]dioxin"[tw] OR "Octachlorodibenzodioxin"[tw] OR "Octachlorooxanthrene"[tw] OR "PCDD"[tw] OR "PCDDs"[tw] OR "Pentachlorodibenzo-p-dioxin"[tw] OR "Pentachlorodibenzodioxin"[tw] OR "Polychlorinated Dibenzodioxins"[tw] OR "TCDBD"[tw] OR "TCDD"[tw] OR "TCDDs"[tw] OR "Tetrachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Tetrachlorodibenzo-p-dioxin"[tw] OR "TETRACHLORODIBENZO-P-DIOXINS"[tw] OR "Tetrachlorodibenzodioxin"[tw] OR "Tetradioxin"[tw] OR "Dibenzo [b, e] [1,4] dioxina, 1,2,3,4,6,7,8-heptacloro -"[tw] OR "Dibenzo(b,e)(1,4)-dioxin, pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,6-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,7-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,8-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2-chloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin,

Table C-2. Database Query Strings

Database search date	Query string
	hexachloro"[tw] OR "Dibenzo(b,e)(1,4)dioxin, hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, octachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3-dichloro-"[tw] OR "Dibenzo-p-dioxin, 1,6-dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo-p-dioxin, 2,3-dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,7-dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,8-dichloro-"[tw] OR "Dibenzo-p-dioxin, 1-chloro-"[tw] OR "Dibenzo-p-dioxin, 2-chloro-"[tw] OR "Dibenzo-p-dioxin, hexachloro-"[tw] OR "Dibenzo-p-dioxin, octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,6-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1-chloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,7-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,8-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2-chloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, tetrachloro-"[tw])) OR ("Dioxins"[mh] NOT hasabstract)) AND (("Dioxins/toxicity"[mh] OR "Dioxins/adverse effects"[mh] OR "Dioxins/poisoning"[mh] OR "Dioxins/pharmacokinetics"[mh]) OR ("Dioxins"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Dioxins"[mh] AND toxicokinetics[mh:noexp]) OR ("Dioxins/blood"[mh] OR "Dioxins/cerebrospinal fluid"[mh] OR "Dioxins/urine"[mh]) OR ("Dioxins"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Dioxins"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein

Table C-2. Database Query Strings

Database search date	Query string
	biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Dioxins/antagonists and inhibitors"[mh]) OR ("Dioxins/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Dioxins"[mh] AND cancer[sb]) OR ("Dioxins/pharmacology"[majr]))) OR (("dioxin"[tw] OR "dioxins"[tw] OR monochlorodibenzodioxin* OR chlorodibenzodioxin* OR dichlorodibenzodioxin* OR trichlorodibenzodioxin* OR tetrachlorodibenzodioxin* OR pentachlorodibenzodioxin* OR hexachlorodibenzodioxin* OR heptachlorodibenzodioxin* OR octachlorodibenzodioxin* OR Chlorooxanthrene OR Dichlorooxanthrene OR Heptachlorooxanthrene OR Hexachlorooxanthrene OR Octachlorooxanthrene OR Pentachlorooxanthrene OR Tetrachlorooxanthrene OR Trichlorooxanthrene OR "Tetradioxin"[tw] OR "Polychlorinated Dibenzodioxin"[tw] OR "Polychlorinated Dibenzodioxins"[tw] OR "Chlorinated Dibenzodioxin"[tw] OR "Chlorinated Dibenzodioxins"[tw] OR "HpCDD"[tw] OR "HxCDD"[tw] OR "OCDD"[tw] OR "PCDD"[tw] OR "PCDDs"[tw] OR "PeCDD"[tw] OR "PnCDD"[tw] OR "TCDBD"[tw] OR "TCDD"[tw] OR "TCDDs"[tw] OR "TeCDD"[tw] OR "1,2,3,4,6,7,8,9-dibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8,9-OCTACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachorodibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8-HEPTACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,6,7,8-heptachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorooxanthrene"[tw] OR "1,2,3,4,6,7,8-Heptapolychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8-HpCDD"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorooxanthrene"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,7,8-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzodioxin"[tw] OR "1,2,3,4,7,8-Hexachlorooxanthrene"[tw] OR "1,2,3,4,7,8-HxCDD"[tw] OR "1,2,3,4,7-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzodioxin"[tw] OR "1,2,3,4,7-Pentachlorooxanthrene"[tw] OR "1,2,3,4-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzodioxin"[tw] OR "1,2,3,4-tetrachlorodibenzodioxine"[tw] OR "1,2,3,4-Tetrachlorooxanthrene"[tw] OR "1,2,3,6,7,8-Hcdd/1,2,3,7,8,9-hcdd"[tw] OR "1,2,3,6,7,8-Hexa polychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzodioxin"[tw] OR "1,2,3,6,7,8-Hexachlorooxanthrene"[tw] OR "1,2,3,6,7,8-HXCDD"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo-p-dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzodioxin"[tw] OR "1,2,3,6,7,9-Hexachlorooxanthrene"[tw] OR "1,2,3,6,7,9-HxCDD"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,7,8,9-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,7,8,9-

Table C-2. Database Query Strings

Database search date	Query string
	Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzodioxin"[tw] OR "1,2,3,7,8,9-Hexachlorooxanthrene"[tw] OR "1,2,3,7,8,9-HxCDD"[tw] OR "1,2,3,7,8-PeCDD"[tw] OR "1,2,3,7,8-Penta polychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzodioxin"[tw] OR "1,2,3,7,8-Pentachlorooxanthrene"[tw] OR "1,2,3,7,8-PnCDD"[tw] OR "1,2,3,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,3,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,2,3,8-Tetrachlorodibenzodioxin"[tw] OR "1,2,3,8-Tetrachlorooxanthrene"[tw] OR "1,2,4,6,7,9-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzodioxin"[tw] OR "1,2,4,6,7,9-Hexachlorooxanthrene"[tw] OR "1,2,4,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,4,7,8-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4,7,8-Pentachlorooxanthrene"[tw] OR "1,2,4-Trichlorodibenzo-1,4-dioxin"[tw] OR "1,2,4-Trichlorodibenzo-p-dioxin"[tw] OR "1,2,4-Trichlorodibenzo-para-dioxin"[tw] OR "1,2,4-Trichlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4-Trichlorodibenzodioxin"[tw] OR "1,2,4-Trichlorooxanthrene"[tw] OR "1,2,7,8,-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,7,8-Tetrachlorooxanthrene"[tw] OR "1,3,6,8-TCDD"[tw] OR "1,3,6,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,3,6,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,3,6,8-Tetrachlorodibenzodioxin"[tw] OR "1,3,6,8-Tetrachlorooxanthrene"[tw] OR "1,3,7,8-TCDD"[tw] OR "1,3,7,8-TeCDD"[tw] OR "1,3,7,8-Tetrachlorodibenzo-4-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo[1,4]dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzodioxin"[tw] OR "1,3,7,8-Tetrachlorooxanthrene"[tw] OR "1,3-Dichlorodibenzo-p-dioxin"[tw] OR "1,3-Dichlorodibenzo-para-dioxin"[tw] OR "1,3-Dichlorooxanthrene"[tw] OR "1,6-Dichlorodibenzo-p-dioxin"[tw] OR "1,6-Dichlorodibenzo-para-dioxin"[tw] OR "1,6-Dichlorooxanthrene"[tw] OR "1-CHLORODIBENZO-P-DIOXIN"[tw] OR "1-Chlorodibenzo[b,e][1,4]dioxin"[tw] OR "1-Chlorodibenzodioxin"[tw] OR "1-Chlorooxanthrene"[tw] OR "1-Monochlorodibenzo-p-dioxin"[tw] OR "1-Monochlorodibenzodioxin"[tw] OR "1234678-HpCDD"[tw] OR "2,3,4,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "2,3,4,7,8-Pentachlorodibenzodioxin"[tw] OR "2,3,6,7-Tetrachlorodibenzo-p-dioxin"[tw] OR "2,3,6,7-Tetrachlorodibenzodioxin"[tw] OR "2,3,7,8-TCDD"[tw] OR "2,3,7,8-Tetra polychlorinated dibenzo-p-dioxin"[tw] OR "2,3,7,8-Tetrachlordibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7,8-Tetrachloro-1,4-dioxin"[tw] OR "2,3,7,8-Tetrachloro-dibenzo-p-dioxin"[tw] OR "2,3,7,8-Tetrachloro-p-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo-1,4-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzodioxin"[tw] OR "2,3,7,8-tetrachlorodibenzodioxine"[tw] OR "2,3,7,8-Tetrachlorooxanthrene"[tw] OR "2,3,7,8-tetraclorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7-TRICHLORODIBENZO-P-DIOXIN"[tw] OR "2,3,7-Trichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7-Trichlorooxanthrene"[tw] OR "2,3-Dichlorodibenzo-4-dioxin"[tw] OR "2,3-Dichlorodibenzo-p-dioxin"[tw] OR "2,3-Dichlorodibenzo-para-dioxin"[tw] OR "2,3-Dichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3-Dichlorodibenzodioxin"[tw] OR "2,3-Dichlorooxanthrene"[tw] OR "2,7-Dichlorodibenzo(b,e)(1,4)dioxin"[tw] OR "2,7-Dichlorodibenzo-4-dioxin"[tw] OR "2,7-DICHLORODIBENZO-P-DIOXIN"[tw] OR "2,7-Dichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,7-Dichlorodibenzodioxin"[tw] OR "2,7-Dichlorooxanthrene"[tw] OR "2,8-Dichlorodibenzo-4-dioxin"[tw] OR "2,8-Dichlorodibenzo-

Table C-2. Database Query Strings

Database search date	Query string
	para-dioxin"[tw] OR "2,8-Dichlorodibenzodioxin"[tw] OR "2,8-Dichlorooxanthrene"[tw] OR "2-Chlorodibenzo-4-dioxin"[tw] OR "2-Chlorodibenzo-p-dioxin"[tw] OR "2-Chlorodibenzo-para-dioxin"[tw] OR "2-Chlorooxanthrene"[tw] OR "2-Monochlorodibenzo-p-dioxin"[tw] OR "Dichlorodibenzo-p-dioxin"[tw] OR "Hcdd mixture"[tw] OR "Heptachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Heptachlorodibenzo-p-dioxin"[tw] OR "Heptachlorodibenzo-p-dioxins"[tw] OR "Heptachlorodibenzo[b,e][1,4]dioxin"[tw] OR "Heptachlorodibenzodioxin"[tw] OR "Hexachlorodibenzo-4-dioxin"[tw] OR "Hexachlorodibenzo-p-dioxin"[tw] OR "Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "Hexachlorodibenzodioxin"[tw] OR "HpCDD"[tw] OR "HxCDD"[tw] OR "Markush_benzodioxin"[tw] OR "OCDD"[tw] OR "Octa polychlorinated dibenzo-p-dioxin"[tw] OR "Octachloro-para-dibenzodioxin"[tw] OR "Octachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Octachlorodibenzo-4-dioxin"[tw] OR "Octachlorodibenzo-p-dioxin"[tw] OR "Octachlorodibenzo[b,e][1,4]dioxin"[tw] OR "Octachlorodibenzodioxin"[tw] OR "Octachlorooxanthrene"[tw] OR "PCDD"[tw] OR "PCDDs"[tw] OR "Pentachlorodibenzo-p-dioxin"[tw] OR "Pentachlorodibenzodioxin"[tw] OR "Polychlorinated Dibenzodioxins"[tw] OR "TCDBD"[tw] OR "TCDD"[tw] OR "TCDDs"[tw] OR "Tetrachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Tetrachlorodibenzo-p-dioxin"[tw] OR "TETRACHLORODIBENZO-P-DIOXINS"[tw] OR "Tetrachlorodibenzodioxin"[tw] OR "Tetradioxin"[tw] OR "Dibenzo [b, e] [1,4] dioxina, 1,2,3,4,6,7,8-heptacloro -"[tw] OR "Dibenzo(b,e)(1,4)-dioxin, pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,6-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,7-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,8-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2-chloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, hexachloro"[tw] OR "Dibenzo(b,e)(1,4)dioxin, hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, octachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3-dichloro-"[tw] OR "Dibenzo-p-dioxin, 1,6-dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo-p-dioxin, 2,3-dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,7-

Table C-2. Database Query Strings

Database search date	Query string
	dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,8-dichloro-"[tw] OR "Dibenzo-p-dioxin, 1-chloro-"[tw] OR "Dibenzo-p-dioxin, 2-chloro-"[tw] OR "Dibenzo-p-dioxin, hexachloro-"[tw] OR "Dibenzo-p-dioxin, octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,6-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1-chloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,7-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,8-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2-chloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, tetrachloro-"[tw]) NOT medline[sb])) AND (2011/01/01:3000[mhda] OR 2011/01/01:3000[crdat] OR 2011/01/01:3000[edat] OR 2010:3000[dp])) ((((("Dioxins/toxicity"[mh] OR "Dioxins/adverse effects"[mh] OR "Dioxins/poisoning"[mh] OR "Dioxins/pharmacokinetics"[mh]) OR ("Dioxins"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Dioxins"[mh] AND toxicokinetics[mh:noexp]) OR ("Dioxins/blood"[mh] OR "Dioxins/cerebrospinal fluid"[mh] OR "Dioxins/urine"[mh]) OR ("Dioxins"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Dioxins"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Dioxins/antagonists and inhibitors"[mh]) OR ("Dioxins/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Dioxins"[mh] AND cancer[sb]) OR ("Dioxins/pharmacology"[majr])) AND (2011/01/01:3000[mhda] OR 2011/01/01:3000[crdat] OR 2011/01/01:3000[edat] OR 2010:3000[dp])) NOT ((((("Polychlorinated Dibenzodioxins/toxicity"[mh] OR "Polychlorinated Dibenzodioxins/adverse effects"[mh] OR "Polychlorinated Dibenzodioxins/poisoning"[mh] OR "Polychlorinated Dibenzodioxins/pharmacokinetics"[mh]) OR ("Polychlorinated Dibenzodioxins"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Polychlorinated Dibenzodioxins"[mh] AND toxicokinetics[mh:noexp]) OR ("Polychlorinated Dibenzodioxins/blood"[mh] OR "Polychlorinated Dibenzodioxins/cerebrospinal fluid"[mh] OR "Polychlorinated

Table C-2. Database Query Strings

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	Dibenzodioxins/urine"[mh]) OR ("Polychlorinated Dibenzodioxins"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Polychlorinated Dibenzodioxins"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Polychlorinated Dibenzodioxins/antagonists and inhibitors"[mh]) OR ("Polychlorinated Dibenzodioxins/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Polychlorinated Dibenzodioxins"[mh] AND cancer[sb]) OR ("Polychlorinated Dibenzodioxins/pharmacology"[majr])) OR ((("Dioxins"[mh] AND (39227-53-7[rn] OR 39227-54-8[rn] OR 50585-39-2[rn] OR 38178-38-0[rn] OR 29446-15-9[rn] OR 33857-26-0[rn] OR 38964-22-6[rn] OR 39227-58-2[rn] OR 33857-28-2[rn] OR 30746-58-8[rn] OR 53555-02-5[rn] OR 34816-53-0[rn] OR 33423-92-6[rn] OR 50585-46-1[rn] OR 1746-01-6[rn] OR 41903-57-5[rn] OR 39227-61-7[rn] OR 40321-76-4[rn] OR 58802-08-7[rn] OR 36088-22-9[rn] OR 57653-85-7[rn] OR 64461-98-9[rn] OR 19408-74-3[rn] OR 39227-62-8[rn] OR 34465-46-8[rn] OR 39227-28-6[rn] OR 35822-46-9[rn] OR 58200-70-7[rn] OR 37871-00-4[rn] OR 3268-87-9[rn])) OR ("Dioxins"[mh] AND (monochlorodibenzodioxin* OR chlorodibenzodioxin* OR dichlorodibenzodioxin* OR trichlorodibenzodioxin* OR tetrachlorodibenzodioxin* OR pentachlorodibenzodioxin* OR hexachlorodibenzodioxin* OR heptachlorodibenzodioxin* OR octachlorodibenzodioxin* OR Chlorooxanthrene OR Dichlorooxanthrene OR Heptachlorooxanthrene OR Hexachlorooxanthrene OR Octachlorooxanthrene OR Pentachlorooxanthrene OR Tetrachlorooxanthrene OR Trichlorooxanthrene OR "Tetradioxin"[tw] OR "polychlorinated dibenzo-p-dioxin"[tw] OR "polychlorinated dibenzo-p-dioxins"[tw] OR "chlorinated dibenzo-p-dioxin"[tw] OR "chlorinated dibenzo-p-dioxins"[tw] OR "polychlorinated dioxins"[tw] OR "chlorinated dioxins"[tw] OR "polychloro dibenzo-p-dioxins"[tw] OR "chloro dibenzo-p-dioxins"[tw] OR "tetrachloro dibenzo-p-dioxin"[tw] OR "chlorodibenzo-p-dioxin"[tw] OR "chlorodibenzo-para-dioxin"[tw] OR "chlorodibenzo-4-dioxin"[tw] OR "chlorodibenzo(b,e)(1,4)dioxin"[tw] OR "chlorodibenzo-1,4-dioxin"[tw] OR "monochlorodibenzo-p-dioxin"[tw] OR "monochlorodibenzo-para-dioxin"[tw] OR "monochlorodibenzo-4-dioxin"[tw] OR "monochlorodibenzo(b,e)(1,4)dioxin"[tw] OR "monochlorodibenzo-1,4-dioxin"[tw] OR "Dichlorodibenzo-p-dioxin"[tw] OR "Dichlorodibenzo-para-dioxin"[tw] OR "Dichlorodibenzo-4-dioxin"[tw] OR "Dichlorodibenzo(b,e)(1,4)dioxin"[tw] OR "dichlorodibenzo-1,4-dioxin"[tw] OR "trichlorodibenzo-p-dioxin"[tw] OR "trichlorodibenzo-para-dioxin"[tw] OR "trichlorodibenzo-4-dioxin"[tw] OR "trichlorodibenzo(b,e)(1,4)dioxin"[tw] OR "trichlorodibenzo-1,4-dioxin"[tw] OR "tetrachlorodibenzo-p-dioxin"[tw] OR "tetrachlorodibenzo-para-dioxin"[tw] OR "tetrachlorodibenzo-4-dioxin"[tw] OR "tetrachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "tetrachlorodibenzo-1,4-dioxin"[tw] OR "pentachlorodibenzo-p-dioxin"[tw] OR "pentachlorodibenzo-para-dioxin"[tw] OR "pentachlorodibenzo-4-dioxin"[tw] OR "pentachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "pentachlorodibenzo-1,4-dioxin"[tw] OR "hexachlorodibenzo-p-dioxin"[tw] OR "hexachlorodibenzo-para-dioxin"[tw] OR "hexachlorodibenzo-4-dioxin"[tw] OR "hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR

Table C-2. Database Query Strings

Database search date	Query string
	"hexachlorodibenzo-1,4-dioxin"[tw] OR "heptachlorodibenzo-p-dioxin"[tw] OR "heptachlorodibenzo-para-dioxin"[tw] OR "heptachlorodibenzo-4-dioxin"[tw] OR "heptachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "heptachlorodibenzo-1,4-dioxin"[tw] OR "octachlorodibenzo-p-dioxin"[tw] OR "octachlorodibenzo-para-dioxin"[tw] OR "octachlorodibenzo-4-dioxin"[tw] OR "octachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "octachlorodibenzo-1,4-dioxin"[tw] OR "Polychlorinated Dibenzodioxin"[tw] OR "Polychlorinated Dibenzodioxins"[tiab] OR "Chlorinated Dibenzodioxin"[tw] OR "Chlorinated Dibenzodioxins"[tw] OR "HpCDD"[tw] OR "HxCDD"[tw] OR "OCDD"[tw] OR "PCDD"[tw] OR "PCDDs"[tw] OR "PeCDD"[tw] OR "PnCDD"[tw] OR "TCDBD"[tw] OR "TCDD"[tw] OR "TCDDs"[tw] OR "TeCDD"[tw] OR "1,2,3,4,6,7,8,9-dibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8,9-OCTACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachorodibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8-HEPTACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,6,7,8-heptachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorooxanthrene"[tw] OR "1,2,3,4,6,7,8-Heptapolychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8-HpCDD"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorooxanthrene"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,7,8-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzodioxin"[tw] OR "1,2,3,4,7,8-Hexachlorooxanthrene"[tw] OR "1,2,3,4,7,8-HxCDD"[tw] OR "1,2,3,4,7-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzodioxin"[tw] OR "1,2,3,4,7-Pentachlorooxanthrene"[tw] OR "1,2,3,4-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzodioxin"[tw] OR "1,2,3,4-tetrachlorodibenzodioxine"[tw] OR "1,2,3,4-Tetrachlorooxanthrene"[tw] OR "1,2,3,6,7,8-Hcdd/1,2,3,7,8,9-hcdd"[tw] OR "1,2,3,6,7,8-Hexa polychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzodioxin"[tw] OR "1,2,3,6,7,8-Hexachlorooxanthrene"[tw] OR "1,2,3,6,7,8-HXCDD"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo-p-dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzodioxin"[tw] OR "1,2,3,6,7,9-Hexachlorooxanthrene"[tw] OR "1,2,3,6,7,9-HxCDD"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,7,8,9-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzodioxin"[tw] OR "1,2,3,7,8,9-Hexachlorooxanthrene"[tw] OR "1,2,3,7,8,9-HxCDD"[tw] OR "1,2,3,7,8-PeCDD"[tw] OR "1,2,3,7,8-Penta polychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,7,8-

Table C-2. Database Query Strings

Database search date	Query string
	Pentachlorodibenzodioxin"[tw] OR "1,2,3,7,8-Pentachlorooxanthrene"[tw] OR "1,2,3,7,8-PnCDD"[tw] OR "1,2,3,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,3,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,2,3,8-Tetrachlorodibenzodioxin"[tw] OR "1,2,3,8-Tetrachlorooxanthrene"[tw] OR "1,2,4,6,7,9-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzodioxin"[tw] OR "1,2,4,6,7,9-Hexachlorooxanthrene"[tw] OR "1,2,4,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,4,7,8-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4,7,8-Pentachlorooxanthrene"[tw] OR "1,2,4-Trichlorodibenzo-1,4-dioxin"[tw] OR "1,2,4-Trichlorodibenzo-p-dioxin"[tw] OR "1,2,4-Trichlorodibenzo-para-dioxin"[tw] OR "1,2,4-Trichlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4-Trichlorodibenzodioxin"[tw] OR "1,2,4-Trichlorooxanthrene"[tw] OR "1,2,7,8,-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,7,8-Tetrachlorooxanthrene"[tw] OR "1,3,6,8-TCDD"[tw] OR "1,3,6,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,3,6,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,3,6,8-Tetrachlorodibenzodioxin"[tw] OR "1,3,6,8-Tetrachlorooxanthrene"[tw] OR "1,3,7,8-TCDD"[tw] OR "1,3,7,8-TeCDD"[tw] OR "1,3,7,8-Tetrachlorodibenzo-4-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo[1,4]dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzodioxin"[tw] OR "1,3,7,8-Tetrachlorooxanthrene"[tw] OR "1,3-Dichlorodibenzo-p-dioxin"[tw] OR "1,3-Dichlorodibenzo-para-dioxin"[tw] OR "1,3-Dichlorooxanthrene"[tw] OR "1,6-Dichlorodibenzo-p-dioxin"[tw] OR "1,6-Dichlorodibenzo-para-dioxin"[tw] OR "1,6-Dichlorooxanthrene"[tw] OR "1-CHLORODIBENZO-P-DIOXIN"[tw] OR "1-Chlorodibenzo[b,e][1,4]dioxin"[tw] OR "1-Chlorodibenzodioxin"[tw] OR "1-Chlorooxanthrene"[tw] OR "1-Monochlorodibenzo-p-dioxin"[tw] OR "1-Monochlorodibenzodioxin"[tw] OR "1234678-HpCDD"[tw] OR "2,3,4,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "2,3,4,7,8-Pentachlorodibenzodioxin"[tw] OR "2,3,6,7-Tetrachlorodibenzo-p-dioxin"[tw] OR "2,3,6,7-Tetrachlorodibenzodioxin"[tw] OR "2,3,7,8-TCDD"[tw] OR "2,3,7,8-Tetra polychlorinated dibenzo-p-dioxin"[tw] OR "2,3,7,8-Tetrachlordibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7,8-Tetrachloro-1,4-dioxin"[tw] OR "2,3,7,8-Tetrachloro-dibenzo-p-dioxin"[tw] OR "2,3,7,8-Tetrachloro-p-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo-1,4-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzodioxin"[tw] OR "2,3,7,8-tetrachlorodibenzodioxine"[tw] OR "2,3,7,8-Tetrachlorooxanthrene"[tw] OR "2,3,7,8-tetraclorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7-TRICHLORODIBENZO-P-DIOXIN"[tw] OR "2,3,7-Trichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7-Trichlorooxanthrene"[tw] OR "2,3-Dichlorodibenzo-4-dioxin"[tw] OR "2,3-Dichlorodibenzo-p-dioxin"[tw] OR "2,3-Dichlorodibenzo-para-dioxin"[tw] OR "2,3-Dichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3-Dichlorodibenzodioxin"[tw] OR "2,3-Dichlorooxanthrene"[tw] OR "2,7-Dichlorodibenzo(b,e)(1,4)dioxin"[tw] OR "2,7-Dichlorodibenzo-4-dioxin"[tw] OR "2,7-DICHLORODIBENZO-P-DIOXIN"[tw] OR "2,7-Dichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,7-Dichlorodibenzodioxin"[tw] OR "2,7-Dichlorooxanthrene"[tw] OR "2,8-Dichlorodibenzo-4-dioxin"[tw] OR "2,8-Dichlorodibenzo-para-dioxin"[tw] OR "2,8-Dichlorodibenzodioxin"[tw] OR "2,8-Dichlorooxanthrene"[tw] OR "2-Chlorodibenzo-4-dioxin"[tw] OR "2-Chlorodibenzo-p-dioxin"[tw] OR "2-Chlorodibenzo-para-dioxin"[tw] OR "2-Chlorooxanthrene"[tw] OR "2-Monochlorodibenzo-p-dioxin"[tw] OR "Dichlorodibenzo-p-dioxin"[tw] OR "Hcdd mixture"[tw] OR "Heptachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Heptachlorodibenzo-p-dioxin"[tw] OR "Heptachlorodibenzo-p-dioxins"[tw] OR "Heptachlorodibenzo[b,e][1,4]dioxin"[tw] OR

Table C-2. Database Query Strings

Database search date	Query string
	"Heptachlorodibenzodioxin"[tw] OR "Hexachlorodibenzo-4-dioxin"[tw] OR "Hexachlorodibenzo-p-dioxin"[tw] OR "Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "Hexachlorodibenzodioxin"[tw] OR "HpCDD"[tw] OR "HxCDD"[tw] OR "Markush_benzodioxin"[tw] OR "OCDD"[tw] OR "Octa polychlorinated dibenzo-p-dioxin"[tw] OR "Octachloro-para-dibenzodioxin"[tw] OR "Octachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Octachlorodibenzo-4-dioxin"[tw] OR "Octachlorodibenzo-p-dioxin"[tw] OR "Octachlorodibenzo[b,e][1,4]dioxin"[tw] OR "Octachlorodibenzodioxin"[tw] OR "Octachlorooxanthrene"[tw] OR "PCDD"[tw] OR "PCDDs"[tw] OR "Pentachlorodibenzo-p-dioxin"[tw] OR "Pentachlorodibenzodioxin"[tw] OR "Polychlorinated Dibenzodioxins"[tw] OR "TCDBD"[tw] OR "TCDD"[tw] OR "TCDDs"[tw] OR "Tetrachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Tetrachlorodibenzo-p-dioxin"[tw] OR "TETRACHLORODIBENZO-P-DIOXINS"[tw] OR "Tetrachlorodibenzodioxin"[tw] OR "Tetradioxin"[tw] OR "Dibenzo [b, e] [1,4] dioxina, 1,2,3,4,6,7,8-heptacloro -"[tw] OR "Dibenzo(b,e)(1,4)-dioxin, pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,6-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,7-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,8-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2-chloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, hexachloro"[tw] OR "Dibenzo(b,e)(1,4)dioxin, hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, octachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3-dichloro-"[tw] OR "Dibenzo-p-dioxin, 1,6-dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo-p-dioxin, 2,3-dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,7-dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,8-dichloro-"[tw] OR "Dibenzo-p-dioxin, 1-chloro-"[tw] OR "Dibenzo-p-dioxin, 2-chloro-"[tw] OR "Dibenzo-p-dioxin, hexachloro-"[tw] OR "Dibenzo-p-dioxin, octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin,

Table C-2. Database Query Strings

Database search date	Query string
	1,2,3,4-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,6-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1-chloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,7-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,8-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2-chloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, tetrachloro-"[tw])) OR (("Dioxins"[mh] NOT (monochlorodibenzodioxin* OR chlorodibenzodioxin* OR dichlorodibenzodioxin* OR trichlorodibenzodioxin* OR tetrachlorodibenzodioxin* OR pentachlorodibenzodioxin* OR hexachlorodibenzodioxin* OR heptachlorodibenzodioxin* OR octachlorodibenzodioxin* OR Chlorooxanthrene OR Dichlorooxanthrene OR Heptachlorooxanthrene OR Hexachlorooxanthrene OR Octachlorooxanthrene OR Pentachlorooxanthrene OR Tetrachlorooxanthrene OR Trichlorooxanthrene OR "Tetradioxin"[tw] OR "polychlorinated dibenzo-p-dioxin"[tw] OR "polychlorinated dibenzo-p-dioxins"[tw] OR "chlorinated dibenzo-p-dioxin"[tw] OR "chlorinated dibenzo-p-dioxins"[tw] OR "polychlorinated dioxins"[tw] OR "chlorinated dioxins"[tw] OR "polychloro dibenzo-p-dioxins"[tw] OR "chloro dibenzo-p-dioxins"[tw] OR "tetrachloro dibenzo-p-dioxin"[tw] OR "chlorodibenzo-p-dioxin"[tw] OR "chlorodibenzo-para-dioxin"[tw] OR "chlorodibenzo-4-dioxin"[tw] OR "chlorodibenzo(b,e)(1,4)dioxin"[tw] OR "chlorodibenzo-1,4-dioxin"[tw] OR "monochlorodibenzo-p-dioxin"[tw] OR "monochlorodibenzo-para-dioxin"[tw] OR "monochlorodibenzo-4-dioxin"[tw] OR "monochlorodibenzo(b,e)(1,4)dioxin"[tw] OR "monochlorodibenzo-1,4-dioxin"[tw] OR "Dichlorodibenzo-p-dioxin"[tw] OR "Dichlorodibenzo-para-dioxin"[tw] OR "Dichlorodibenzo-4-dioxin"[tw] OR "Dichlorodibenzo(b,e)(1,4)dioxin"[tw] OR "dichlorodibenzo-1,4-dioxin"[tw] OR "trichlorodibenzo-p-dioxin"[tw] OR "trichlorodibenzo-para-dioxin"[tw] OR "trichlorodibenzo-4-dioxin"[tw] OR "trichlorodibenzo(b,e)(1,4)dioxin"[tw] OR "trichlorodibenzo-1,4-dioxin"[tw] OR "tetrachlorodibenzo-p-dioxin"[tw] OR "tetrachlorodibenzo-para-dioxin"[tw] OR "tetrachlorodibenzo-4-dioxin"[tw] OR "tetrachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "tetrachlorodibenzo-1,4-dioxin"[tw] OR "pentachlorodibenzo-p-dioxin"[tw] OR "pentachlorodibenzo-para-dioxin"[tw] OR "pentachlorodibenzo-4-dioxin"[tw] OR "pentachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "pentachlorodibenzo-1,4-dioxin"[tw] OR "hexachlorodibenzo-p-dioxin"[tw] OR "hexachlorodibenzo-para-dioxin"[tw] OR "hexachlorodibenzo-4-dioxin"[tw] OR "hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "hexachlorodibenzo-1,4-dioxin"[tw] OR "heptachlorodibenzo-p-dioxin"[tw] OR "heptachlorodibenzo-para-dioxin"[tw] OR "heptachlorodibenzo-4-dioxin"[tw] OR "heptachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "heptachlorodibenzo-1,4-dioxin"[tw] OR "octachlorodibenzo-p-dioxin"[tw] OR "octachlorodibenzo-para-dioxin"[tw] OR "octachlorodibenzo-4-dioxin"[tw] OR "octachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "octachlorodibenzo-1,4-dioxin"[tw] OR "Polychlorinated Dibenzodioxin"[tw] OR "Polychlorinated Dibenzodioxins"[tiab] OR "Chlorinated Dibenzodioxin"[tw] OR "Chlorinated Dibenzodioxins"[tw] OR "HpCDD"[tw] OR "HxCDD"[tw] OR "OCDD"[tw] OR "PCDD"[tw] OR "PCDDs"[tw] OR "PeCDD"[tw] OR "PnCDD"[tw] OR "TCDBD"[tw] OR

Table C-2. Database Query Strings

Database search date	Query string
	"TCDD"[tw] OR "TCDDs"[tw] OR "TeCDD"[tw] OR "1,2,3,4,6,7,8,9-dibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8,9-OCTACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachorodibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8-HEPTACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,6,7,8-heptachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorooxanthrene"[tw] OR "1,2,3,4,6,7,8-Heptapolychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8-HpCDD"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorooxanthrene"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,7,8-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzodioxin"[tw] OR "1,2,3,4,7,8-Hexachlorooxanthrene"[tw] OR "1,2,3,4,7,8-HxCDD"[tw] OR "1,2,3,4,7-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzodioxin"[tw] OR "1,2,3,4,7-Pentachlorooxanthrene"[tw] OR "1,2,3,4-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzodioxin"[tw] OR "1,2,3,4-tetrachlorodibenzodioxine"[tw] OR "1,2,3,4-Tetrachlorooxanthrene"[tw] OR "1,2,3,6,7,8-Hcdd/1,2,3,7,8,9-hcdd"[tw] OR "1,2,3,6,7,8-Hexa polychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzodioxin"[tw] OR "1,2,3,6,7,8-Hexachlorooxanthrene"[tw] OR "1,2,3,6,7,8-HXCDD"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo-p-dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzodioxin"[tw] OR "1,2,3,6,7,9-Hexachlorooxanthrene"[tw] OR "1,2,3,6,7,9-HxCDD"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,7,8,9-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzodioxin"[tw] OR "1,2,3,7,8,9-Hexachlorooxanthrene"[tw] OR "1,2,3,7,8,9-HxCDD"[tw] OR "1,2,3,7,8-PeCDD"[tw] OR "1,2,3,7,8-Penta polychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzodioxin"[tw] OR "1,2,3,7,8-Pentachlorooxanthrene"[tw] OR "1,2,3,7,8-PnCDD"[tw] OR "1,2,3,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,3,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,2,3,8-Tetrachlorodibenzodioxin"[tw] OR "1,2,3,8-Tetrachlorooxanthrene"[tw] OR "1,2,4,6,7,9-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzodioxin"[tw] OR "1,2,4,6,7,9-Hexachlorooxanthrene"[tw] OR "1,2,4,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,4,7,8-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4,7,8-Pentachlorooxanthrene"[tw] OR "1,2,4-Trichlorodibenzo-1,4-dioxin"[tw] OR "1,2,4-

Table C-2. Database Query Strings

Database search date	Query string
	Trichlorodibenzo-p-dioxin"[tw] OR "1,2,4-Trichlorodibenzo-para-dioxin"[tw] OR "1,2,4-Trichlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4-Trichlorodibenzodioxin"[tw] OR "1,2,4-Trichlorooxanthrene"[tw] OR "1,2,7,8,-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,7,8-Tetrachlorooxanthrene"[tw] OR "1,3,6,8-TCDD"[tw] OR "1,3,6,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,3,6,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,3,6,8-Tetrachlorodibenzodioxin"[tw] OR "1,3,6,8-Tetrachlorooxanthrene"[tw] OR "1,3,7,8-TCDD"[tw] OR "1,3,7,8-TeCDD"[tw] OR "1,3,7,8-Tetrachlorodibenzo-4-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo[1,4]dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzodioxin"[tw] OR "1,3,7,8-Tetrachlorooxanthrene"[tw] OR "1,3-Dichlorodibenzo-p-dioxin"[tw] OR "1,3-Dichlorodibenzo-para-dioxin"[tw] OR "1,3-Dichlorooxanthrene"[tw] OR "1,6-Dichlorodibenzo-p-dioxin"[tw] OR "1,6-Dichlorodibenzo-para-dioxin"[tw] OR "1,6-Dichlorooxanthrene"[tw] OR "1-CHLORODIBENZO-P-DIOXIN"[tw] OR "1-Chlorodibenzo[b,e][1,4]dioxin"[tw] OR "1-Chlorodibenzodioxin"[tw] OR "1-Chlorooxanthrene"[tw] OR "1-Monochlorodibenzo-p-dioxin"[tw] OR "1-Monochlorodibenzodioxin"[tw] OR "1234678-HpCDD"[tw] OR "2,3,4,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "2,3,4,7,8-Pentachlorodibenzodioxin"[tw] OR "2,3,6,7-Tetrachlorodibenzo-p-dioxin"[tw] OR "2,3,6,7-Tetrachlorodibenzodioxin"[tw] OR "2,3,7,8-TCDD"[tw] OR "2,3,7,8-Tetra polychlorinated dibenzo-p-dioxin"[tw] OR "2,3,7,8-Tetrachlordibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7,8-Tetrachloro-1,4-dioxin"[tw] OR "2,3,7,8-Tetrachloro-dibenzo-p-dioxin"[tw] OR "2,3,7,8-Tetrachloro-p-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo-1,4-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzodioxin"[tw] OR "2,3,7,8-tetrachlorodibenzodioxine"[tw] OR "2,3,7,8-Tetrachlorooxanthrene"[tw] OR "2,3,7,8-tetraclorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7-TRICHLORODIBENZO-P-DIOXIN"[tw] OR "2,3,7-Trichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7-Trichlorooxanthrene"[tw] OR "2,3-Dichlorodibenzo-4-dioxin"[tw] OR "2,3-Dichlorodibenzo-p-dioxin"[tw] OR "2,3-Dichlorodibenzo-para-dioxin"[tw] OR "2,3-Dichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3-Dichlorodibenzodioxin"[tw] OR "2,3-Dichlorooxanthrene"[tw] OR "2,7-Dichlorodibenzo(b,e)(1,4)dioxin"[tw] OR "2,7-Dichlorodibenzo-4-dioxin"[tw] OR "2,7-DICHLORODIBENZO-P-DIOXIN"[tw] OR "2,7-Dichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,7-Dichlorodibenzodioxin"[tw] OR "2,7-Dichlorooxanthrene"[tw] OR "2,8-Dichlorodibenzo-4-dioxin"[tw] OR "2,8-Dichlorodibenzo-para-dioxin"[tw] OR "2,8-Dichlorodibenzodioxin"[tw] OR "2,8-Dichlorooxanthrene"[tw] OR "2-Chlorodibenzo-4-dioxin"[tw] OR "2-Chlorodibenzo-p-dioxin"[tw] OR "2-Chlorodibenzo-para-dioxin"[tw] OR "2-Chlorooxanthrene"[tw] OR "2-Monochlorodibenzo-p-dioxin"[tw] OR "Dichlorodibenzo-p-dioxin"[tw] OR "Hcdd mixture"[tw] OR "Heptachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Heptachlorodibenzo-p-dioxin"[tw] OR "Heptachlorodibenzo-p-dioxins"[tw] OR "Heptachlorodibenzo[b,e][1,4]dioxin"[tw] OR "Heptachlorodibenzodioxin"[tw] OR "Hexachlorodibenzo-4-dioxin"[tw] OR "Hexachlorodibenzo-p-dioxin"[tw] OR "Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "Hexachlorodibenzodioxin"[tw] OR "HpCDD"[tw] OR "HxCDD"[tw] OR "Markush_benzodioxin"[tw] OR "OCDD"[tw] OR "Octa polychlorinated dibenzo-p-dioxin"[tw] OR "Octachloro-para-dibenzodioxin"[tw] OR "Octachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Octachlorodibenzo-4-dioxin"[tw] OR "Octachlorodibenzo-p-dioxin"[tw] OR "Octachlorodibenzo[b,e][1,4]dioxin"[tw] OR "Octachlorodibenzodioxin"[tw] OR "Octachlorooxanthrene"[tw] OR "PCDD"[tw] OR "PCDDs"[tw] OR "Pentachlorodibenzo-p-dioxin"[tw] OR "Pentachlorodibenzodioxin"[tw] OR

Table C-2. Database Query Strings

Database search date	Query string
	"Polychlorinated Dibenzodioxins"[tw] OR "TCDBD"[tw] OR "TCDD"[tw] OR "TCDDs"[tw] OR "Tetrachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Tetrachlorodibenzo-p-dioxin"[tw] OR "TETRACHLORODIBENZO-P-DIOXINS"[tw] OR "Tetrachlorodibenzodioxin"[tw] OR "Tetradioxin"[tw] OR "Dibenzo [b, e] [1,4] dioxina, 1,2,3,4,6,7,8-heptacloro -"[tw] OR "Dibenzo(b,e)(1,4)-dioxin, pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,6-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,7-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,8-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2-chloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, hexachloro"[tw] OR "Dibenzo(b,e)(1,4)dioxin, hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, octachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3-dichloro-"[tw] OR "Dibenzo-p-dioxin, 1,6-dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo-p-dioxin, 2,3-dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,7-dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,8-dichloro-"[tw] OR "Dibenzo-p-dioxin, 1-chloro-"[tw] OR "Dibenzo-p-dioxin, 2-chloro-"[tw] OR "Dibenzo-p-dioxin, hexachloro-"[tw] OR "Dibenzo-p-dioxin, octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,6-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1-chloro-

Table C-2. Database Query Strings

Database search date	Query string
	"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,7-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,8-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2-chloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, tetrachloro-"[tw])) NOT hasabstract)) AND (("Dioxins/toxicity"[mh] OR "Dioxins/adverse effects"[mh] OR "Dioxins/poisoning"[mh] OR "Dioxins/pharmacokinetics"[mh]) OR ("Dioxins"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Dioxins"[mh] AND toxicokinetics[mh:noexp]) OR ("Dioxins/blood"[mh] OR "Dioxins/cerebrospinal fluid"[mh] OR "Dioxins/urine"[mh]) OR ("Dioxins"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Dioxins"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Dioxins/antagonists and inhibitors"[mh]) OR ("Dioxins/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Dioxins"[mh] AND cancer[sb]) OR ("Dioxins/pharmacology"[majr]))) OR (("dioxin"[tw] OR "dioxins"[tw] OR monochlorodibenzodioxin* OR chlorodibenzodioxin* OR dichlorodibenzodioxin* OR trichlorodibenzodioxin* OR tetrachlorodibenzodioxin* OR pentachlorodibenzodioxin* OR hexachlorodibenzodioxin* OR heptachlorodibenzodioxin* OR octachlorodibenzodioxin* OR Chlorooxanthrene OR Dichlorooxanthrene OR Heptachlorooxanthrene OR Hexachlorooxanthrene OR Octachlorooxanthrene OR Pentachlorooxanthrene OR Tetrachlorooxanthrene OR Trichlorooxanthrene OR "Tetradioxin"[tw] OR "Polychlorinated Dibenzodioxin"[tw] OR "Polychlorinated Dibenzodioxins"[tw] OR "Chlorinated Dibenzodioxin"[tw] OR "Chlorinated Dibenzodioxins"[tw] OR "HpCDD"[tw] OR "HxCDD"[tw] OR "OCDD"[tw] OR "PCDD"[tw] OR "PCDDs"[tw] OR "PeCDD"[tw] OR "PnCDD"[tw] OR "TCDBD"[tw] OR "TCDD"[tw] OR "TCDDs"[tw] OR "TeCDD"[tw] OR "1,2,3,4,6,7,8,9-dibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8,9-OCTACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,8,9-Octachorodibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,6,7,8-HEPTACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,6,7,8-heptachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,8-Heptachlorooxanthrene"[tw] OR "1,2,3,4,6,7,8-Heptapolychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,8-HpCDD"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzodioxin"[tw] OR "1,2,3,4,6,7,9-Heptachlorooxanthrene"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,4,7,8-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,4,7,8-

Table C-2. Database Query Strings

Database search date	Query string
	Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzodioxin"[tw] OR "1,2,3,4,7,8-Hexachlorooxanthrene"[tw] OR "1,2,3,4,7,8-HxCDD"[tw] OR "1,2,3,4,7-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4,7-Pentachlorodibenzodioxin"[tw] OR "1,2,3,4,7-Pentachlorooxanthrene"[tw] OR "1,2,3,4-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,4-Tetrachlorodibenzodioxin"[tw] OR "1,2,3,4-tetrachlorodibenzodioxine"[tw] OR "1,2,3,4-Tetrachlorooxanthrene"[tw] OR "1,2,3,6,7,8-Hcdd/1,2,3,7,8,9-hcdd"[tw] OR "1,2,3,6,7,8-Hexa polychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzodioxin"[tw] OR "1,2,3,6,7,8-Hexachlorooxanthrene"[tw] OR "1,2,3,6,7,8-HXCDD"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo-p-dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzodioxin"[tw] OR "1,2,3,6,7,9-Hexachlorooxanthrene"[tw] OR "1,2,3,6,7,9-HxCDD"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,7,8,9-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzo[1,4]dioxin"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzodioxin"[tw] OR "1,2,3,7,8,9-Hexachlorooxanthrene"[tw] OR "1,2,3,7,8,9-HxCDD"[tw] OR "1,2,3,7,8-PeCDD"[tw] OR "1,2,3,7,8-Penta polychlorinated dibenzo-p-dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,3,7,8-Pentachlorodibenzodioxin"[tw] OR "1,2,3,7,8-Pentachlorooxanthrene"[tw] OR "1,2,3,7,8-PnCDD"[tw] OR "1,2,3,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,3,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,2,3,8-Tetrachlorodibenzodioxin"[tw] OR "1,2,3,8-Tetrachlorooxanthrene"[tw] OR "1,2,4,6,7,9-HEXACHLORODIBENZO-P-DIOXIN"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzo-para-dioxin"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzodioxin"[tw] OR "1,2,4,6,7,9-Hexachlorooxanthrene"[tw] OR "1,2,4,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "1,2,4,7,8-Pentachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4,7,8-Pentachlorooxanthrene"[tw] OR "1,2,4-Trichlorodibenzo-1,4-dioxin"[tw] OR "1,2,4-Trichlorodibenzo-p-dioxin"[tw] OR "1,2,4-Trichlorodibenzo-para-dioxin"[tw] OR "1,2,4-Trichlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,4-Trichlorodibenzodioxin"[tw] OR "1,2,4-Trichlorooxanthrene"[tw] OR "1,2,7,8,-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,2,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,2,7,8-Tetrachlorooxanthrene"[tw] OR "1,3,6,8-TCDD"[tw] OR "1,3,6,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,3,6,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,3,6,8-Tetrachlorodibenzodioxin"[tw] OR "1,3,6,8-Tetrachlorooxanthrene"[tw] OR "1,3,7,8-TCDD"[tw] OR "1,3,7,8-TeCDD"[tw] OR "1,3,7,8-Tetrachlorodibenzo-4-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo-para-dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo[1,4]dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "1,3,7,8-Tetrachlorodibenzodioxin"[tw] OR "1,3,7,8-Tetrachlorooxanthrene"[tw] OR "1,3-Dichlorodibenzo-p-dioxin"[tw] OR "1,3-Dichlorodibenzo-para-dioxin"[tw] OR "1,3-Dichlorooxanthrene"[tw] OR "1,6-Dichlorodibenzo-p-dioxin"[tw] OR "1,6-Dichlorodibenzo-para-dioxin"[tw] OR "1,6-Dichlorooxanthrene"[tw] OR "1-CHLORODIBENZO-P-DIOXIN"[tw] OR "1-Chlorodibenzo[b,e][1,4]dioxin"[tw] OR "1-Chlorodibenzodioxin"[tw] OR "1-

Table C-2. Database Query Strings

Database search date	Query string
	Chlorooxanthrene"[tw] OR "1-Monochlorodibenzo-p-dioxin"[tw] OR "1-Monochlorodibenzodioxin"[tw] OR "1234678-HpCDD"[tw] OR "2,3,4,7,8-Pentachlorodibenzo-p-dioxin"[tw] OR "2,3,4,7,8-Pentachlorodibenzodioxin"[tw] OR "2,3,6,7-Tetrachlorodibenzo-p-dioxin"[tw] OR "2,3,6,7-Tetrachlorodibenzodioxin"[tw] OR "2,3,7,8-TCDD"[tw] OR "2,3,7,8-Tetra polychlorinated dibenzo-p-dioxin"[tw] OR "2,3,7,8-Tetrachlordibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7,8-Tetrachloro-1,4-dioxin"[tw] OR "2,3,7,8-Tetrachloro-dibenzo-p-dioxin"[tw] OR "2,3,7,8-Tetrachloro-p-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo-1,4-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo-p-dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7,8-Tetrachlorodibenzodioxin"[tw] OR "2,3,7,8-tetrachlorodibenzodioxine"[tw] OR "2,3,7,8-Tetrachlorooxanthrene"[tw] OR "2,3,7,8-tetraclorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7-TRICHLORODIBENZO-P-DIOXIN"[tw] OR "2,3,7-Trichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3,7-Trichlorooxanthrene"[tw] OR "2,3-Dichlorodibenzo-4-dioxin"[tw] OR "2,3-Dichlorodibenzo-p-dioxin"[tw] OR "2,3-Dichlorodibenzo-para-dioxin"[tw] OR "2,3-Dichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,3-Dichlorodibenzodioxin"[tw] OR "2,3-Dichlorooxanthrene"[tw] OR "2,7-Dichlorodibenzo(b,e)(1,4)dioxin"[tw] OR "2,7-Dichlorodibenzo-4-dioxin"[tw] OR "2,7-DICHLORODIBENZO-P-DIOXIN"[tw] OR "2,7-Dichlorodibenzo[b,e][1,4]dioxin"[tw] OR "2,7-Dichlorodibenzodioxin"[tw] OR "2,7-Dichlorooxanthrene"[tw] OR "2,8-Dichlorodibenzo-4-dioxin"[tw] OR "2,8-Dichlorodibenzo-para-dioxin"[tw] OR "2,8-Dichlorodibenzodioxin"[tw] OR "2,8-Dichlorooxanthrene"[tw] OR "2-Chlorodibenzo-4-dioxin"[tw] OR "2-Chlorodibenzo-p-dioxin"[tw] OR "2-Chlorodibenzo-para-dioxin"[tw] OR "2-Chlorooxanthrene"[tw] OR "2-Monochlorodibenzo-p-dioxin"[tw] OR "Dichlorodibenzo-p-dioxin"[tw] OR "Hcdd mixture"[tw] OR "Heptachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Heptachlorodibenzo-p-dioxin"[tw] OR "Heptachlorodibenzo-p-dioxins"[tw] OR "Heptachlorodibenzo[b,e][1,4]dioxin"[tw] OR "Heptachlorodibenzodioxin"[tw] OR "Hexachlorodibenzo-4-dioxin"[tw] OR "Hexachlorodibenzo-p-dioxin"[tw] OR "Hexachlorodibenzo[b,e][1,4]dioxin"[tw] OR "Hexachlorodibenzodioxin"[tw] OR "HpCDD"[tw] OR "HxCDD"[tw] OR "Markush_benzodioxin"[tw] OR "OCDD"[tw] OR "Octa polychlorinated dibenzo-p-dioxin"[tw] OR "Octachloro-para-dibenzodioxin"[tw] OR "Octachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Octachlorodibenzo-4-dioxin"[tw] OR "Octachlorodibenzo-p-dioxin"[tw] OR "Octachlorodibenzo[b,e][1,4]dioxin"[tw] OR "Octachlorodibenzodioxin"[tw] OR "Octachlorooxanthrene"[tw] OR "PCDD"[tw] OR "PCDDs"[tw] OR "Pentachlorodibenzo-p-dioxin"[tw] OR "Pentachlorodibenzodioxin"[tw] OR "Polychlorinated Dibenzodioxins"[tw] OR "TCDBD"[tw] OR "TCDD"[tw] OR "TCDDs"[tw] OR "Tetrachlorodibenzo(b,e)(1,4)dioxin"[tw] OR "Tetrachlorodibenzo-p-dioxin"[tw] OR "TETRACHLORODIBENZO-P-DIOXINS"[tw] OR "Tetrachlorodibenzodioxin"[tw] OR "Tetradioxin"[tw] OR "Dibenzo [b, e] [1,4] dioxina, 1,2,3,4,6,7,8-heptacloro -"[tw] OR "Dibenzo(b,e)(1,4)-dioxin, pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,3-

Table C-2. Database Query Strings

Database search date	Query string
	dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 1,6-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,3-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,7-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2,8-dichloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, 2-chloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, heptachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, hexachloro"[tw] OR "Dibenzo(b,e)(1,4)dioxin, hexachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, octachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, pentachloro-"[tw] OR "Dibenzo(b,e)(1,4)dioxin, tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo-p-dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 1,3-dichloro-"[tw] OR "Dibenzo-p-dioxin, 1,6-dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo-p-dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo-p-dioxin, 2,3-dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,7-dichloro-"[tw] OR "Dibenzo-p-dioxin, 2,8-dichloro-"[tw] OR "Dibenzo-p-dioxin, 1-chloro-"[tw] OR "Dibenzo-p-dioxin, 2-chloro-"[tw] OR "Dibenzo-p-dioxin, hexachloro-"[tw] OR "Dibenzo-p-dioxin, octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,7-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4,7,8-pentachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,4-trichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,3-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1,6-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 1-chloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3,7-trichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,3-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,7-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2,8-dichloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, 2-chloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, heptachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, hexachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, octachloro-"[tw] OR "Dibenzo[b,e][1,4]dioxin, tetrachloro-"[tw]) NOT medline[sb])) AND (2011/01/01:3000[mhda] OR 2011/01/01:3000[crdat] OR 2011/01/01:3000[edat] OR 2010:3000[dp]))))
01/2011	#1 Search (39227-53-7[rn] OR 39227-54-8[rn] OR 50585-39-2[rn] OR 38178-38-0[rn] OR 29446-15-9[rn] OR 33857-26-0[rn] OR 38964-22-6[rn] OR 39227-58-2[rn] OR 33857-28-2[rn] OR 30746-58-8[rn] OR 53555-02-5[rn] OR 34816-53-0[rn] OR 33423-92-6[rn] OR 50585-46-1[rn] OR 1746 01-6[rn] OR 39227 61-7[rn] OR 40321-76-4[rn] OR 58802-08-7[rn] OR 57653-85-7[rn] OR 64461-98-9[rn] OR 19408-74-3[rn] OR 39227-62-8[rn] OR 34465-46-8[rn] OR 35822-46-9[rn] OR 58200-70-7[rn] OR 37871-00-4[rn] OR 3268 87-9[rn] OR 41903 57-5[rn] OR 36088-22-9[rn] OR 39227-28-6[rn])

Table C-2. Database Query Strings

Database search date	Query string
	#2 Search dioxins[mh] #3 Search #1 OR #2 #4 Search #3 AND 1996:2012[dp] #5 Search #3 AND 1996:2012[mhda] #6 Search #5 AND ("dioxins/adverse effects"[MeSH Terms] OR "dioxins/antagonists and inhibitors"[MeSH Terms] OR "dioxins/blood"[MeSH Terms] OR "dioxins/cerebrospinal fluid"[MeSH Terms] OR "dioxins/pharmacokinetics"[MeSH Terms] OR "dioxins/poisoning"[MeSH Terms] OR "dioxins/toxicity"[MeSH Terms] OR "dioxins/urine"[MeSH Terms]) #7 Search #5 AND dioxins[me] AND (animals[mh] OR humans[mh]) #8 Search #5 AND ("dioxins/me"[majr] AND ("animals"[MeSH Terms] OR "humans"[MeSH Terms]) #9 Search (#5 AND "dioxins/metabolism"[MeSH Major Topic]) AND ("animals"[MeSH Terms] OR "humans"[MeSH Terms]) #10 Search #5 AND (ci[sh] OR environmental exposure[mh]) #11 Search #6 OR #9 OR #10 #12 Search #11 AND dioxins[majr] #13 Search (dioxin OR dioxins OR CHLORODIBENZODIOXIN* OR DICHLORODIBENZODIOXIN* OR DIBENZODIOXIN* OR TRICHLORODIBENZODIOXIN* OR TETRACHLORODIBENZODIOXIN* OR CHLORODIBENZODIOXIN* OR PENTACHLORODIBENZODIOXIN* OR HEXACHLORODIBENZODIOXIN* OR HEPTACHLORODIBENZODIOXIN* OR OCTACHLORODIBENZODIOXIN* OR monochlorodibenzodioxin* OR (cdds[title] OR tcdd*[title] OR pcdd*[title])) AND (in process[sb] OR publisher[sb]) #14 Search #11 OR #13
NTRL	
12/2021	"dioxin" OR "dioxins" OR monochlorodibenzodioxin OR chlorodibenzodioxin OR dichlorodibenzodioxin OR trichlorodibenzodioxin OR tetrachlorodibenzodioxin OR pentachlorodibenzodioxin OR hexachlorodibenzodioxin OR heptachlorodibenzodioxin OR octachlorodibenzodioxin OR Chlorooxanthrene OR Dichlorooxanthrene OR Heptachlorooxanthrene OR Hexachlorooxanthrene OR Octachlorooxanthrene OR Pentachlorooxanthrene OR Tetrachlorooxanthrene OR Trichlorooxanthrene OR Tetradioxin OR "Polychlorinated Dibenzodioxin" OR "Polychlorinated Dibenzodioxins" OR "Chlorinated Dibenzodioxin" OR "Chlorinated Dibenzodioxins" OR "HpCDD" OR "HxCDD" OR "OCDD" OR "PCDD" OR "PCDDs" OR "PeCDD" OR "PnCDD" OR "TCDBD" OR "TCDD" OR "TCDDs" OR "TeCDD"
Toxline	
01/2011	Date limited 1996:2011 39227-53-7 OR 39227-54-8 OR 50585-39-2 OR 38178-38-0 OR 29446-15-9 OR 33857-26-0 OR 38964-22-6 OR 39227-58-2 OR 33857-28-2 OR 30746-58-8 OR 53555-02-5 OR 34816-53-0 OR 33423-92-6 OR 50585-46-1 OR 1746-01-6 OR 39227-61-7 OR 40321-76-4 OR 58802-08-7 OR 57653-85-7 OR 64461-98-9 OR 19408-74-3 OR 39227-62-8 OR 34465-46-8 OR 35822-46-9 OR 58200-70-7 OR 37871-00-4 OR 3268-87-9 OR 41903-57-5 OR 36088-22-9 OR 39227-28-6
Toxcenter	
12/2021	FILE 'TOXCENTER' ENTERED AT 12:08:45 ON 02 DEC 2021 CHARGED TO COST=EH038.16.01.LB.04 L1 28610 SEA FILE=TOXCENTER 39227-53-7 OR 39227-54-8 OR 50585-39-2 OR 38178-38-0 OR 29446-15-9 OR 33857-26-0 OR 38964-22-6 OR

Table C-2. Database Query Strings

Database search date	Query string
	39227-58-2 OR 33857-28-2 OR 30746-58-8 OR 53555-02-5 OR 34816-53-0 OR 33423-92-6 OR 50585-46-1 OR 1746-01-6 OR 41903-57-5
	L2 8297 SEA FILE=TOXCENTER 39227-61-7 OR 40321-76-4 OR 58802-08-7 OR 36088-22-9 OR 57653-85-7 OR 64461-98-9 OR 19408-74-3 OR 39227-62-8 OR 34465-46-8 OR 39227-28-6 OR 35822-46-9 OR 58200-70-7 OR 37871-00-4 OR 3268-87-9
	L3 29768 SEA FILE=TOXCENTER L1 OR L2
	L4 29683 SEA FILE=TOXCENTER L3 NOT TSCATS/FS
	L5 27024 SEA FILE=TOXCENTER L4 NOT PATENT/DT
	L6 5274 SEA FILE=TOXCENTER L5 AND PY>2009
	ACT TOXQUERY/Q

	L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L22 QUE (ENDOCRIN? AND DISRUPT?)
	L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)

Table C-2. Database Query Strings

Database search date	Query string
	L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L29 QUE (NEPHROTOX? OR HEPATOTOX?) L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L35 QUE L32 OR L33 OR L34 L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 --------- L38 3459 SEA FILE=TOXCENTER L6 AND L37 L39 43 SEA FILE=TOXCENTER L38 AND MEDLINE/FS L40 3219 DUP REM L38 (240 DUPLICATES REMOVED) ANSWERS '1-3219' FROM FILE TOXCENTER D SCAN L40
02/2011	(FILE 'HOME' ENTERED AT 14:50:19 ON 01 FEB 2011) FILE 'TOXCENTER' ENTERED AT 14:50:57 ON 01 FEB 2011 CHARGED TO COST=FA529.CF999.0.000.000.ODC CDDS L1 29180 S 39227-53-7 OR 39227-54-8 OR 50585-39-2 OR 38178-38-0 OR 29446 L2 6620 S 39227-62-8 OR 34465-46-8 OR 35822-46-9 OR 58200-70-7 OR 37871 L3 30711 S L1 OR L2 L4 30626 S L3 NOT TSCATS/FS L5 28136 S L4 NOT PATENT/DT L6 15110 S L5 AND PY>1995 ACT TOX/Q --------- L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMA L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT L9 QUE (ACUTE OR SUBACUTE OR LD50 OR LC50) L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT

Table C-2. Database Query Strings

Database search date	Query string
	L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L12 QUE (VAPOR? OR VAPOUR? OR AEROSOL?)
	L13 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L14 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET? OR DRINKING
	L15 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)
	L16 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L17 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OV
	L18 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L19 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERAT
	L20 QUE (SPERM? OR NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPME
	L21 QUE (ENDOCRIN? AND DISRUPT?)
	L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOP
	L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN?)
	L28 QUE GENETIC(W)TOXIC?
	L29 QUE L7 OR L8 OR L9 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 O
	L30 QUE L29 OR L24 OR L25 OR L26 OR L27 OR L28
	L31 QUE L30 OR L10

	L32 8654 S L6 AND L30
	L33 2634 S L32 AND MEDLINE/FS
	L34 2144 S L32 AND BIOSIS/FS
	L35 3685 S L32 AND CAPLUS/FS
	L36 191 S L32 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L37 5952 DUP REM L33 L34 L36 L35 (2702 DUPLICATES REMOVED)
	SAVE TEMP L37 CDDS/A
	L38 2634 S L37
	L39 1298 S L37
	L40 1885 S L37
	L41 135 S L37
	L42 960 S (L37 AND BIOSIS/FS) AND PY>1998
	L43 2634 S L37
	L44 1298 S L37
	L45 1885 S L37
	L46 135 S L37
	L47 1885 S L37 AND CAPLUS/FS
	L48 1149 S L47 AND 4-?/CC
	L49 2634 S L37

Table C-2. Database Query Strings

Database search date	Query string
	L50 1298 S L37 L51 1885 S L37 L52 135 S L37 L53 135 S L37 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L54 2244 S L42 OR L48 OR L53 FILE 'REGISTRY' ENTERED AT 15:07:42 ON 01 FEB 2011 CHARGED TO COST=FA529.CF999.0.000.000.ODC CDDS L55 9 S 39227-62-8 OR 34465-46-8 OR 35822-46-9 OR 58200-70-7 OR 37871 SELECT L55 1-9 CN L56 21 S 39227-53-7 OR 39227-54-8 OR 50585-39-2 OR 38178-38-0 OR 29446 SELECT L56 1-21 CN FILE 'TOXCENTER' ENTERED AT 15:09:53 ON 01 FEB 2011 CHARGED TO COST=FA529.CF999.0.000.000.ODC CDDS L57 1030 S L54 AND (DIOXIN/TI OR DIOXINS/TI) L58 1100 S L54 AND E1-191/TI L59 1330 S L57 OR L58

Table C-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
12/2021	Compounds searched: 39227-53-7; 39227-54-8; 50585-39-2; 38178-38-0; 29446-15-9; 33857-26-0; 38964-22-6; 39227-58-2; 33857-28-2; 30746-58-8; 53555-02-5; 34816-53-0; 33423-92-6; 50585-46-1; 1746-01-6; 41903-57-5; 39227-61-7; 40321-76-4; 58802-08-7; 36088-22-9; 57653-85-7; 64461-98-9; 19408-74-3; 39227-62-8; 34465-46-8; 39227-28-6; 35822-46-9; 58200-70-7; 37871-00-4; 3268-87-9
NTP	
12/2021	39227-53-7 39227-54-8 50585-39-2 38178-38-0 29446-15-9 33857-26-0 38964-22-6 39227-58-2 33857-28-2 30746-58-8 53555-02-5 34816-53-0 33423-92-6 50585-46-1 1746-01-6 41903-57-5 39227-61-7

Table C-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	40321-76-4 58802-08-7 36088-22-9 57653-85-7 64461-98-9 19408-74-3 39227-62-8 34465-46-8 39227-28-6 35822-46-9 58200-70-7 37871-00-4 3268-87-9 "dioxin" "dioxins" "chlorinated dibenzodioxins" "polychlorinated dibenzodioxins" "cdds" "pcdds"
Regulations.gov	
12/2021	Limited to Dockets or EPA notices 39227-53-7 39227-54-8 50585-39-2 38178-38-0 29446-15-9 33857-26-0 38964-22-6 39227-58-2 33857-28-2 30746-58-8 53555-02-5 34816-53-0 33423-92-6 50585-46-1 1746-01-6 41903-57-5 39227-61-7 40321-76-4 58802-08-7 36088-22-9 57653-85-7 64461-98-9 19408-74-3 39227-62-8 34465-46-8 39227-28-6 35822-46-9 58200-70-7 37871-00-4 3268-87-9 Dibenzodioxins "dibenzo-p-dioxin" "tetrachlorodibenzo-p-dioxin" Dioxin

Table C-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
NIH RePORTER	
12/2022	Search Criteria-- Fiscal Year: Active Projects Text Search: "dioxin" OR "dioxins" (advanced) Limit to: Project Title, Project Terms, Project Abstracts Search Criteria-- Fiscal Year: Active Projects Text Search: monochlorodibenzodioxin* OR chlorodibenzodioxin* OR dichlorodibenzodioxin* OR trichlorodibenzodioxin* OR tetrachlorodibenzodioxin* OR pentachlorodibenzodioxin* OR hexachlorodibenzodioxin* OR heptachlorodibenzodioxin* OR octachlorodibenzodioxin* OR Chlorooxanthrene OR Dichlorooxanthrene OR Heptachlorooxanthrene OR Hexachlorooxanthrene OR Octachlorooxanthrene OR Pentachlorooxanthrene OR Tetrachlorooxanthrene OR Trichlorooxanthrene OR "Tetradioxin" OR "Polychlorinated Dibenzodioxin" OR "Polychlorinated Dibenzodioxins" OR "Chlorinated Dibenzodioxin" OR "Chlorinated Dibenzodioxins" OR "HpCDD" OR "HxCDD" OR "OCDD" OR "PCDD" OR "PCDDs" OR "PeCDD" OR "PnCDD" OR "TCDBD" OR "TCDD" OR "TCDDs" OR "TeCDD" (advanced) Limit to: Project Title, Project Terms, Project Abstracts Search Criteria-- Fiscal Year: Active Projects Text Search: "1,2,3,4,6,7,8,9-dibenzo-p-dioxin" OR "1,2,3,4,6,7,8,9-Octachlorodibenzo(1,4)dioxin" OR "1,2,3,4,6,7,8,9-Octachlorodibenzo(b,e)(1,4)dioxin" OR "1,2,3,4,6,7,8,9-OCTACHLORODIBENZO-P-DIOXIN" OR "1,2,3,4,6,7,8,9-Octachlorodibenzo[1,4]dioxin" OR "1,2,3,4,6,7,8,9-Octachlorodibenzodioxin" OR "1,2,3,4,6,7,8,9-Octachorodibenzo-p-dioxin" OR "1,2,3,4,6,7,8-Heptachlorodibenzo(b,e)(1,4)dioxin" OR "1,2,3,4,6,7,8-HEPTACHLORODIBENZO-P-DIOXIN" OR "1,2,3,4,6,7,8-Heptachlorodibenzo-para-dioxin" OR "1,2,3,4,6,7,8-Heptachlorodibenzo[1,4]dioxin" OR "1,2,3,4,6,7,8-Heptachlorodibenzo[b,e][1,4]dioxin" OR "1,2,3,4,6,7,8-heptachlorodibenzodioxin" OR "1,2,3,4,6,7,8-Heptachlorooxanthrene" OR "1,2,3,4,6,7,8-Heptapolychlorinated dibenzo-p-dioxin" OR "1,2,3,4,6,7,8-HpCDD" OR "1,2,3,4,6,7,9-Heptachlorodibenzo-p-dioxin" OR "1,2,3,4,6,7,9-Heptachlorodibenzo-para-dioxin" OR "1,2,3,4,6,7,9-Heptachlorodibenzodioxin" OR "1,2,3,4,6,7,9-Heptachlorooxanthrene" OR "1,2,3,4,7,8-Hexachlorodibenzo(b,e)(1,4)dioxin" OR "1,2,3,4,7,8-HEXACHLORODIBENZO-P-DIOXIN" OR "1,2,3,4,7,8-Hexachlorodibenzo[1,4]dioxin" OR "1,2,3,4,7,8-Hexachlorodibenzo[b,e][1,4]dioxin" OR "1,2,3,4,7,8-Hexachlorodibenzodioxin" OR "1,2,3,4,7,8-Hexachlorooxanthrene" OR "1,2,3,4,7,8-HxCDD" OR "1,2,3,4,7-Pentachlorodibenzo-p-dioxin" OR "1,2,3,4,7-Pentachlorodibenzo-para-dioxin" OR "1,2,3,4,7-Pentachlorodibenzo[b,e][1,4]dioxin" OR "1,2,3,4,7-Pentachlorodibenzodioxin" OR "1,2,3,4,7-Pentachlorooxanthrene" OR "1,2,3,4-Tetrachlorodibenzo-p-dioxin" OR "1,2,3,4-Tetrachlorodibenzo-para-dioxin" OR "1,2,3,4-Tetrachlorodibenzo[b,e][1,4]dioxin" OR "1,2,3,4-Tetrachlorodibenzodioxin" OR "1,2,3,4-tetrachlorodibenzodioxine" OR "1,2,3,4-Tetrachlorooxanthrene" OR "1,2,3,6,7,8-Hcdd/1,2,3,7,8,9-hcdd" OR "1,2,3,6,7,8-Hexa polychlorinated dibenzo-p-dioxin" OR "1,2,3,6,7,8-Hexachlorodibenzo(b,e)(1,4)dioxin" OR "1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin" OR "1,2,3,6,7,8-Hexachlorodibenzo-para-dioxin" OR "1,2,3,6,7,8-Hexachlorodibenzo[1,4]dioxin" OR "1,2,3,6,7,8-Hexachlorodibenzo[b,e][1,4]dioxin" OR "1,2,3,6,7,8-Hexachlorodibenzodioxin" OR "1,2,3,6,7,8-Hexachlorooxanthrene" OR "1,2,3,6,7,8-HXCDD" OR "1,2,3,6,7,9-Hexachlorodibenzo-p-dioxin" OR "1,2,3,6,7,9-Hexachlorodibenzo-para-dioxin" OR "1,2,3,6,7,9-Hexachlorodibenzo[b,e][1,4]dioxin" OR "1,2,3,6,7,9-

Table C-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	Hexachlorodibenzodioxin" OR "1,2,3,6,7,9-Hexachlorooxanthrene" OR "1,2,3,6,7,9-HxCDD" OR "1,2,3,7,8,9-Hexachlorodibenzo(b,e)(1,4)dioxin" OR "1,2,3,7,8,9-HEXACHLORODIBENZO-P-DIOXIN" (advanced) Limit to: Project Title, Project Terms, Project Abstracts Search Criteria-- Fiscal Year: Active Projects Text Search: "1,2,3,7,8,9-Hexachlorodibenzo[1,4]dioxin" OR "1,2,3,7,8,9-Hexachlorodibenzo[b,e][1,4]dioxin" OR "1,2,3,7,8,9-Hexachlorodibenzodioxin" OR "1,2,3,7,8,9-Hexachlorooxanthrene" OR "1,2,3,7,8,9-HxCDD" OR "1,2,3,7,8-PeCDD" OR "1,2,3,7,8-Penta polychlorinated dibenzo-p-dioxin" OR "1,2,3,7,8-Pentachlorodibenzo(b,e)(1,4)dioxin" OR "1,2,3,7,8-Pentachlorodibenzo-p-dioxin" OR "1,2,3,7,8-Pentachlorodibenzo[b,e][1,4]dioxin" OR "1,2,3,7,8-Pentachlorodibenzodioxin" OR "1,2,3,7,8-Pentachlorooxanthrene" OR "1,2,3,7,8-PnCDD" OR "1,2,3,8-Tetrachlorodibenzo-p-dioxin" OR "1,2,3,8-Tetrachlorodibenzo-para-dioxin" OR "1,2,3,8-Tetrachlorodibenzodioxin" OR "1,2,3,8-Tetrachlorooxanthrene" OR "1,2,4,6,7,9-HEXACHLORODIBENZO-P-DIOXIN" OR "1,2,4,6,7,9-Hexachlorodibenzo-para-dioxin" OR "1,2,4,6,7,9-Hexachlorodibenzo[b,e][1,4]dioxin" OR "1,2,4,6,7,9-Hexachlorodibenzodioxin" OR "1,2,4,6,7,9-Hexachlorooxanthrene" OR "1,2,4,7,8-Pentachlorodibenzo-p-dioxin" OR "1,2,4,7,8-Pentachlorodibenzo[b,e][1,4]dioxin" OR "1,2,4,7,8-Pentachlorooxanthrene" OR "1,2,4-Trichlorodibenzo-1,4-dioxin" OR "1,2,4-Trichlorodibenzo-p-dioxin" OR "1,2,4-Trichlorodibenzo-para-dioxin" OR "1,2,4-Trichlorodibenzo[b,e][1,4]dioxin" OR "1,2,4-Trichlorodibenzodioxin" OR "1,2,4-Trichlorooxanthrene" OR "1,2,7,8,-Tetrachlorodibenzo[b,e][1,4]dioxin" OR "1,2,7,8-Tetrachlorodibenzo-p-dioxin" OR "1,2,7,8-Tetrachlorooxanthrene" OR "1,3,6,8-TCDD" OR "1,3,6,8-Tetrachlorodibenzo-p-dioxin" OR "1,3,6,8-Tetrachlorodibenzo-para-dioxin" OR "1,3,6,8-Tetrachlorodibenzodioxin" OR "1,3,6,8-Tetrachlorooxanthrene" OR "1,3,7,8-TCDD" OR "1,3,7,8-TeCDD" OR "1,3,7,8-Tetrachlorodibenzo-4-dioxin" OR "1,3,7,8-Tetrachlorodibenzo-p-dioxin" OR "1,3,7,8-Tetrachlorodibenzo-para-dioxin" OR "1,3,7,8-Tetrachlorodibenzo[1,4]dioxin" OR "1,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin" OR "1,3,7,8-Tetrachlorodibenzodioxin" OR "1,3,7,8-Tetrachlorooxanthrene" OR "1,3-Dichlorodibenzo-p-dioxin" OR "1,3-Dichlorodibenzo-para-dioxin" OR "1,3-Dichlorooxanthrene" OR "1,6-Dichlorodibenzo-p-dioxin" OR "1,6-Dichlorodibenzo-para-dioxin" OR "1,6-Dichlorooxanthrene" OR "1-CHLORODIBENZO-P-DIOXIN" OR "1-Chlorodibenzo[b,e][1,4]dioxin" OR "1-Chlorodibenzodioxin" OR "1-Chlorooxanthrene" OR "1-Monochlorodibenzo-p-dioxin" OR "1-Monochlorodibenzodioxin" OR "1234678-HpCDD" OR "2,3,4,7,8-Pentachlorodibenzo-p-dioxin" OR "2,3,4,7,8-Pentachlorodibenzodioxin" OR "2,3,6,7-Tetrachlorodibenzo-p-dioxin" OR "2,3,6,7-Tetrachlorodibenzodioxin" OR "2,3,7,8-TCDD" (advanced) Limit to: Project Title, Project Terms, Project Abstracts Search Criteria-- Fiscal Year: Active Projects Text Search: "2,3,7,8-Tetra polychlorinated dibenzo-p-dioxin" OR "2,3,7,8-Tetrachlordibenzo[b,e][1,4]dioxin" OR "2,3,7,8-Tetrachloro-1,4-dioxin" OR "2,3,7,8-Tetrachloro-dibenzo-p-dioxin" OR "2,3,7,8-Tetrachloro-p-dioxin" OR "2,3,7,8-Tetrachlorodibenzo(b,e)(1,4)dioxin" OR "2,3,7,8-Tetrachlorodibenzo-1,4-dioxin" OR "2,3,7,8-Tetrachlorodibenzo-p-dioxin" OR "2,3,7,8-Tetrachlorodibenzo[b,e][1,4]dioxin" OR "2,3,7,8-Tetrachlorodibenzodioxin" OR "2,3,7,8-tetrachlorodibenzodioxine" OR "2,3,7,8-Tetrachlorooxanthrene" OR "2,3,7,8-tetraclorodibenzo[b,e][1,4]dioxin" OR "2,3,7-TRICHLORODIBENZO-P-DIOXIN" OR "2,3,7-Trichlorodibenzo[b,e][1,4]dioxin" OR "2,3,7-Trichlorooxanthrene" OR "2,3-Dichlorodibenzo-4-dioxin" OR "2,3-

Table C-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	Dichlorodibenzo-p-dioxin" OR "2,3-Dichlorodibenzo-para-dioxin" OR "2,3-Dichlorodibenzo[b,e][1,4]dioxin" OR "2,3-Dichlorodibenzodioxin" OR "2,3-Dichlorooxanthrene" OR "2,7-Dichlorodibenzo(b,e)(1,4)dioxin" OR "2,7-Dichlorodibenzo-4-dioxin" OR "2,7-DICHLORODIBENZO-P-DIOXIN" OR "2,7-Dichlorodibenzo[b,e][1,4]dioxin" OR "2,7-Dichlorodibenzodioxin" OR "2,7-Dichlorooxanthrene" OR "2,8-Dichlorodibenzo-4-dioxin" OR "2,8-Dichlorodibenzo-para-dioxin" OR "2,8-Dichlorodibenzodioxin" OR "2,8-Dichlorooxanthrene" OR "2-Chlorodibenzo-4-dioxin" OR "2-Chlorodibenzo-p-dioxin" OR "2-Chlorodibenzo-para-dioxin" OR "2-Chlorooxanthrene" OR "2-Monochlorodibenzo-p-dioxin" OR "Dichlorodibenzo-p-dioxin" OR "Hcdd mixture" OR "Heptachlorodibenzo(b,e)(1,4)dioxin" OR "Heptachlorodibenzo-p-dioxin" OR "Heptachlorodibenzo-p-dioxins" OR "Heptachlorodibenzo[b,e][1,4]dioxin" OR "Heptachlorodibenzodioxin" OR "Hexachlorodibenzo-4-dioxin" OR "Hexachlorodibenzo-p-dioxin" OR "Hexachlorodibenzo[b,e][1,4]dioxin" OR "Hexachlorodibenzodioxin" OR "HpCDD" OR "HxCDD" OR "Markush_benzodioxin" OR "OCDD" OR "Octa polychlorinated dibenzo-p-dioxin" OR "Octachloro-para-dibenzodioxin" OR "Octachlorodibenzo(b,e)(1,4)dioxin" OR "Octachlorodibenzo-4-dioxin" OR "Octachlorodibenzo-p-dioxin" OR "Octachlorodibenzo[b,e][1,4]dioxin" OR "Octachlorodibenzodioxin" OR "Octachlorooxanthrene" OR "PCDD" OR "PCDDs" OR "Pentachlorodibenzo-p-dioxin" OR "Pentachlorodibenzodioxin" OR "Polychlorinated Dibenzodioxins" OR "TCDBD" OR "TCDD" OR "TCDDs" OR "Tetrachlorodibenzo(b,e)(1,4)dioxin" OR "Tetrachlorodibenzo-p-dioxin" OR "TETRACHLORODIBENZO-P-DIOXINS" OR "Tetrachlorodibenzodioxin" OR "Tetradioxin" (advanced) Limit to: Project Title, Project Terms, Project Abstracts Search Criteria-- Fiscal Year: Active Projects Text Search: "Dibenzo [b, e] [1,4] dioxina, 1,2,3,4,6,7,8-heptacloro -" OR "Dibenzo(b,e)(1,4)-dioxin, pentachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,6,7,8-heptachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,6,7,9-heptachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,7,8-hexachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4,7-pentachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,4-tetrachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,6,7,8-hexachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,6,7,9-hexachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,7,8-pentachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,2,3,8-tetrachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4,6,7,9-hexachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4,7,8-pentachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,2,4-trichloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,2,7,8-tetrachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,3,6,8-tetrachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,3,7,8-tetrachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,3-dichloro-" OR "Dibenzo(b,e)(1,4)dioxin, 1,6-dichloro-" OR "Dibenzo(b,e)(1,4)dioxin, 2,3,7,8-tetrachloro-" OR "Dibenzo(b,e)(1,4)dioxin, 2,3,7-trichloro-" OR "Dibenzo(b,e)(1,4)dioxin, 2,3-dichloro-" OR "Dibenzo(b,e)(1,4)dioxin, 2,7-dichloro-" OR "Dibenzo(b,e)(1,4)dioxin, 2,8-dichloro-" OR "Dibenzo(b,e)(1,4)dioxin, 2-chloro-" OR "Dibenzo(b,e)(1,4)dioxin, heptachloro-" OR "Dibenzo(b,e)(1,4)dioxin, hexachloro" OR "Dibenzo(b,e)(1,4)dioxin, hexachloro-" OR "Dibenzo(b,e)(1,4)dioxin, octachloro-" OR "Dibenzo(b,e)(1,4)dioxin, pentachloro-" OR "Dibenzo(b,e)(1,4)dioxin, tetrachloro-" OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,8,9-octachloro-" OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,8-heptachloro-" OR "Dibenzo-p-dioxin, 1,2,3,4,6,7,9-heptachloro-" OR "Dibenzo-p-dioxin, 1,2,3,4,7,8-hexachloro-" OR "Dibenzo-p-dioxin, 1,2,3,4,7-pentachloro-" OR "Dibenzo-p-dioxin, 1,2,3,4-tetrachloro-" OR "Dibenzo-p-dioxin, 1,2,3,6,7,8-hexachloro-" OR "Dibenzo-p-dioxin, 1,2,3,6,7,9-hexachloro-" OR "Dibenzo-p-dioxin, 1,2,3,7,8,9-hexachloro-" OR "Dibenzo-p-dioxin, 1,2,3,7,8-

Table C-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	pentachloro-" OR "Dibenzo-p-dioxin, 1,2,3,8-tetrachloro-" OR "Dibenzo-p-dioxin, 1,2,4,6,7,9-hexachloro-" OR "Dibenzo-p-dioxin, 1,2,4,7,8-pentachloro-" OR "Dibenzo-p-dioxin, 1,2,4-trichloro-" OR "Dibenzo-p-dioxin, 1,2,7,8-tetrachloro-" OR "Dibenzo-p-dioxin, 1,3,6,8-tetrachloro-" OR "Dibenzo-p-dioxin, 1,3,7,8-tetrachloro-" OR "Dibenzo-p-dioxin, 1,3-dichloro-" OR "Dibenzo-p-dioxin, 1,6-dichloro-" OR "Dibenzo-p-dioxin, 2,3,7,8-tetrachloro-" OR "Dibenzo-p-dioxin, 2,3,7-trichloro-" OR "Dibenzo-p-dioxin, 2,3-dichloro-" (advanced) Limit to: Project Title, Project Terms, Project Abstracts Search Criteria-- Fiscal Year: Active Projects Text Search: "Dibenzo-p-dioxin, 2,7-dichloro-" OR "Dibenzo-p-dioxin, 2,8-dichloro-" OR "Dibenzo-p-dioxin, 1-chloro-" OR "Dibenzo-p-dioxin, 2-chloro-" OR "Dibenzo-p-dioxin, hexachloro-" OR "Dibenzo-p-dioxin, octachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,8,9-octachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,8-heptachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,6,7,9-heptachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,7,8-hexachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4,7-pentachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,4-tetrachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,6,7,8-hexachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,6,7,9-hexachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,7,8,9-hexachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,7,8-pentachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,3,8-tetrachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,4,6,7,9-hexachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,4,7,8-pentachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,4-trichloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,2,7,8-tetrachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,3,6,8-tetrachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,3,7,8-tetrachloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,3-dichloro-" OR "Dibenzo[b,e][1,4]dioxin, 1,6-dichloro-" OR "Dibenzo[b,e][1,4]dioxin, 1-chloro-" OR "Dibenzo[b,e][1,4]dioxin, 2,3,7,8-tetrachloro-" OR "Dibenzo[b,e][1,4]dioxin, 2,3,7-trichloro-" OR "Dibenzo[b,e][1,4]dioxin, 2,3-dichloro-" OR "Dibenzo[b,e][1,4]dioxin, 2,7-dichloro-" OR "Dibenzo[b,e][1,4]dioxin, 2,8-dichloro-" OR "Dibenzo[b,e][1,4]dioxin, 2-chloro-" OR "Dibenzo[b,e][1,4]dioxin, heptachloro-" OR "Dibenzo[b,e][1,4]dioxin, hexachloro-" OR "Dibenzo[b,e][1,4]dioxin, octachloro-" OR "Dibenzo[b,e][1,4]dioxin, tetrachloro-" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2011 and 2021 results were:

- Number of records identified from PubMed, NTRL, Toxline, and TOXCENTER (after duplicate removal): 5,535
- Number of records identified from addendum search and other strategies: 742
- Total number of records to undergo literature screening: 6,277

C.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on CDDs:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table C-1 for inclusion criteria) were moved to the

second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

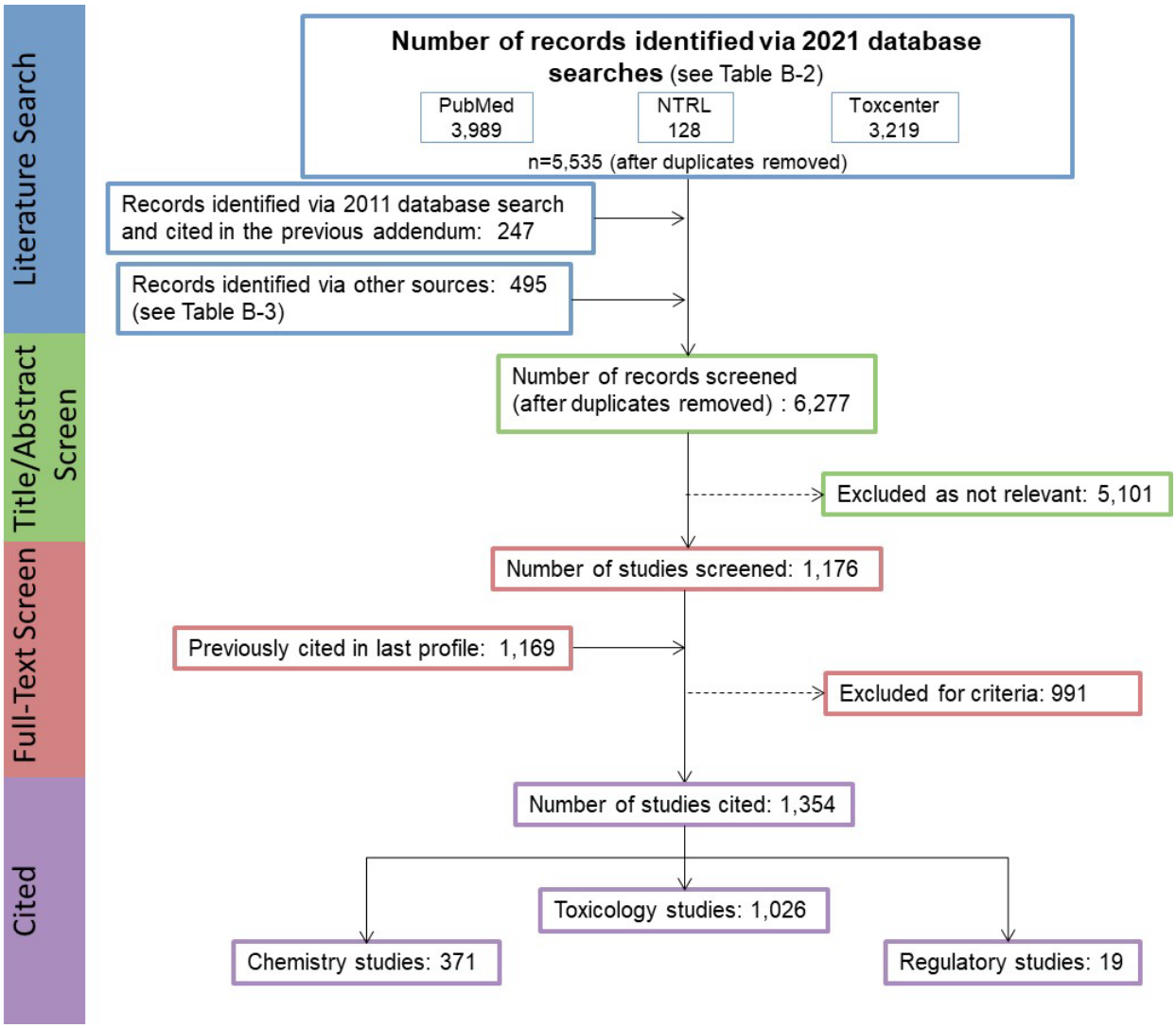
- Number of titles and abstracts screened: 6,277
- Number of studies considered relevant and moved to the next step: 1,176

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 1,176
- Number of studies cited in the pre-public draft of the toxicological profile: 1,169
- Total number of studies cited in the profile: 1,354

A summary of the results of the literature search and screening is presented in Figure C-1.

Figure C-1. January 2011 and December 2021 Literature Search Results and Screen for Chlorinated Dibenzo-*p*-Dioxins



APPENDIX D. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR CHLORINATED DIBENZO-*P*-DIOXINS

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to CDDs, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to thallium:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

D.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to CDDs. The inclusion criteria used to identify relevant studies examining the health effects of CDDs are presented in Table D-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table D-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects

Table D-1. Inclusion Criteria for Identifying Health Effects Studies

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

D.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of CDDs. The literature search framework for the toxicological profile is discussed in detail in Appendix C.

D.2.1 Literature Search

As noted in Appendix C, the current literature search was intended to update the 1998 toxicological profile for CDDs; thus, the literature search was restricted to studies published between January 1996 and December 2021. See Appendix C for the databases searched and the search strategy.

A total of 6,277 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

D.2.2 Literature Screening

As described in Appendix C, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of CDDs.

Title and Abstract Screen. In the Title and Abstract Screen step, 6,277 records were reviewed; 362 documents were considered to meet the health effects inclusion criteria in Table D-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 600 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed.

D.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table D-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table D-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for CDDs and overviews of the results of oral and dermal exposure studies (no inhalation exposure animals studies were identified) are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (2-2, 2-3, 2-4, and 2-5).

D.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for CDDs identified in human studies and 2,3,7,8-TCDD and other CDDs in animal studies are presented in Tables D-3, D-4, and D-5, respectively. Available human studies include occupational exposure studies, studies of communities living near point sources, communities affected by accidental releases, and general population studies. The toxicity of CDDs, particularly 2,3,7,8-TCDD, has been extensively evaluated in a number of laboratory animal species. Most of the studies involved acute-duration oral exposure. Primarily based on the animal studies, the most sensitive effects include developmental toxicity, immunotoxicity, reproductive toxicity, and hepatotoxicity. Developmental, immunological, reproductive, and hepatic toxicity are widely established critical endpoints of CDDs. Thus, ATSDR has opted to not conduct a systematic review.

Table D-3. Overview of the Health Outcomes for CDDs Evaluated in Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Cohort	2	3	8		3	1	4	3	8		8	3	4	14	69		26
	2	2	6		0	1	3	1	6		5	3	2	8	48		19
Case-control									1				1	4	6		7
									1				1	2	2		7
Cross-sectional	2	5	16	6	5	2	11	4	8		21	14	15	8	12		2
	2	3	10	3	1	0	9	1	8		17	12	11	5	7		0
Case report/case series	2						2		7								1
	2						2		6								1

Number of studies examining endpoint	0	1–4	5–9	10–14	15–19	20–24	≥25
Number of studies reporting outcome	0	1–4	5–9	10–14	15–19	20–24	≥25

Table D-4. Overview of the Health Outcomes for 2,3,7,8-TCDD Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	
Oral studies																	
Acute-duration	44	1	3	6	8	2	27	4	2	1	14	51	3	18	163	7	0
	35	0	2	5	4	2	24	2	2	1	12	43	2	16	158	7	0
Intermediate-duration	20	8	5	6	8	7	15	7	4	2	10	20		21	11	3	1
	13	2	4	4	6	6	15	4	3	2	7	17		15	11	2	0
Chronic-duration	5	5	5	4	4	3	4	4	5	3	6	5	4	7	1	1	8
	3	3	3	1	1	0	4	2	2	0	4	3	1	4	1	1	6
Dermal studies																	
Acute-duration									1	1							
									1	1							
Intermediate-duration	3	1					3		4			1					3
	3	1					3		4			1					3
Chronic-duration	1	1	1	1	1		1	1	1					1			1
	0	0	0	0	0		0	0	0					0			1

Number of studies examining endpoint	0	1–4	5–9	10–14	15–20	20–24	25–29	≥30	
Number of studies reporting outcome	0	1–4	5–9	10–14	15–20	20–24	25–29	≥30	

APPENDIX D

Table D-5. Overview of the Health Outcomes for Other CDD Congeners Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	
Oral studies																	
Acute-duration	10				1	6	4	1			7	11		3	10		1
	8				0	6	0	1			7	10		0	4		1
Intermediate-duration	5				5		6		2		3	2					
	5				5		5		2		3	2					
Chronic-duration	4	4	4	4	4	4	4	4	4	4							4
	3	1	0	0	0	0	4	0	0	0							3
Dermal studies																	
Acute-duration										3							
										3							
Intermediate-duration																	
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10	

APPENDIX E. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page E-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page E-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

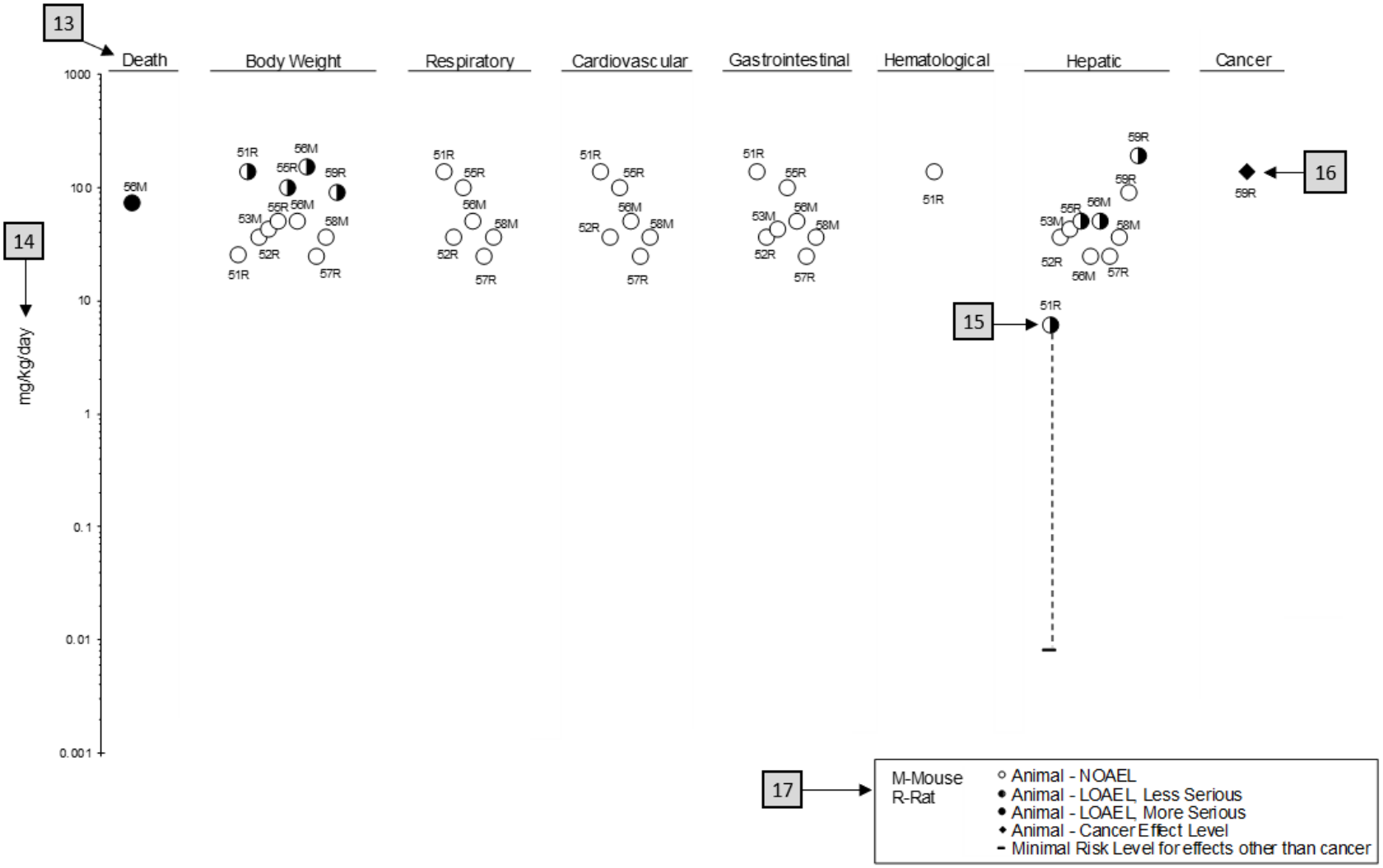
(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX F. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/clinician-briefs-overviews.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 400 7th Street, S.W., Suite 5W, Washington, DC 20024 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX G. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or malignant tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The exposure level of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this exposure level, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—Occupational exposure limits recommended by the National Institute for Occupational Safety and Health (NIOSH) as time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX H. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
ED_{30}	effective dose, 30% response
ED_{50}	effective dose, 50% response
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration

FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
GD	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram

NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TEQ	Toxic equivalency
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor

U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result