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.

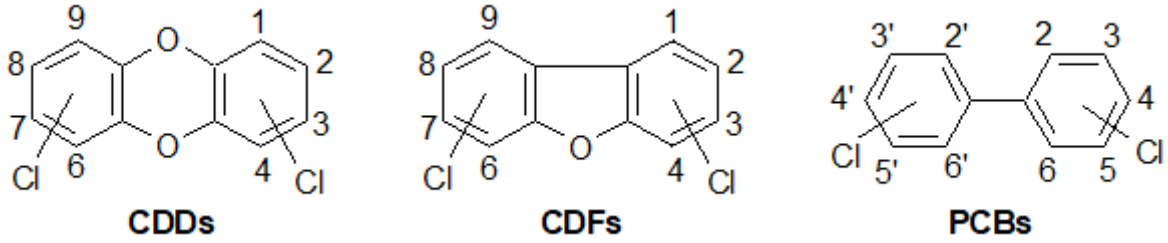
The U.S. Environmental Protection Agency (EPA) 2004 Dioxin Reassessment characterized background exposures to dioxin-like compounds, including an estimate of an average background intake dose and an average background body burden (Lorber et al. 2009). These quantities were derived from data generated 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)

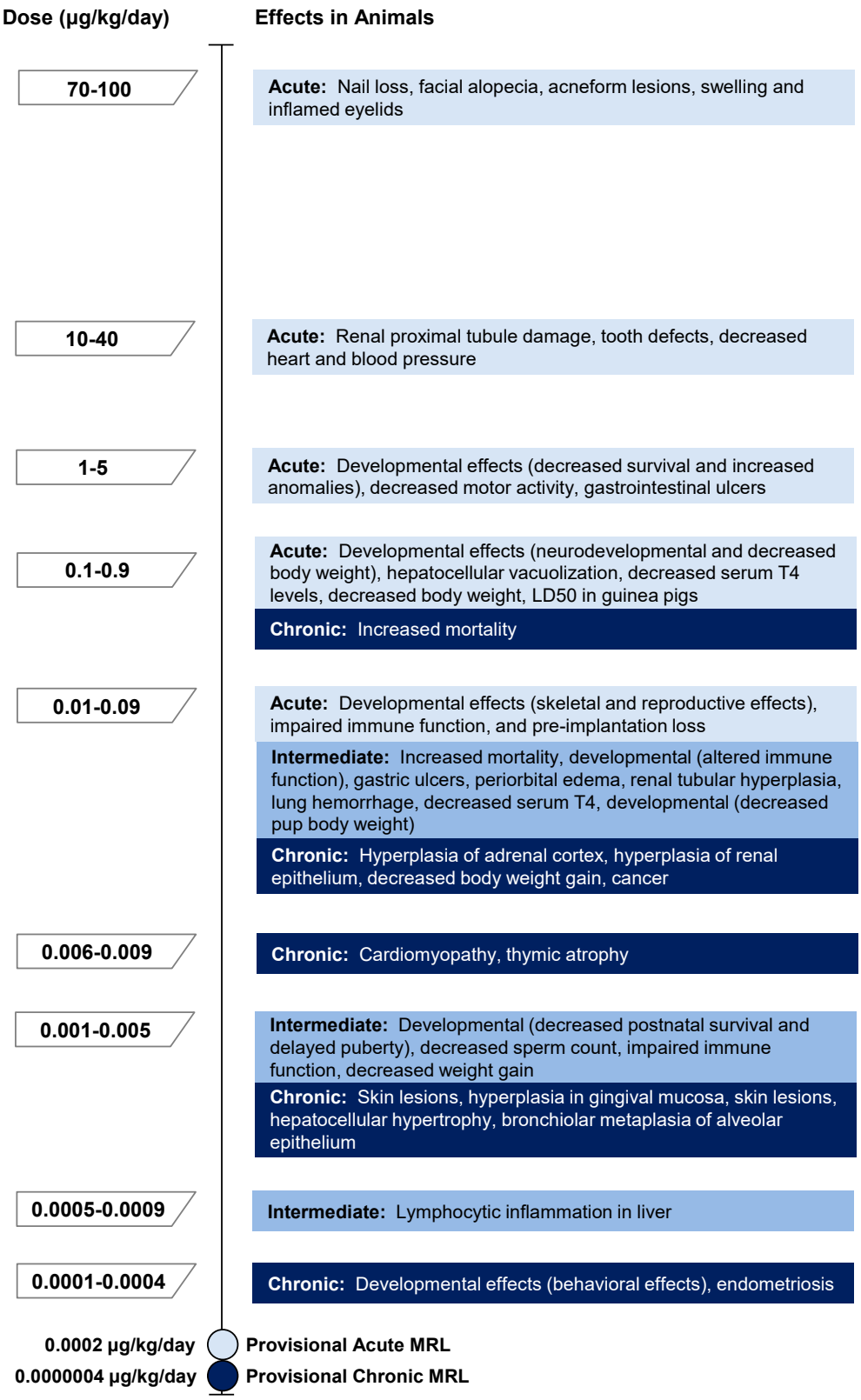
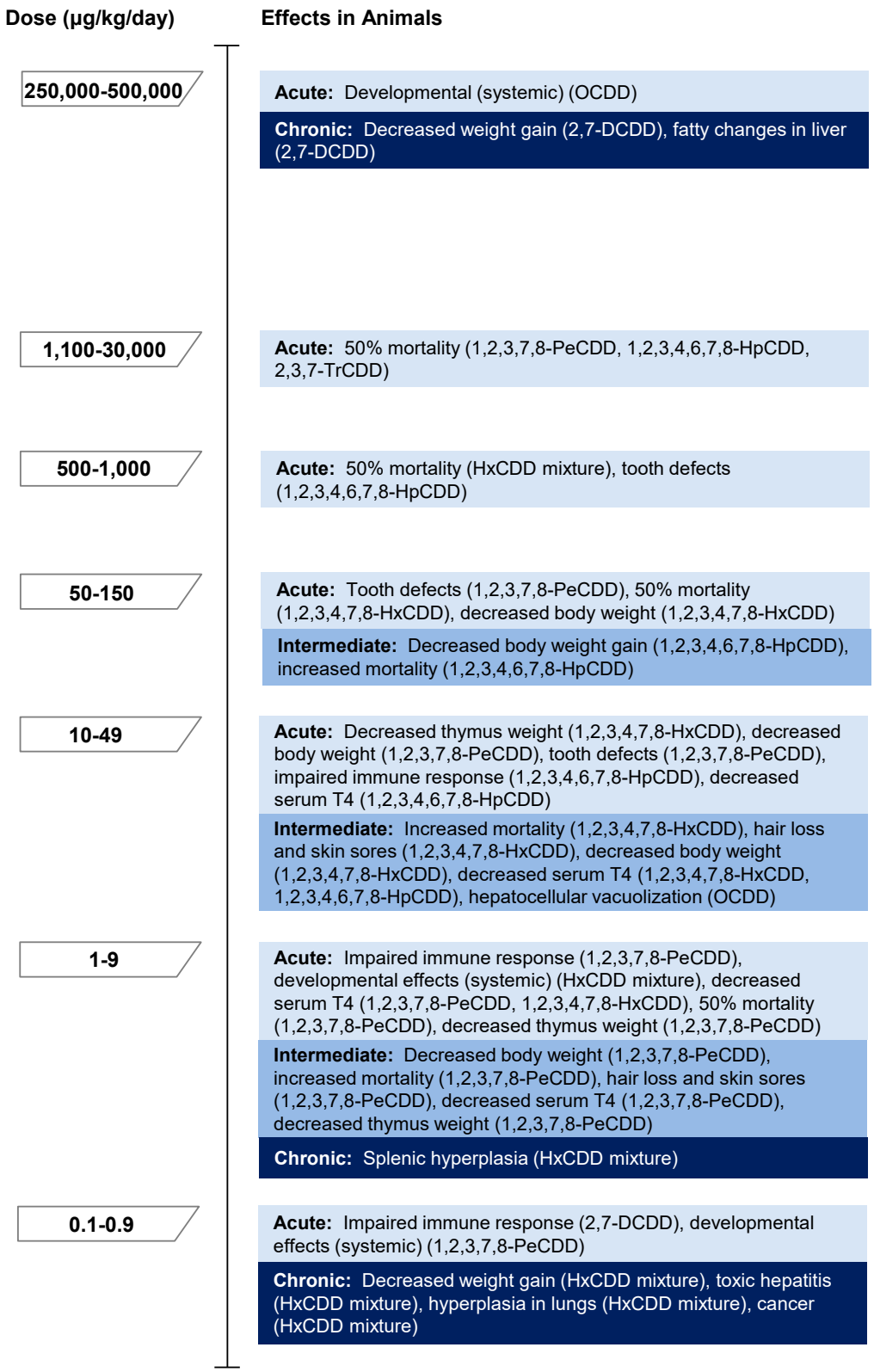


Figure 1-3. Health Effects Found in Animals Following Oral Exposure to Other Chlorinated Dibenzo-*p*-Dioxins (CDDs)



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.

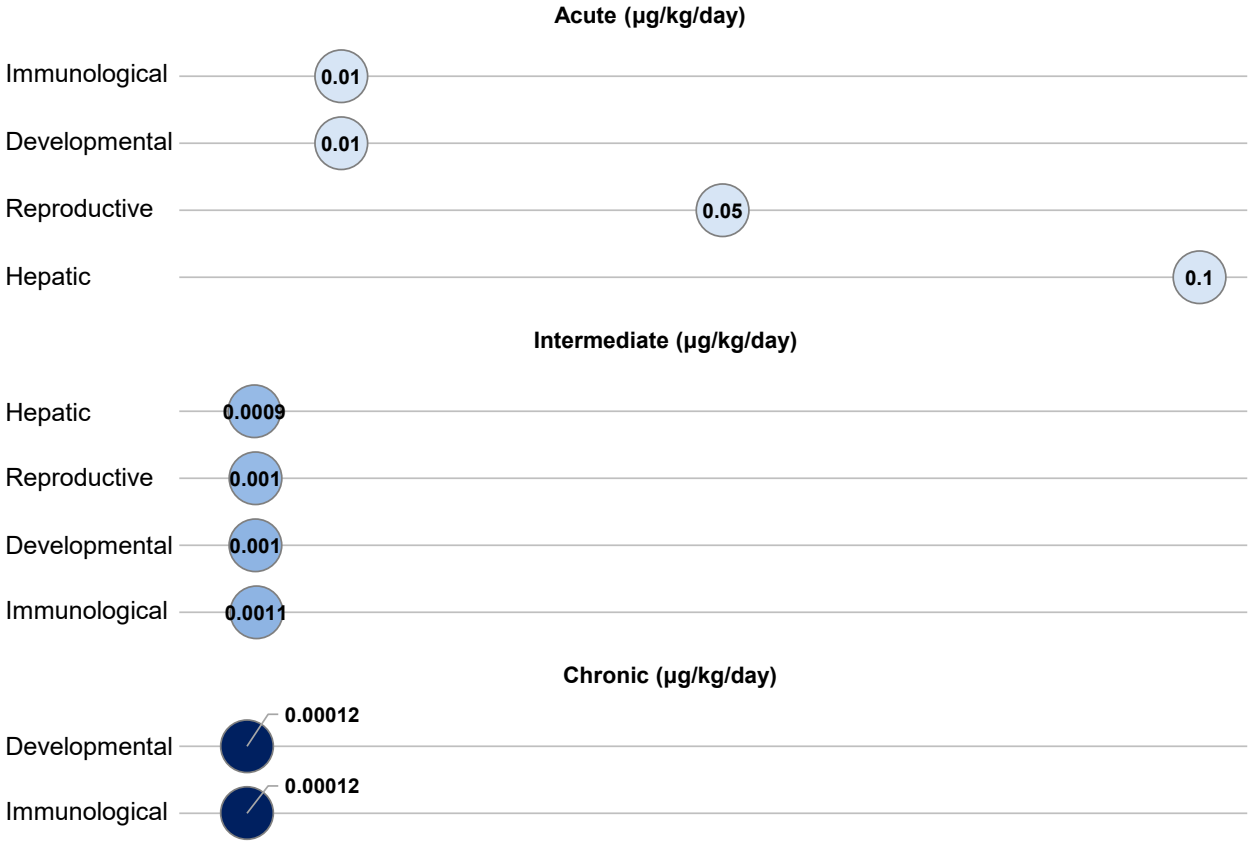


Figure 1-5. Summary of Sensitive Targets of 2,7-Dichlorodibenzo-*p*-Dioxin (2,7-DCDD) – Oral

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.

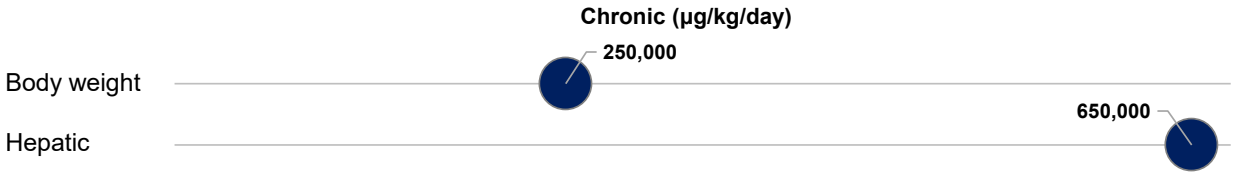


Figure 1-6. Summary of Sensitive Targets of 2,3,7-Trichlorodibenzo-*p*-Dioxin (2,3,7-TrCDD) – Oral

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.

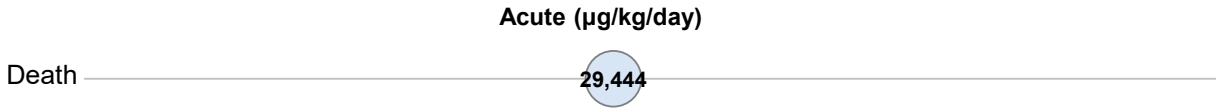


Figure 1-7. Summary of Sensitive Targets of 1,2,3,7,8-Pentachlorodibenzo-*p*-Dioxin (1,2,3,7,8-PeCDD) – Oral

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.

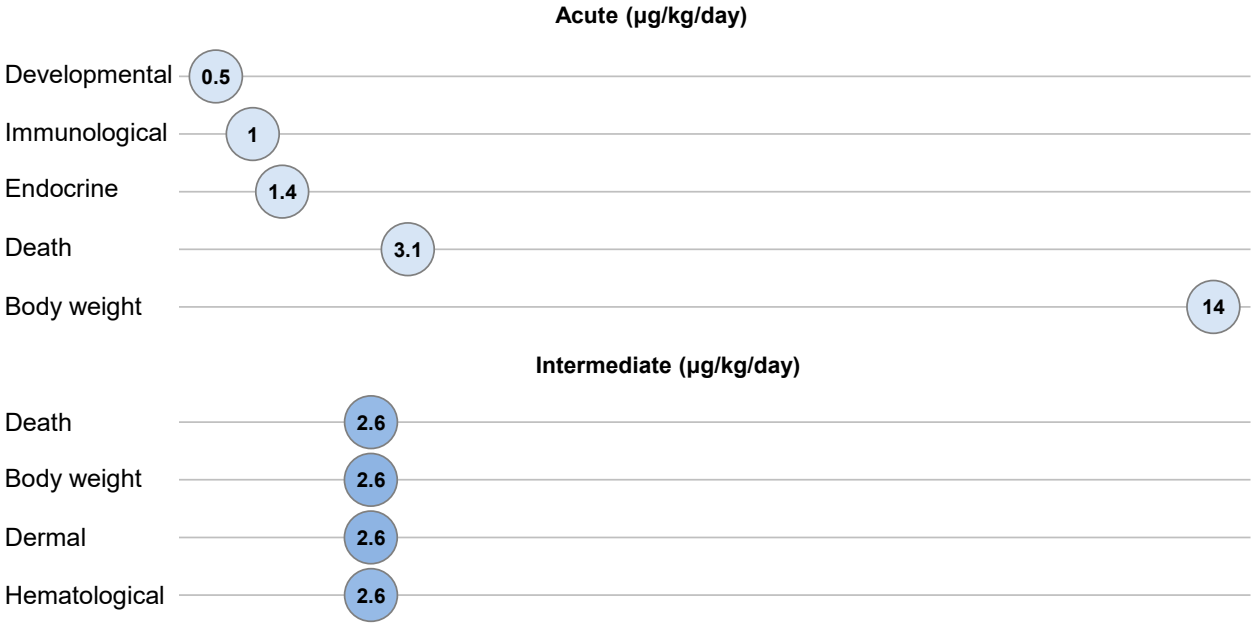


Figure 1-8. Summary of Sensitive Targets of 1,2,4,7,8-Pentachlorodibenzo-*p*-Dioxin (1,2,4,7,8-PeCDD) – Oral

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.

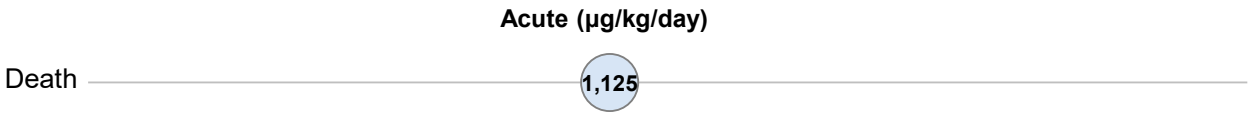


Figure 1-9. Summary of Sensitive Targets of 1,2,3,4,7,8-Hexachlorodibenzo-*p*-Dioxin (1,2,3,4,7,8-HxCDD) – Oral

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.

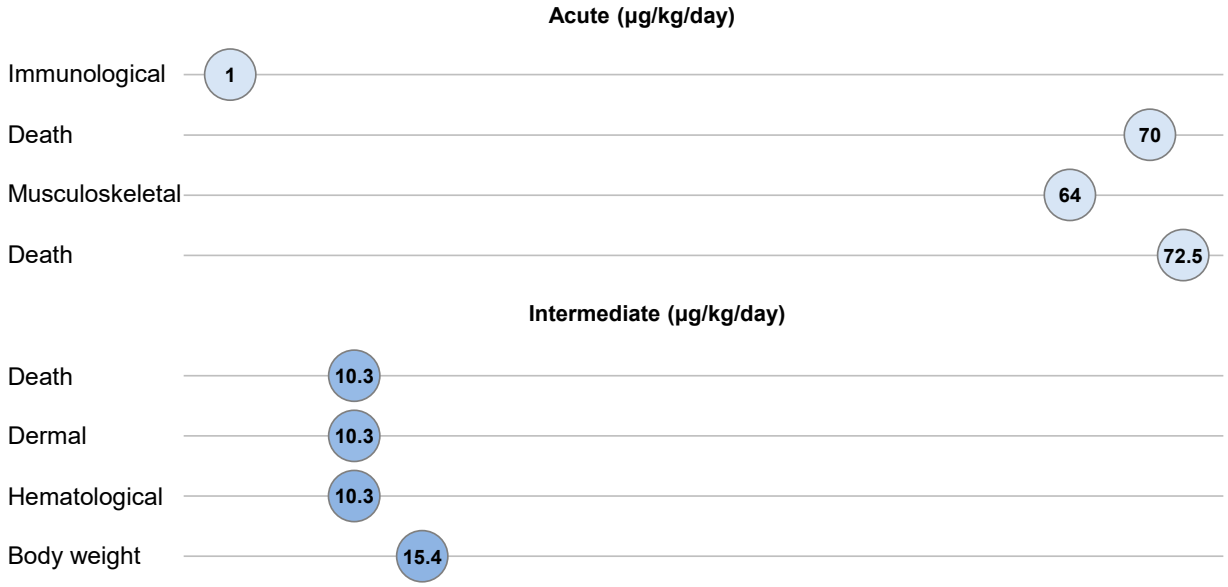


Figure 1-10. Summary of Sensitive Targets of 1,2,3,6,7,8-Hexachlorodibenzo-*p*-Dioxin (1,2,3,6,7,8-HxCDD) – Oral

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.

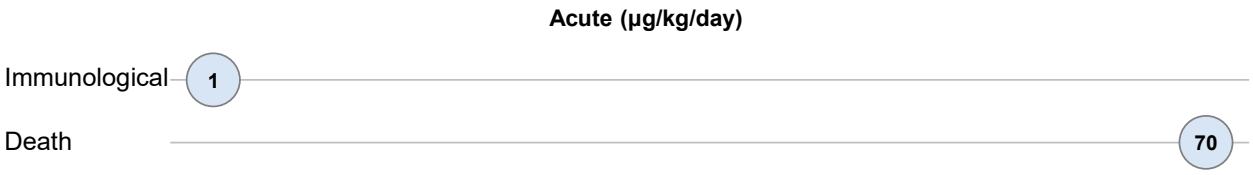


Figure 1-11. Summary of Sensitive Targets of 1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-Dioxin (HpCDD) – Oral

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.

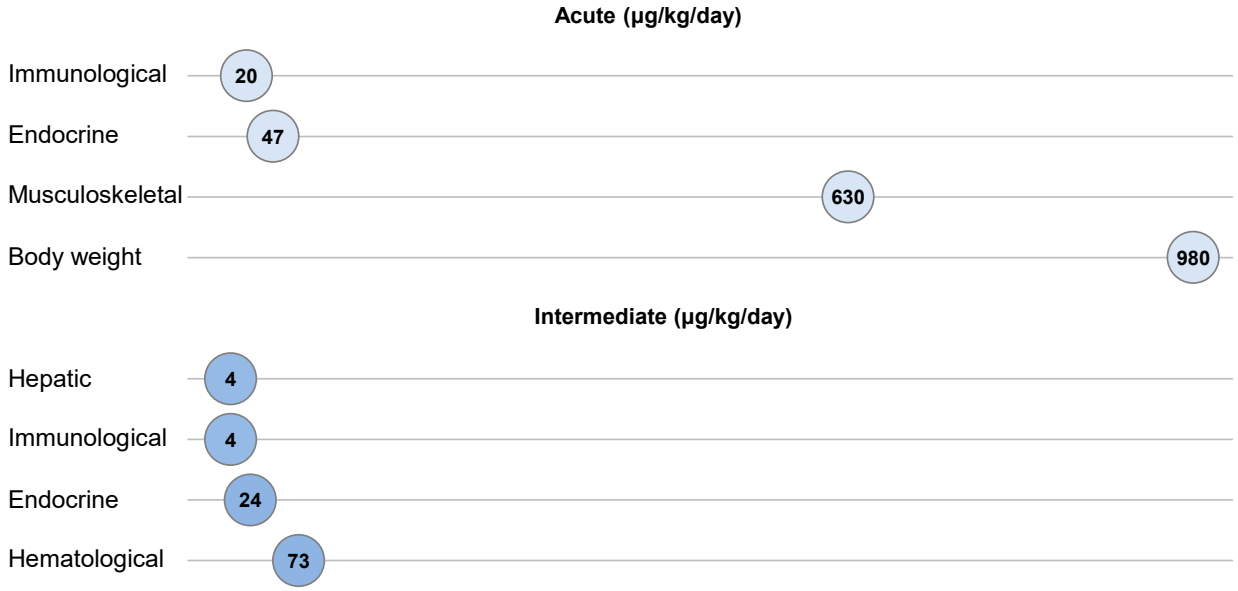


Figure 1-12. Summary of Sensitive Targets of Octachlorodibenzo-*p*-Dioxin (OCDD) – Oral

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.

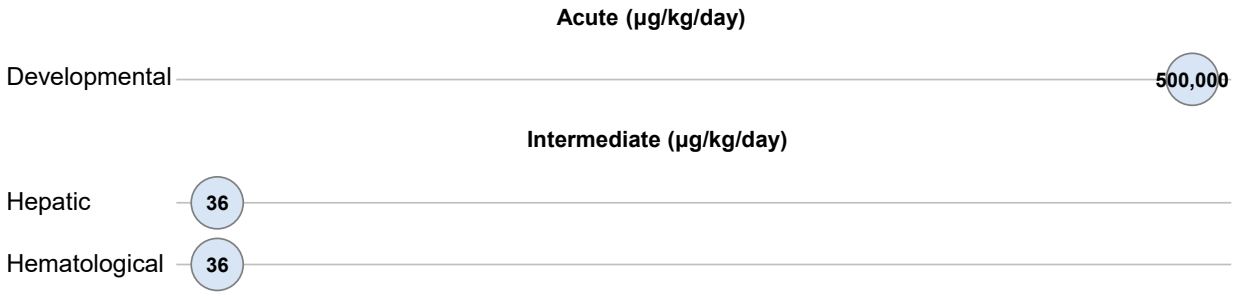


Table 1-1. Minimal Risk Levels (MRLs) for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)[a]

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