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

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Database search date	Query string
	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.

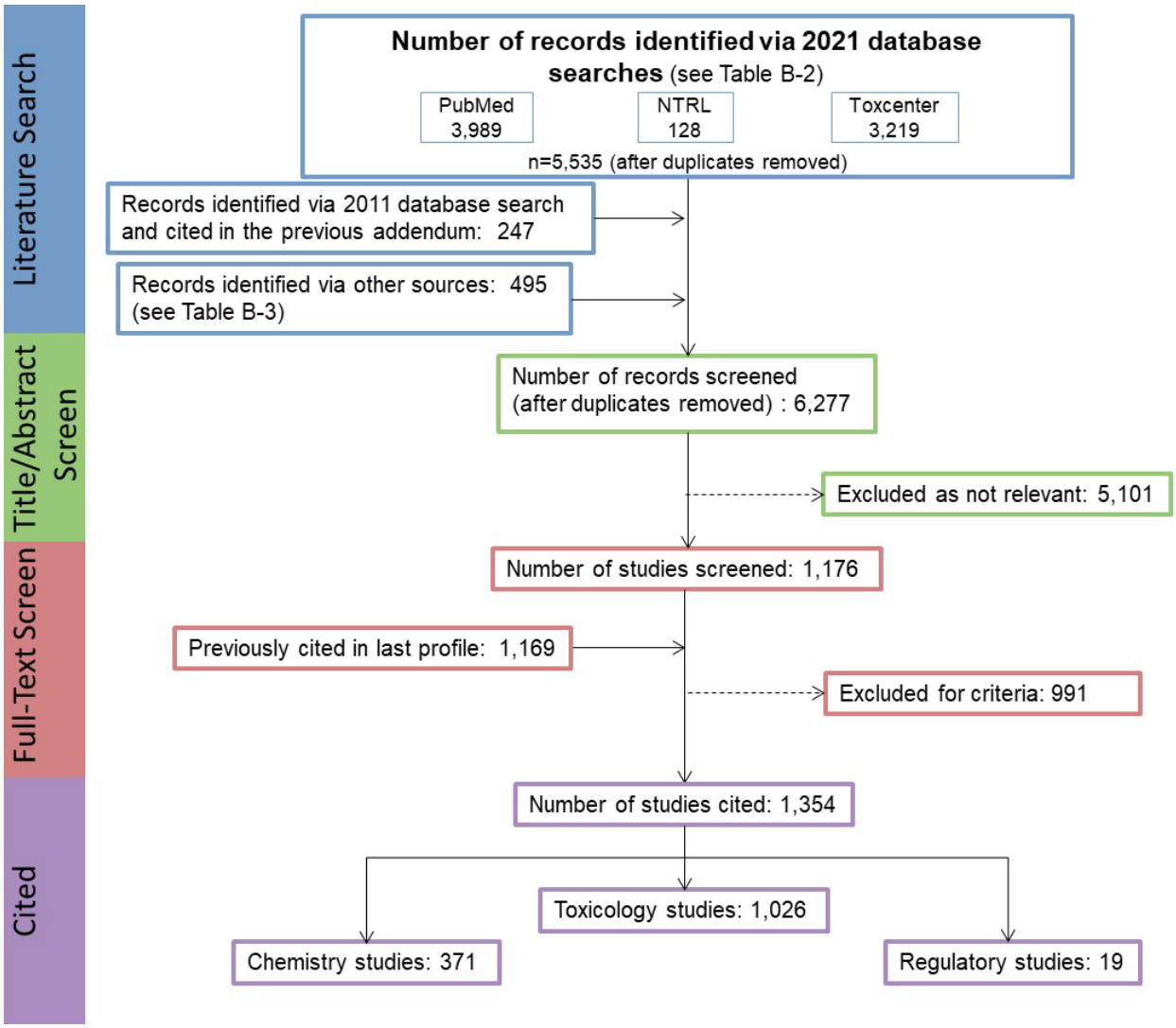
- Number of titles and abstracts screened: 6,277
- Number of studies considered relevant and moved to the next step: 1,176

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.

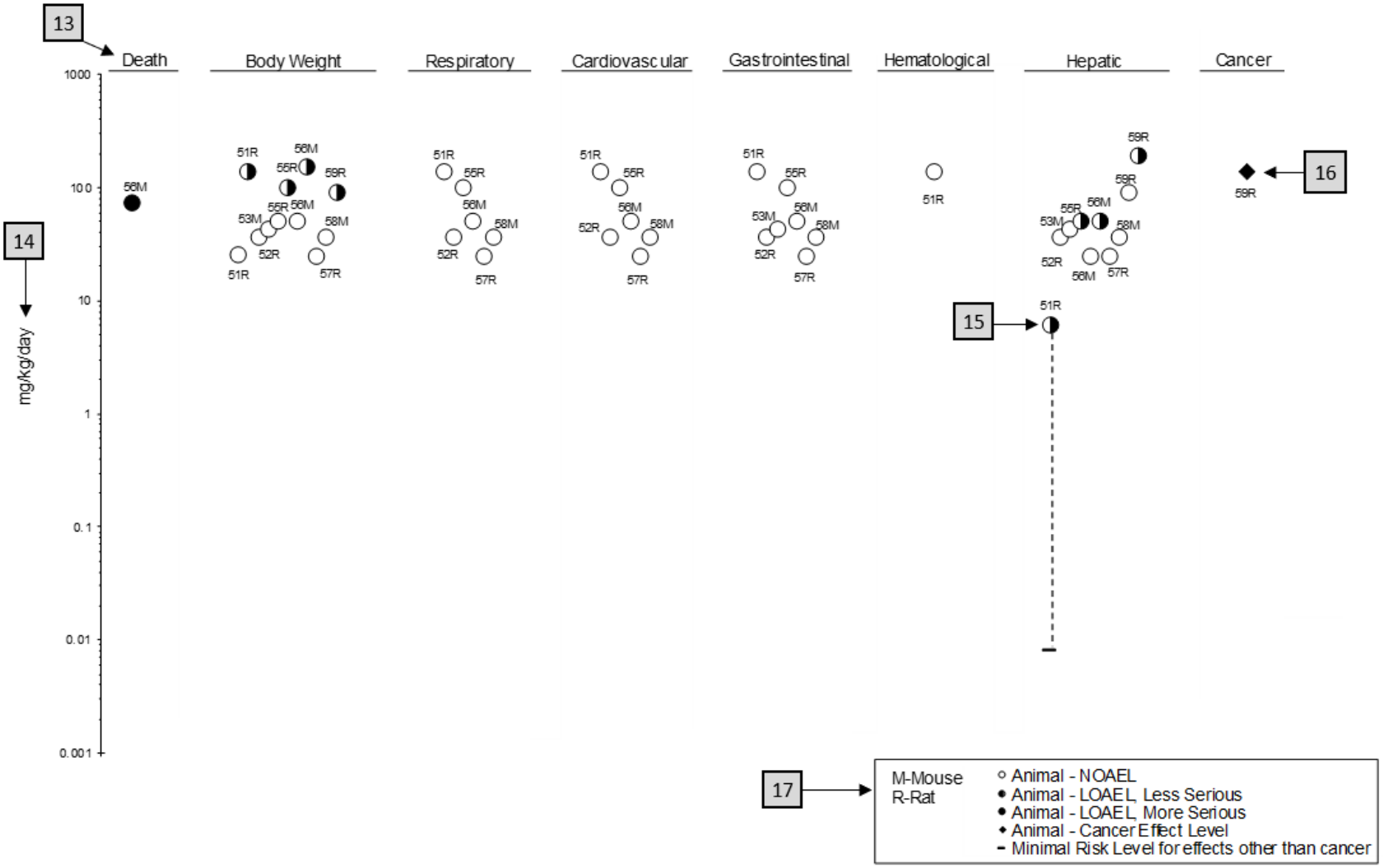
(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

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