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. Serious health effects (such as irreparable damage to the liver or kidneys, or 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.

APPENDIX A

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.

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INTRODUCTION

In the environment, humans are rarely exposed to a single CDF congener; exposure is typically to complex mixtures of CDFs, CDDs, and PCBs. For most adverse health effects, 2,3,7,8-substituted CDFs and CDDs, and some non-ortho substituted PCBs share a common mechanism of action that is mediated through the Ah receptor. To evaluate the toxicity associated with exposure to mixtures of CDFs, CDDs, and PCBs, a TEF approach has been developed for 2,3,7,8-substituted congeners. The TEF approach involves assessment of the comparative effects of individual congeners on various biological endpoints; derivation of TEFs is based on the upper range of potency data for these effects. The TEF approach compares the relative potency of individual congeners to that of 2,3,7,8-TCDD, which is the most extensively studied of the halogenated aromatic hydrocarbons that interact with the Ah receptor. The TEF for 2,3,7,8-TCDD is defined as unity; TEFs for all other CDD congeners, CDFs, and dioxin-like PCBs are ≤1, thus reflecting their lower toxic potency. The WHO 2005 TEFs for 2,3,7,8-substituted CDFs are presented in Table A-1; see Table 2-1 for a list of TEFs for CDDs and PCBs (van den Berg et al. 2006). The TEQ for a mixture of congeners is the sum of the products of the TEFs for each congener and its concentration in the mixture.

Table A-1. Summary of World Health Organization (WHO) 2005 Toxicity Equivalency Factors (TEFs) for 2,3,7,8-Substituted Chlorodibenzofurans (CDFs)

Compound	TEF
2,3,7,8-TetraCDF	0.1
1,2,3,7,8-PentaCDF	0.03
2,3,4,7,8-PentaCDF	0.3
1,2,3,4,7,8-HexaCDF	0.1
1,2,3,6,7,8-HexaCDF	0.1
1,2,3,7,8,9-HexaCDF	0.1
2,3,4,6,7,8-HexaCDF	0.1
1,2,3,4,6,7,8-HeptaCDF	0.01
1,2,3,4,7,8,9-HeptaCDF	0.01
OctaCDF	0.0003

Source: van den Berg et al. 2006

MRLs derived for 2,3,7,8-substituted CDFs based on empirical data are presented in Table A-2. Toxicity data were only available for seven 2,3,7,8-substituted CDF congeners and the databases were considered

adequate to derive an intermediate MRL for 1,2,3,7,8-pentaCDF; acute, intermediate and chronic oral MRLs for 2,3,4,7,8-pentaCDF; and an intermediate MRL for 1,2,3,6,7,8-hexaCDF.

Table A-2. Oral Minimal Risk Levels for 2,3,7,8-Substituted Chlorodibenzofurans (CDFs) Derived Using Congener Specific Toxicity Data

	MRL		
CDF congener	Acute (µg/kg/day)	Intermediate (µg/kg/day)	Chronic (µg/kg/day)
2,3,7,8-TetraCDF	ND	ND	ND
1,2,3,7,8-PentaCDF	ND	0.007 ($7x10^{-3}$)	ND
2,3,4,7,8-PentaCDF	0.0005 ($5x10^{-4}$)	0.000007 ($7x10^{-6}$)	0.000004 ($4x10^{-6}$)
1,2,3,4,7,8-HexaCDF	ND	ND	ND
1,2,3,6,7,8-HexaCDF	ND	0.005 ($5x10^{-3}$)	ND
1,2,3,4,6,7,8-HeptaCDF	ND	ND	ND
OctaCDF	ND	ND	ND

ND = not derived due to inadequacies of the database

An alternative approach would be to derive MRLs for 2,3,7,8-substituted CDF congeners using 2,3,7,8-TCDD MRLs adjusted by the TEF and assuming that the TEFs are equal in magnitude across all exposure durations. As presented in ATSDR (1998), acute-, intermediate-, and chronic-duration oral MRLs are available for 2,3,7,8-TCDD. The acute oral MRL of 0.0002 µg/kg/day is based on impaired immune response in mice, the intermediate oral MRL of 0.00002 µg/kg/day is based on decreased thymus weight in guinea pigs, and the chronic oral MRL of 0.000001 µg/kg/day is based on developmental effects in monkeys. To calculate a TEF-derived CDF MRL, the duration-specific 2,3,7,8-TCDD MRL is divided by the TEF for the CDF congener. For example,

TEF-derived acute oral MRL for 2,3,4,7,8-pentaCDF = 2,3,7,8-TCDD acute oral MRL ÷ TEF
TEF-derived acute oral MRL for 2,3,4,7,8-pentaCDF = 0.0002 µg/kg/day ÷ 0.3
TEF-derived acute oral MRL for 2,3,4,7,8-pentaCDF = 0.0007 µg/kg/day

CDF MRLs derived using this approach are presented in Table A-3. The TEF-derived MRLs for the 2,3,4,7,8-pentaCDF chronic duration and for 1,2,3,6,7,8-hexaCDF intermediate duration are similar to empirically based MRLs. The TEF-derived intermediate oral MRL for 1,2,3,7,8-pentaCDF and the acute-duration MRL for 2,3,4,7,8-pentaCDF are an order of magnitude lower than the empirically based MRLs, and the TEF-derived intermediate oral MRL for 2,3,4,7,8-pentaCDF is an order of magnitude higher than

the empirically based MRL. Empirical-based MRLs are preferred over the TEF-based MRLs because they are based on experimental data for the exposure route and duration.

Table A-3. Oral Minimal Risk Levels for Chlorodibenzofurans (CDFs) Derived Using a Toxicity Equivalency Factor (TEF) Approach

	MRL[a]		
CDF congener	Acute (µg/kg/day)	Intermediate (µg/kg/day)	Chronic (µg/kg/day)
2,3,7,8-TetraCDF	0.002	0.0002	0.00001
1,2,3,7,8-PentaCDF	0.007	0.0007	0.00003
2,3,4,7,8-PentaCDF	0.0007	0.00007	0.000003
1,2,3,4,7,8-HexaCDF	0.002	0.0002	0.00001
1,2,3,6,7,8-HexaCDF	0.002	0.0002	0.00001
1,2,3,7,8,9-HexaCDF	0.002	0.0002	0.00001
2,3,4,6,7,8-HexaCDF	0.002	0.0002	0.00001
1,2,3,4,6,7,8-HeptaCDF	0.02	0.002	0.0001
1,2,3,4,7,8,9-HeptaCDF	0.02	0.002	0.0001
OctaCDF	0.7	0.07	0.003

[a]MRLs are calculated by dividing the MRL for 2,3,7,8-tetraCDD by the TEF. The acute, intermediate, and chronic oral MRLs for 2,3,7,8-CDD are 0.0002, 0.00002, and 0.000001 µg/kg/day (ATSDR 1998), respectively. The TEFs are presented in Table A-1.

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,7,8-Tetrachlorodibenzofuran
CAS Numbers: 51207-31-9
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Acute, Intermediate, and Chronic

MRL Summary: There are insufficient data for the derivation of acute-, intermediate-, or chronic-duration inhalation MRLs for 2,3,7,8-tetraCDF 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-tetraCDF following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,7,8-Tetrachlorodibenzofuran
CAS Numbers: 51207-31-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: The acute-duration oral database for 2,3,7,8-tetraCDF is considered inadequate for derivation of an MRL. Although the available studies identify several targets of toxicity, the database was considered inadequate for identifying the most sensitive target of toxicity.

Rationale for Not Deriving an MRL: A small number of acute oral exposure studies evaluated the toxicity of 2,3,7,8-tetraCDF. Studies by Moore et al. (1976, 1979) evaluated a number of potential endpoints following a single gavage exposure of monkeys, mice, or guinea pigs; the animals were allowed to recover for 30 (mice and guinea pigs) or 60 (monkeys) days. The remaining studies focused on thyroid hormone levels (Crofton et al. 2005; Ross et al. 2000) or developmental toxicity (Taura et al. 2014; Weber et al. 1984, 1985), but did not evaluate other endpoints. The results of these studies are summarized in Table A-4. A mouse study reporting no histological alterations in major tissues or organs at <6,000 µg/kg (Moore et al. 1976, 1979) is not included in the table.

Table A-4. Summary of Health Effects Following Acute-Duration Oral Exposure to 2,3,7,8-Tetrachlorodibenzofuran

Species, duration	NOAEL (µg/kg/day)	LOAEL (µg/kg/day)	Effect	Reference
Body weight effects				
Monkey 1 day		500	Decreased body weight gain (magnitude not reported)	Moore et al. 1979
		1,000 (serious LOAEL)	Weight loss	
Guinea pig 1 day		1	Decreased body weight gain (magnitude not reported)	Moore et al. 1979
		10 (serious LOAEL)	Rapid and progressive weight loss	
Hematological effects				
Monkey 1 day		500	Mild anemia	Moore et al. 1979
Dermal and ocular effects				
Monkey 1 day		500	Facial edema, occluded or dilated ceruminous and sebaceous glands, nail loss, epidermal hyperkeratosis Occluded or dilated meibomian glands, eyelash loss	Moore et al. 1979

Table A-4. Summary of Health Effects Following Acute-Duration Oral Exposure to 2,3,7,8-Tetrachlorodibenzofuran

Species, duration	NOAEL (µg/kg/day)	LOAEL (µg/kg/day)	Effect	Reference
Endocrine effects				
Rat 4 days		4.65	Decrease (30%) in serum total T4 levels	Crofton et al. 2005
Rat 4 days	0.3	1	Decrease (26%) in serum total T4 levels	Ross et al. 2000
Immunological effects				
Guinea pig 1 day		5	Marked decrease in thymus size	Moore et al. 1979
Developmental effects				
Mouse GD 10		10 (serious LOAEL)	Hydronephrosis	Weber et al. 1984
Rat GD 15	15	50	Altered sexual behavior in male offspring (ED_{50} for decreases in serum luteinizing hormone levels at 21.5–25.5 µg/kg and growth hormone at 12.6–27.4 µg/kg)	Taura et al. 2014
Mouse GD 10		250 (serious LOAEL)	Fetal mortality, hydronephrosis	Weber et al. 1984
Mouse GD 10		300 (serious LOAEL)	Hydronephrosis	Weber et al. 1985

ED_{50} = 50% effective dose; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; T4 = thyroxine

Four studies have identified LOAEL values between 1 and 10 µg/kg: decreases in serum total T4 levels in rats at 1 and 4.65 µg/kg (Crofton et al. 2005; Ross et al. 2000), marked decrease in thymus size in guinea pigs at 5 µg/kg (Moore et al. 1979), and fetal hydronephrosis at 10 µg/kg (Weber et al. 1984). Although the intermediate-duration data for 2,3,7,8-tetraCDF and acute- and intermediate-duration databases for 2,3,4,7,8-pentaCDF provide support for identifying the thyroid, thymus, and developing fetus as sensitive targets of toxicity, the acute-duration oral database for 2,3,7,8-tetraCDF was not considered adequate for identifying the most sensitive target of acute oral toxicity of 2,3,7,8-tetraCDF. The acute oral database is missing a reliable study that examined multiple potential targets of toxicity. The Crofton et al. (2005), Ross et al. (2000), and Weber et al. (1984) studies only examined single endpoints. The Moore et al. (1979) study examined a number of potential endpoints; however, interpretation of the findings is limited by inadequate reporting of the study results. The study evaluated three compounds (2,3,7,8-tetraCDF, 2,3,4,7,8-pentaCDF, and 2,3,7,8-tetrabromodibenzofuran) and it is unclear if the reported effects were observed for all three compounds or for just some of the compounds; no information on the incidence or severity of the lesions was provided. Additionally, the 30-day recovery period makes it difficult to identify NOAEL and LOAEL values.

Agency Contacts (Chemical Managers): Hana R. Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,7,8-Tetrachlorodibenzofuran
CAS Numbers: 51207-31-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: The database was not considered adequate for derivation of an intermediate-duration oral MRL because deaths were observed at the lowest doses tested in two monkey studies (McNulty et al. 1981).

Rationale for Not Deriving an MRL: Four studies have evaluated the toxicity of 2,3,7,8-tetraCDF in laboratory animals orally exposed for intermediate durations. A summary of the results of these studies is presented in Table A-5. Several targets of toxicity were identified, including the thymus, stomach, bile duct, skin, and eyes. The lowest dose tested was 0.21 µg/kg/day; this dose level was associated with 1/3 deaths in monkeys (McNulty et al. 1981), thus precluding derivation of an MRL.

Table A-5. Summary of Health Effects Following Intermediate-Duration Oral Exposure to 2,3,7,8-Tetrachlorodibenzofuran

Species, duration	NOAEL (µg/kg/day)	LOAEL (µg/kg/day)	Effect	Reference
Monkey 6 months		0.21 (serious LOAEL)	• Death in 1/3 monkeys[a] • Metaplasia of gastric mucosa • Altered bile duct epithelium • Partial sebaceous gland atrophy, hyperkeratotic nail beds • Periorbital edema, meibomian gland enlargement • Thymic atrophy[a]	McNulty et al. 1981
Guinea pig 1 day/week 6 weeks	0.17	0.5	• Thymic atrophy • Macrophage inhibition	Luster et al. 1979a, 1979b
Guinea pig 1 day/week 6 weeks		1 (serious LOAEL)	• 30% mortality[a]	Luster et al. 1979a, 1979b
Monkey 2 months		2.1 (serious LOAEL)	• Death in 1/3 monkeys[a] • Intramucosal cysts • Altered bile duct epithelium • Facial and body hair loss, nail loss, absent sebaceous glands[a] • Periorbital edema • Thymic atrophy[a]	McNulty et al. 1981

Table A-5. Summary of Health Effects Following Intermediate-Duration Oral Exposure to 2,3,7,8-Tetrachlorodibenzofuran

Species, duration	NOAEL (µg/kg/day)	LOAEL (µg/kg/day)	Effect	Reference
Mouse 5 days/week 30 days	100	300	• 37% decrease in total leukocytes • Marked decrease in thymus weight	Luster et al. 1979a, 1979b

[a]Considered a serious health effect.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Agency Contacts (Chemical Managers): Hana R. Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,7,8-Tetrachlorodibenzofuran
CAS Numbers: 51207-31-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for 2,3,7,8-tetraCDF due to the lack of studies evaluating chronic toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 2,3,7,8-tetraCDF following chronic-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,8-Pentachlorodibenzofuran
CAS Numbers: 67517-48-0
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of acute-, intermediate-, or chronic-duration inhalation MRLs for 1,2,3,4,8-pentaCDF 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 1,2,3,4,8-pentaCDF following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,8-Pentachlorodibenzofuran
CAS Numbers: 67517-48-0
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of an acute-duration oral MRL for 1,2,3,4,8-pentaCDF due to the lack of studies evaluating toxicity following acute oral exposure.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,4,8-pentaCDF following acute-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,8-Pentachlorodibenzofuran
CAS Numbers: 67517-48-0
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of an acute-duration oral MRL for 1,2,3,4,8-pentaCDF because the only available intermediate-duration oral study did not identify targets of toxicity.

Rationale for Not Deriving an MRL: Information available on the intermediate-duration oral toxicity of 1,2,3,4,8-pentaCDF is limited to a 13-week dietary study in rats. In this study (Pluess et al. 1988a), no alterations in body weight, hematology, clinical chemistry, organ weight, or histology were observed at the highest dose tested (600 µg/kg/day). Thus, this study did not identify a critical target or provide dose-response data and was not considered adequate for derivation of an intermediate-duration oral MRL.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,8-Pentachlorodibenzofuran
CAS Numbers: 67517-48-0
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for 1,2,3,4,8-pentaCDF due to the lack of studies evaluating toxicity following chronic oral exposure.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,4,8-pentaCDF following chronic-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,7,8-Pentachlorodibenzofuran
CAS Numbers: 57117-41-6
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Acute, Intermediate, and Chronic

MRL Summary: There are insufficient data for the derivation of acute-, intermediate-, or chronic-duration inhalation MRLs for 1,2,3,7,8-pentaCDF 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-pentaCDF following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,7,8-Pentachlorodibenzofuran
CAS Numbers: 57117-41-6
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: The acute-duration oral database for 1,2,3,7,8-pentaCDF was considered inadequate for derivation of an MRL because the three available studies examined a limited number of endpoints and there is considerable uncertainty as to whether the most sensitive target of toxicity has been identified.

Rationale for Not Deriving an MRL: The available acute-duration studies for 1,2,3,7,8-pentaCDF, which are summarized in Table A-6, are limited in that they each only examined a single endpoint. Two studies observed decreases in serum total T4 levels in rats administered 1,2,3,7,8-pentaCDF for 4 days, with LOAEL values of 10 and 15.5 µg/kg/day (Crofton et al. 2005; Ross et al. 2000). Neither study evaluated other toxicologically relevant endpoints. The third study is a developmental toxicity study that reported an increase in the number of litters with hydronephrosis in the offspring of mice administered ≥30 µg/kg/day 1,2,3,7,8-pentaCDF on GDs 10–13 (Birnbaum et al. 1987a). At higher doses (≥100 µg/kg), the study reported decreases in maternal weight gain and increase in the number of litters with cleft palate; there were no effects on fetal viability, mortality, or weight at ≤200 µg/kg/day.

Table A-6. Summary of Health Effects Following Acute-Duration Oral Exposure to 1,2,3,7,8-Pentachlorodibenzofuran

Species, duration	NOAEL (µg/kg/day)	LOAEL (µg/kg/day)	Effect	Reference
Endocrine effects				
Rat 4 days		15.6	30% decreased serum total T4 levels	Crofton et al. 2005
Rat 4 days	3	10	15% decreased serum total T4 levels	Ross et al. 2000
Developmental effects				
Mouse GDs 10–13	10	30 (serious LOAEL)	Hydronephrosis	Birnbaum et al. 1987a

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; T4 = thyroxine

Because the available studies examined a limited number of potential endpoints, the database was considered inadequate for derivation of an acute-duration oral MRL. Specifically, the database lacks studies examining the liver and thymus which have been identified as sensitive targets following intermediate-duration exposure to 1,2,3,7,8-pentaCDF.

Agency Contacts (Chemical Managers): Hana R. Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,7,8-Pentachlorodibenzofuran
CAS Numbers: 57117-41-6
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.007 µg/kg/day ($7x10^{-3}$ µg/kg/day)
Critical Effect: Increase in relative liver weight
Reference: Pluess et al. 1988a
Point of Departure: $BMDL_{1SD}$ of 0.68 µg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 36
Species: Rat

MRL Summary: An intermediate-duration oral MRL of 0.007 µg/kg/day ($7x10^{-3}$ µg/kg/day) was derived for 1,2,3,7,8-pentaCDF based on increased relative liver weight in male rats exposed to 20 µg/kg/day 1,2,3,7,8-pentaCDF in the diet for 13 weeks (Pluess et al. 1988a). The MRL is derived from a $BMDL_{1SD}$ of 0.68 µg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: One study evaluated the oral toxicity of 1,2,3,7,8-pentaCDF in laboratory animals following intermediate-duration oral exposure (Pluess et al. 1988a). In rats exposed to 20 µg/kg/day 1,2,3,7,8-pentaCDF in the diet for 13 weeks, decreased body weight gain (6.5–11%), increased relative liver weight (males only), histological alterations in the liver (hepatic vacuolization with lipid accumulation and single cell necrosis), and decreased absolute thymus weight were observed; no toxicologically relevant alterations were observed at 2 µg/kg/day.

The histological alterations in the liver, increased relative liver weight in males, and decreased thymus weight were selected as co-critical effects.

Selection of the Principal Study: The Pluess et al. (1988a) study was selected as the principal study because it had an adequate experimental design, examined multiple potential targets of toxicity, and provided dose-response data for sensitive endpoints.

Summary of the Principal Study:

Pluess N, Poiger H, Hohbach C, et al. 1988a. Subchronic toxicity of some chlorinated dibenzofurans (PCDFs) and a mixture of PCDFs and chlorinated dibenzodioxins (PCDDs) in rats. Chemosphere. 17:973-984.

Groups of six male and six female Iva:SIV 50(SD) rats were exposed to 0, 2, 20, or 200 µg/kg 1,2,3,7,8-pentaCDF in the diet for 13 weeks. Daily doses were estimated using a reference food intake of 0.016 kg/day and reference body weight of 0.152 kg (EPA 1989b); the estimated doses were 0, 0.2, 2, and 20 µg/kg/day in the 0, 2, 20, and 200 µg/kg groups, respectively. The following parameters were used to evaluate toxicity: weekly body weight and food consumption measurements, hematological parameters (red blood cells, total and differential white blood cells, reticulocyte, and thrombocyte counts, hemoglobin levels, and packed cell volume), serum clinical chemistry indices (bilirubin, triglycerides, urea, cholesterol, alkaline phosphatase, ALT), organ weights (liver, thymus, spleen, kidneys, heart, and

testes), and histopathology (lungs, liver, thymus, spleen, kidneys, heart, thyroid/parathyroids, adrenals, mesenteric and submandibular lymph nodes, uterus, ovaries, and testes).

No deaths were noted in either sex. Significant decreases in terminal body weight of approximately 6 and 11% were observed in males and females, respectively, exposed to 20 µg/kg/day. No alterations in food consumption were observed. Significantly increased packed cell volume (6.9 and 4.3%) were observed in males and females, respectively, and a 7% decrease in hemoglobin was observed in females at 20 µg/kg/day. No other significant hematological alterations were reported. Significantly decreased ALT (19%) and serum urea (15%) levels were observed in males at ≥2 µg/kg/day and decreased urea (23%) was observed in females at 20 µg/kg/day. No significant effects on serum bilirubin, cholesterol, alkaline phosphatase or triglycerides were observed. The toxicological significance of relatively small changes in hematological and serum chemistry indices is uncertain. A significant increase in relative liver weight (18.2%) in males and vacuolization with increased lipid content, single cell necrosis, and slight Kupffer cell hyperplasia (sex not specified) were observed at 20 µg/kg/day; the study did not provide incidence data. Significantly decreased absolute thymus weight (46 and 29% in males and females) was observed in both sexes at 20 µg/kg/day and histologic evidence of possible early thymic atrophy in females (no additional information provided) was observed at 20 µg/kg. No treatment-related histological effects were observed in the heart, adrenal glands, kidneys, lymph nodes, spleen, testes, uterus, or ovaries.

Selection of the Point of Departure for the MRL: A $BMDL_{1SD}$ of 0.68 µg/kg/day for decreases in thymus weight in female rats was selected as the point of departure (POD).

Benchmark dose (BMD) modeling was conducted to identify a potential POD using the relative liver weight in male and female rats and absolute thymus weight in the male and female rats from the Pluess et al. (1988a) study; the data are summarized in Table A-7. The lack of incidence data precluded using BMD modeling for the histological alterations in the liver. The data were fit to most of the available continuous models in EPA's Benchmark Dose Software (BMDS, version 3.1.2) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). A BMR of 1 standard deviation from the control mean was selected in the absence of a biologically based BMR.

The model predictions for the increases in relative liver weight in male rats are shown in Table A-8. The best fitting model was the Exponential 4 model with constant variance, illustrated in Figure A-1; the model estimated BMD_{1SD} and $BMDL_{1SD}$ values of 1.62 and 0.68 µg/kg/day, respectively. The model predictions for increased relative liver weight in female rats are shown in Table A-9. The best-fitting model was the Exponential 4 with constant variance (Figure A-2); the BMD_{1SD} estimated in this model was 1.67 µg/kg/day and the $BMDL_{1SD}$ was 0.60 µg/kg/day. None of the models (with constant variance or nonconstant variance) provided adequate fit to the data for decreases in thymus weight in male rats. In female rats, the model predictions for decreased thymus weight are presented in Table A-10. All models provided adequate fit with constant variance. The best fitting model was the Exponential 5 model; this model estimated a BMD_{1SD} of 2.73 µg/kg/day and $BMDL_{1SD}$ of 0.91 µg/kg/day; the model is presented in Figure A-3.

Table A-7. Relative Liver Weight and Absolute Thymus Weights in Male and Female Rats Exposed to 1,2,3,7,8-Pentachlorodibenzofuran in the Diet for 13 Weeks

Dose level	Relative liver weight (mean±SD) (g/100 g)		Absolute thymus weight (mean±SD) (g)	
(µg/kg/day)	Males	Females	Males	Females
0	3.35±0.26	3.37±0.23	0.48±0.02	0.48±0.09
0.2	3.35±0.36	3.36±0.15	0.45±0.07	0.47±0.07
2	3.61±0.16	3.63±0.20[a]	0.42±0.07	0.43±0.04
20	3.95±0.19[a]	3.90±0.41	0.26±0.05[a]	0.34±0.06[a]

[a]Significantly different from controls, $p<0.05$.

SD = standard deviation

Source: Pluess et al. 1988a

Table A-8. Results from BMD Analysis (Constant Variance) of Relative Liver Weight in Male Rats Exposed to 1,2,3,7,8-Pentachlorodibenzofuran in the Diet for 13 Weeks (Pluess et al. 1988a)

					Scaled residuals[c]	
Model	BMD_{1SD}[a] (µg/kg/day)	$BMDL_{1SD}$[a] (µg/kg/day)	Test 4 p-value[b]	AIC	Dose below BMD	Dose above BMD
Exponential 2[d]	9.41	6.72	0.210	7.15	1.43	-0.632
Exponential 3[d]	9.41	6.72	0.210	7.15	1.43	-0.632
Exponential 4[d,e]	**1.62**	**0.68**	**0.792**	**6.10**	**0.03**	**0.169**
Exponential 5[d]			NA	8.03	0.00	0.001
Hill[d]			NA	8.03	0.00	0.01
Polynomial Degree 3[d]	8.97	6.26	0.220	7.06	1.42	-0.613
Polynomial Degree 2[d]	8.97	6.26	0.220	7.06	1.42	-0.613
Power[d]	8.97	6.26	0.220	7.06	1.42	-0.613
Linear	8.97	6.26	0.220	7.06	1.42	-0.613

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Recommended model. There was an adequate fit to the variance when assuming constant variance. Of the models providing adequate fit, the BMDLs were not sufficiently close (differed by >3-fold); therefore, the model with the lowest BMDL was selected (Exponential 4 model).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control); NA = not applicable, goodness-of-fit test cannot be calculated

Figure A-1. Fit of Exponential Degree 4 Model (with Constant Variance) to Relative Liver Weight in Male Rats Exposed to 1,2,3,7,8-Pentachlorodibenzofuran

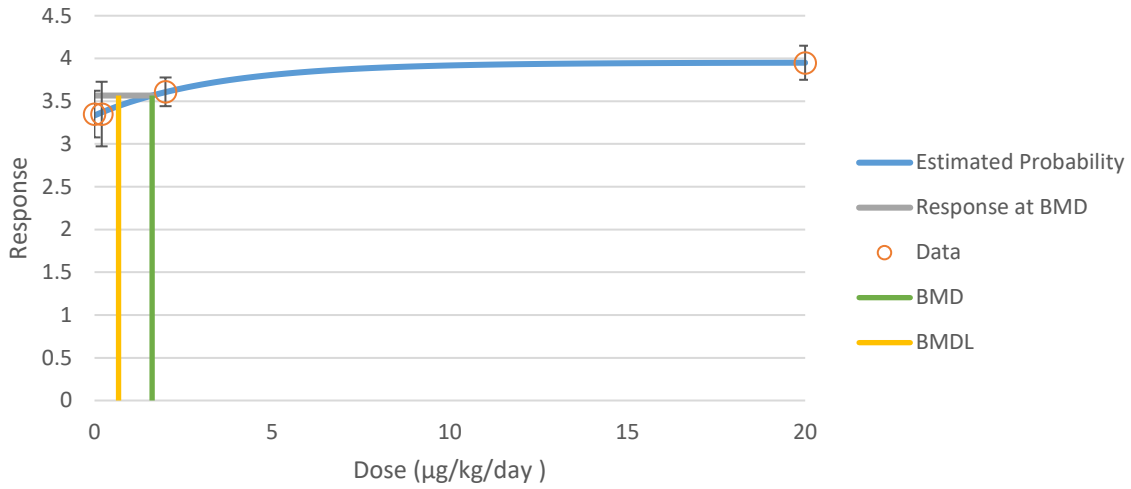


Table A-9. Results from BMD Analysis (Constant Variance) of Relative Liver Weight in Female Rats Exposed to 1,2,3,7,8-Pentachlorodibenzofuran in the Diet for 13 Weeks (Pluess et al. 1988a)

Model	BMD_{1SD}[a] (µg/kg/day)	$BMDL_{1SD}$[a] (µg/kg/day)	Test 4 p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Exponential 2[d]	11.13	7.64	0.207	9.36	-0.12	-0.59
Exponential 3[d]	11.13	7.64	0.207	9.36	-0.12	-0.59
Exponential 4[d,e]	**1.67**	**0.60**	**0.734**	**8.32**	**0.05**	**0.22**
Exponential 5[d]			NA	10.21	0.00	0.05
Hill[d]			NA	10.21	0.00	0.05
Polynomial Degree 3[d]	10.72	7.18	0.214	9.29	1.43	-0.57
Polynomial Degree 2[d]	10.72	7.18	0.214	9.29	1.43	-0.57
Power[d]	10.72	7.18	0.214	9.29	1.43	-0.57
Linear	10.72	7.18	0.214	9.29	1.43	-0.57

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Recommended model. There was an adequate fit to the variance when assuming constant variance. Of the reliable models providing adequate fit, the BMDLs were not sufficiently close (differed by >3-fold); therefore, the model with the lowest BMDL was selected (Exponential 4).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control); NA = not applicable, goodness-of-fit test cannot be calculated

Figure A-2. Fit of Exponential Degree 4 Model (with Constant Variance) to Relative Liver Weight in Female Rats Exposed to 1,2,3,7,8-Pentachlorodibenzofuran

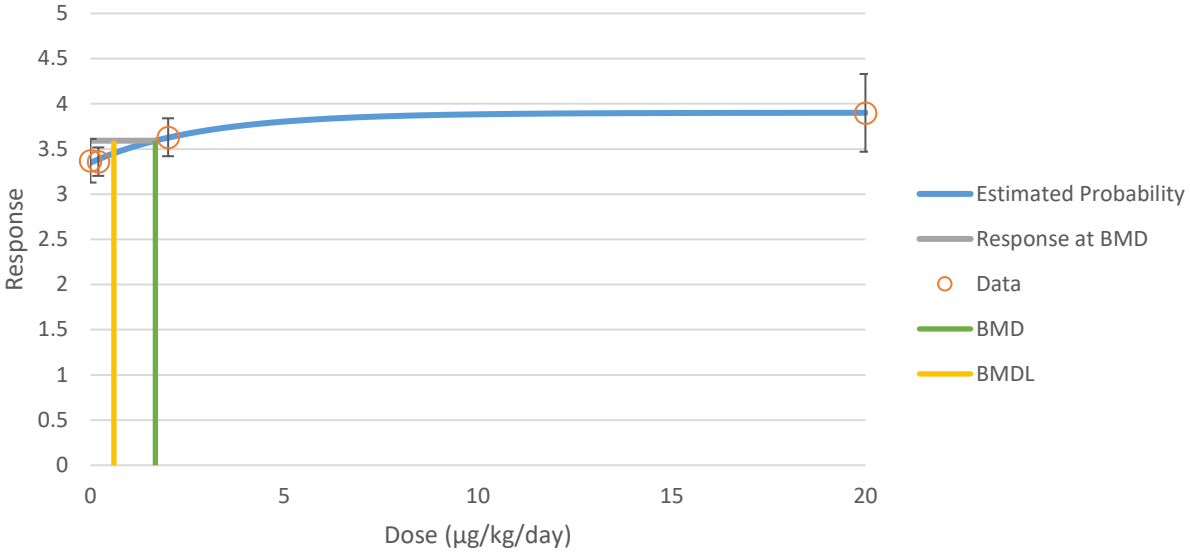


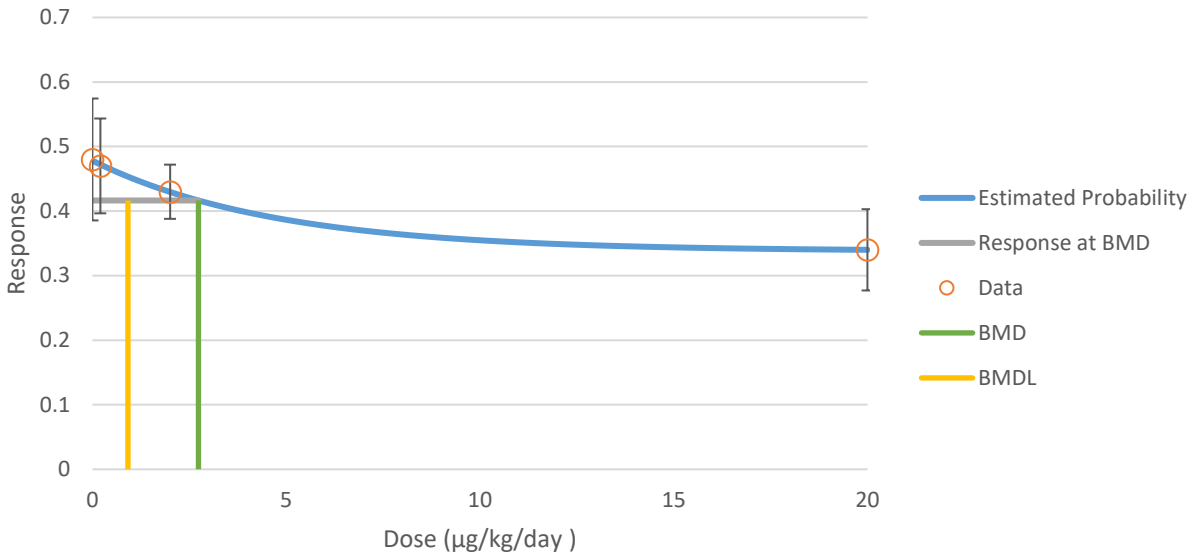
Table A-10. Results from BMD Analysis (Constant Variance) of Absolute Thymus Weight in Female Rats Exposed to 1,2,3,7,8-Pentachlorodibenzofuran in the Diet for 13 Weeks (Pluess et al. 1988a)

Model	BMD_{1SD}[a] (µg/kg/day)	$BMDL_{1SD}$[a] (µg/kg/day)	Test 4 p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Exponential 2[d]	8.94	5.74	0.590	-58.634	-0.836	0.531
Exponential 3[d]	8.94	5.74	0.590	-58.634	-0.836	0.531
Exponential 4[d]	8.93	0.77	0.305	-56.636	-0.835	0.530
Exponential 5[d,e]	**2.73**	**0.91**	**0.905**	**-57.676**	**0.013**	**0.077**
Hill[d]			0.921	-57.676	0.015	0.063
Polynomial Degree 3[d]	9.89	6.76	0.554	-58.509	-0.879	0.566
Polynomial Degree 2[d]	9.89	6.76	0.554	-58.509	-0.879	0.566
Power[d]	9.89	6.75	0.554	-58.509	-0.879	0.566
Linear	9.89	6.76	0.554	-58.509	-0.879	0.566

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Recommended model. There was an adequate fit to the variance when assuming constant variance. Of the models providing adequate fit, the BMDLs were not sufficiently close (differed by >3-fold); therefore, the model with the lowest BMDL was selected (Exponential 5 model).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control)

Figure A-3. Fit of Exponential 5 Model (with Constant Variance) to Absolute Thymus Weight in Female Rats Exposed to 1,2,3,7,8-Pentachlorodibenzofuran



Potential POD candidates based on histological alterations in the liver, increased relative liver weight in male and female rats, and decreased absolute thymus weight in male and female rats are summarized in Table A-11. The $BMDL_{1SD}$ of 0.68 µg/kg/day for increased relative liver weight in male rats was selected as the POD because it has the lowest BMD_{1SD}.

Table A-11. Candidate Points of Departure 1,2,3,7,8-Pentachlorodibenzofuran Intermediate-Duration Oral MRL

Endpoint	NOAEL (µg/kg/day)	LOAEL (µg/kg/day)	BMD_{1SD} (µg/kg/day)	$BMDL_{1SD}$ (µg/kg/day)
Histological alterations in the liver (vacuolization with increased lipid content, single cell necrosis and slight Kupffer cell hyperplasia)	2	20		
Increases in relative liver weight in males			1.62	0.68
Increases in relative liver weight in females			1.67	0.60
Decrease in absolute thymus weight in males	2	20		
Decrease in absolute thymus weight in females			2.73	0.91

BMD = benchmark dose; BMDL = 95% lower limit on the BMD; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse-effect level

Calculations

Uncertainty Factor: The $BMDL_{1SD}$ is divided by a total uncertainty factor (UF) of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

$MRL = BMDL_{1SD} \div UF$

$0.68\ \mu g/kg/day \div (10 \times 10) = 0.007\ \mu g/kg/day$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Identification of the thymus as a critical target of 1,2,3,7,8-pentaCDF toxicity is supported by findings of decreased thymus weight, thymic atrophy, and impaired immune response in studies evaluating other 2,3,7,8-substituted congeners (Brewster et al. 1988; Johnson et al. 2000; Kerkvliet et al. 1985; Luster et al. 1979a, 1979b; McNulty et al. 1981; Moore et al. 1979, NTP 2006; Oishi et al. 1978; Oishi and Hiraga 1980; Pluess et al. 1988a, 1988b; Taura et al. 2014).

Agency Contacts (Chemical Managers): Hana R. Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,7,8-Pentachlorodibenzofuran
CAS Numbers: 57117-41-6
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for 1,2,3,7,8-pentaCDF due to the lack of studies evaluating chronic toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,7,8-pentaCDF following chronic-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,7,8-Pentachlorodibenzofuran
CAS Numbers: 57117-31-4
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Acute, Intermediate, and Chronic

MRL Summary: There are insufficient data for the derivation of acute-, intermediate-, or chronic-duration inhalation MRLs for 2,3,4,7,8-pentaCDF 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 2,3,4,7,8-pentaCDF following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,7,8-Pentachlorodibenzofuran
CAS Numbers: 57117-31-4
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.0005 µg/kg/day ($5x10^{-4}$ µg/kg/day)
Critical Effect: Decreased thymus weight in pups
Reference: Madsen and Larsen 1989
Point of Departure: NOAEL of 0.5 µg/kg/day
Uncertainty and Modifying Factors: 100 (UF), 10 (MF)
LSE Graph Key: 12
Species: Rat

MRL Summary: An acute-duration oral MRL of 0.0005 µg/kg/day ($5x10^{-4}$ µg/kg/day) was derived for 2,3,4,7,8-pentaCDF based on decreases in pup thymus weight in the offspring of rats administered 2 µg/kg on GD 16 (Madsen and Larsen 1989); the NOAEL for this effect was 0.5 µg/kg. The MRL is based on a NOAEL of 0.5 µg/kg and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) and a modifying factor of 10 for database deficiencies.

Selection of the Critical Effect: A number of laboratory animal studies have evaluated the toxicity of 2,3,4,7,8-pentaCDF following acute-duration oral exposure. A summary of the results of these studies are presented in Table A-12. Studies by Brewster et al. (1988) and Moore et al. (1979) examined a range of endpoints and reported hepatic and immunological effects at the lowest doses tested; however, both studies included a 30–35-day recovery post-exposure. Studies evaluating immunological endpoints reported decreased thymus weight at ≥3 µg/kg/day (Brewster et al. 1988; Moore et al. 1979; Taura et al. 2014) and impaired immune response at 10.119 µg/kg/day (Johnson et al. 2000). Developmental studies have reported decreased fetal weight, impaired development of the reproductive system, decreased thymus weight, and hydronephrosis (Birnbaum et al. 1987a, 1987b; Couture et al. 1989; Madsen and Larsen 1989; Salisbury and Marcinkiewicz 2002).

Several studies have identified LOAEL values between 1 and 5 µg/kg. Effects observed at these doses include decreases in mature offspring weight at 1 µg/kg (decreased pup body weight was observed at 10 µg/kg) (Salisbury and Marcinkiewicz 2002), impaired development of the reproductive system at 1 µg/kg (Salisbury and Marcinkiewicz 2002), decreased neonatal relative thymus weight at 2 µg/kg (Madsen and Larsen 1989), decreased thymus size in adults at 3 µg/kg (Moore et al. 1979), and hydronephrosis at 5 µg/kg (Birnbaum et al. 1987b). Only one of these studies identified a NOAEL; no significant alterations in neonatal thymus weight were observed at 0.5 µg/kg (Madsen and Larsen 1989). These data provide evidence that immunotoxicity and developmental toxicity are the most sensitive targets of toxicity following acute oral exposure to 2,3,4,7,8-pentaCDF.

Table A-12. Summary of Health Effects Following Acute-Duration Oral Exposure to 2,3,4,7,8-Pentachlorodibenzofuran

Species, duration	NOAEL (µg/kg/day)	LOAEL (µg/kg/day)	Effect	Reference
Hepatic effects				
Rat 1 day		100	Lipid accumulation, increased cholesterol (60%)	Brewster et al. 1988
Endocrine effects				
Rat 4 days		27.5	Decrease in serum total T4 levels (30%)	Crofton et al. 2005
Rat 4 days	9	30	Decrease in serum total T4 levels (27%)	Ross et al. 2000
Immunological effects				
Guinea pig 1 day		3	Marked decrease in thymus size	Moore et al. 1979
Mouse 1 day		10.119	50% reduction in immune response to SRBC	Johnson et al. 2000
Rat 1 day		71.9	ED_{50} for decreased thymus weight in pubertal rats	Taura et al. 2014
Rat 1 day		100	Decreased thymus weight (30–90%)	Brewster et al. 1988
Developmental effects				
Rat GD 15		1 (serious LOAEL)	Decreased offspring body weight on PND 140 (~7%), decreased number of days spent in estrus (33%), and decreased ovulation rate (57%)	Salisbury and Marcinkiewicz 2002
Rat GD 16	0.5	2	Decreased neonatal relative thymus weight (14%)	Madsen and Larsen 1989
Mouse GDs 10–13		5 (serious LOAEL)	Hydronephrosis	Birnbaum et al. 1987b
Mouse GDs 10–13	3	10 (serious LOAEL)	Hydronephrosis	Birnbaum et al. 1987a
Rat GD 15		12.6	ED_{50} for decreased growth hormone in female fetuses	Taura et al. 2014
Rat GD 8, 10, or 12		30	Decreased fetal body weight	Couture et al. 1989
Rat GD 15	15	50	Altered sexual behavior in male offspring	Taura et al. 2014
Rat GD 15		56.3	ED_{50} for decreased fetal weights in males	Taura et al. 2014

Table A-12. Summary of Health Effects Following Acute-Duration Oral Exposure to 2,3,4,7,8-Pentachlorodibenzofuran

Species, duration	NOAEL (µg/kg/day)	LOAEL (µg/kg/day)	Effect	Reference
Mouse GDs 10–13		80	Impaired embryonic erythropoiesis in the liver, increased number of hepatocytes, reduction in liver sinusoids	Khera 1992

ED_{50} = 50% effective dose; GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PND = postnatal day; SRBC = sheep red blood cell; T4 = thyroxine

Selection of the Principal Study: The Madsen and Larsen (1989) study was selected as the principal study because it identified a NOAEL for developmental effects.

Summary of the Principal Study:

Madsen C, Larsen JC. 1989. Relative toxicity of chlorinated dibenzo-p-dioxins, and dibenzofurans measured by thymus weight and liver enzyme induction in perinatally dosed rats, 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF, 1,2,3,7,8-PeCDD. Chemosphere 18:955-966.

Groups of 8–10 pregnant Wistar, SPF-rats were administered via gavage 0, 0.5, 2, or 10 µg/kg 2,3,4,7,8-pentaCDF in soybean oil on GD 16. Pups were sacrificed at 1 week of age. Parameters used to assess toxicity in the pups included measurement of thymus and liver weights, and activities of microsomal monooxygenase, 7-ethoxycoumarin deethylase, biphenyl-2-hydroxylase, and biphenyl-4-hydroxylase. No additional developmental endpoints and no maternal endpoints were evaluated. The investigators also conducted a cross-fostering study in which groups of 10 pregnant rats were administered 0 or 10 µg/kg 2,3,4,7,8-pentaCDF in soybean oil on GD 16. Within 17 hours of birth, the *in utero* exposed pups were fostered by control dams and control pups were fostered by 2,3,4,7,8-pentaCDF-exposed dams.

Dose-related decreased mean litter relative thymus weights were observed (approximately 6, 14, and 30% at 0.5, 2, and 10 µg/kg, respectively). The decrease in thymus weight was statistically significant ($p \leq 0.05$) at 2 ug/kg using the Mann-Whitney test. Dose-related increased mean fetal hepatic microsomal 7-ethoxycoumarin deethylase, biphenyl-2-hydroxylase, and biphenyl-4-hydroxylase activities were observed at 2 µg/kg. In the cross-fostering experiment, significant decreases in relative thymus weights were observed in the *in utero* only, lactation only, and *in utero* and lactation groups. The investigators noted that *in utero* and exposure via milk contributed almost equally to the thymus effects in the offspring.

Selection of the Point of Departure for the MRL: The NOAEL of 0.5 µg/kg was selected as the point of departure for the MRL. The thymus weight data presented in the Madsen and Larsen (1989) study was not considered suitable for benchmark dose (BMD) modeling because mean thymus weights and standard deviations were not reported.

Uncertainty Factor: The NOAEL is divided by a total uncertainty factor (UF) of 100 and modifying factor (MF) of 10:

- UF of 10 for extrapolation from animals to humans
- UF of 10 for human variability
- MF of 10 for database deficiencies

A modifying factor of 10 was used to account for the lack of a study identifying a NOAEL for impaired development of the reproductive system and the steep dose-response between the NOAEL of 0.5 µg/kg in the Madsen and Larsen (1989) study and the serious LOAEL of 1 µg/kg in the Salisbury and Marcinkiewicz (2002) study.

MRL = LOAEL ÷ (UF x MF)
0.5 µg/kg/day ÷ (10 x 10 x 10) = 0.0005 µg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: As discussed in the Selection of the Critical Effect section, several studies support developmental toxicity, including impaired development of the reproductive system, as a sensitive target and several studies have identified similar LOAEL values for developmental and immunological endpoints.

Agency Contacts (Chemical Managers): Hana R. Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,7,8-Pentachlorodibenzofuran
CAS Numbers: 57117-31-4
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.000007 µg/kg/day (7 x 10^{-6} µg/kg/day)
Critical Effect: Decreased serum total T4 levels
Reference: NTP 2006
Point of Departure: $BMDL_{1SD}$ of 0.00095 µg/kg ($BMDL_{ADJ}$ of 0.00068 µg/kg/day)
Uncertainty Factor: 100
LSE Graph Key: 38
Species: Rat

MRL Summary: An intermediate-duration oral MRL of 0.000007 µg/kg/day (7x10^{-6} µg/kg/day) was derived for 2,3,4,7,8-pentaCDF based on decreases in serum total T4 levels in female rats administered via gavage 0.006 µg/kg 2,3,4,7,8-pentaCDF 5 days/week for 31 weeks (NTP 2006). The MRL is based on a $BMDL_{1SD}$ of 0.00098 µg/kg, which was adjusted to continuous duration exposure to a $BMDL_{ADJ}$ of 0.00068 µg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Four studies evaluated the toxicity of 2,3,4,7,8-pentaCDF following intermediate-duration oral exposure. The targets of toxicity include the thyroid gland, liver, thymus, and reproductive system; the NOAEL and LOAEL values for these effects are presented in Table A-13.

Table A-13. Summary of Health Effects Following Intermediate-Duration Oral Exposure to 2,3,4,7,8-Pentachlorodibenzofuran

Species, duration	NOAEL (µg/kg/day)	LOAEL (µg/kg/day)	Effect	Reference
Rat 14 weeks (5 days/week)	0.02	0.044 0.092	• Thyroid gland follicular cell hypertrophy • Hepatocellular hypertrophy • Decreased serum total T4 levels (25%)	NTP 2006
Rat 31 weeks (5 days/week)		0.006 0.044	• Decreased serum total T4 levels (16%) • Hepatocellular hypertrophy	NTP 2006
Rat 13 weeks (daily)		0.2	• Increased serum bilirubin levels (35–52%) • Decreased serum triglyceride levels in males (18%) • Slight fatty degeneration in liver • Decreased absolute thymus weight in females (24%)	Pluess et al. 1988a

Table A-13. Summary of Health Effects Following Intermediate-Duration Oral Exposure to 2,3,4,7,8-Pentachlorodibenzofuran

Species, duration	NOAEL (µg/kg/day)	LOAEL (µg/kg/day)	Effect	Reference
Mouse 5 times in 16 weeks	30	100	• Endometriosis	Johnson et al. 1997

The available data suggest that the alterations in thyroid hormone levels and hepatocellular hypertrophy are the most sensitive endpoints following intermediate-duration oral exposure to 2,3,4,7,8-pentaCDF. At higher doses, decreased thymus weight, and endometriosis were observed.

Selection of the Principal Study: The 31-week NTP (2006) study was selected as the principal study because it identified lower LOAEL values for thyroid and liver effects than the 14-week NTP (2006) study and for decreased thymus weight or endometriosis.

Summary of the Principal Study:

NTP. 2006. Toxicology and carcinogenesis studies of 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) (CAS No. 57117-31-4) in female Harlan Sprague-Dawley rats (gavage studies). NTP TR 525.

Groups of 10 female Harlan Sprague-Dawley rats were administered via gavage 0, 6, 20, 44, 92, or 200 ng/kg (0, 0.006, 0.02, 0.044, 0.092, and 0.2 µg/kg) 2,3,4,7,8-pentaCDF in a corn oil:acetone vehicle 5 days/week for 31 weeks. The following parameters were used to assess toxicity: clinical observations, body weight, organ weights (kidney, liver, lung, ovary, spleen, thymus, and thyroid), thyroid hormone levels (TSH, T3, T4), cell proliferation measured in liver and duodenum samples, cytochrome P450 activities in liver and lung samples, and histopathological examination of the adrenal gland, liver, lung, mammary gland, ovary, pancreas, pituitary gland, spleen, stomach, thymus, thyroid gland, uterus, and vagina in the 0 and 0.2 µg/kg groups; liver, thymus, and uterus were evaluated in all groups.

No deaths were observed in rats exposed for 31 weeks. Body weights in the CDF groups were within 10% of controls. After 31 weeks of exposure, significantly decreased serum total T4 levels were observed at ≥0.006 µg/kg (16, 18, 25, 29, and 40% at 0.006, 0.02, 0.044, 0.092, and 0.2 µg/kg, respectively), serum free T4 levels were decreased at 0.2 µg/kg, and serum total T3 levels were increased at 0.092 and 0.2 µg/kg. Increases in relative liver weight were observed at ≥0.02 µg/kg. Significant increases in the incidence of hepatocellular hypertrophy and liver pigmentation were observed at ≥0.044 µg/kg. Nonsignificant increases in the incidence and severity of cystic endometrial hyperplasia were also observed at 0.2 µg/kg. The incidence of thymus cortical atrophy was nonsignificantly increased in rats exposed to 0.2 µg/kg; an increase in the severity of the lesion was also observed.

Selection of the Point of Departure for the MRL: The point of departure is a $BMDL_{1SD}$ of 0.00095 µg/kg for decreases in serum total T4 levels.

BMD modeling was conducted to identify a potential POD using the data for serum total T4 levels and hepatocellular hypertrophy incidence, which are summarized in Table A-14. The data were fit to all available continuous models (serum T4 levels) or dichotomous models (hepatocellular hypertrophy) in EPA's BMDS (version 3.1.2) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. A BMR of 1 standard

deviation from the control mean was selected in the absence of a biologically based BMR for the serum T4 levels. A BMR of 10% extra risk was selected for the hepatocellular hypertrophy modeling.

Table A-14. Serum Total T4 Levels in Female Rats Administered 2,3,4,7,8-Pentachlorodibenzofuran 5 Days/Week for 31 Weeks

		Serum total T4 levels		Hepatocellular hypertrophy incidence
Dose Level (µg/kg)	Number of animals per group	Mean (µg/dL)	Standard deviation[a]	
0	10	4.17	0.329	0/10
0.006	10	3.52[b]	0.471	1/10
0.02	10	3.41[b]	0.648	3/10
0.044	10	3.12[b]	1.031	6/10[b]
0.092	10	2.96[b]	0.772	8/10[b]
0.2	10	2.5[b]	0.705	8/10[b]

[a]Standard deviations estimated from reported standard error of the mean (SEM).
[b]Significantly different from vehicle control, $p<0.01$.

Source: NTP 2006

None of the available BMD models provided adequate fit to the serum T4 data with constant variance. Three models (Exponential 4, Exponential 5, and Hill) provided adequate fit with nonconstant variance; the results are summarized in Table A-15. The BMDL values from these models were sufficiently close and the model with the lowest AIC (Hill model) was selected. This model estimated a BMD_{1SD} of 0.00251 µg/kg and a $BMDL_{1SD}$ of 0.00095 µg/kg. The Hill model fit is illustrated in Figure A-4.

Most dichotomous models provided adequate fit to the hepatocellular hypertrophy incidence data; the results are summarized in Table A-16. The BMDL values were not sufficiently close and the model with the lowest $BMDL_{10}$ (LogProbit model) was selected; the fit of the LogProbit model is illustrated in Figure A-5. This model estimated a BMD_{10} of 0.0054 µg/kg and a $BMDL_{10}$ of 0.0010 µg/kg.

The $BMDL_{1SD}$ of 0.00095 µg/kg for alterations in serum T4 levels was selected as the POD because the BMD_{1SD} for this endpoint is lower than the BMD_{10} for hepatocellular hypertrophy.

Table A-15. Results from BMD Analysis (Nonconstant Variance) of Serum Total T4 Levels in Female Rats Administered 2,3,4,7,8-Pentachlorodibenzofuran 5 Days/Week for 31 Weeks (NTP 2006)

Model	BMD_{1SD}[a] (µg/kg)	$BMDL_{1SD}$[a] (µg/kg)	Test 4 p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Exponential 2[d]			0.00254	135.204	-0.181	2.111
Exponential 3[d]			0.00254	124.016	-0.815	0.226
Exponential 4[d]	0.00332	0.00219	0.362	124.016	-0.807	0.225
Exponential 5[d]	0.00332	0.00219	0.362	122.778	0.037	0.037
Hill[d,e]	**0.00251**	**0.00095**	**0.581**	136.393	**-0.480**	**2.275**
Polynomial Degree 5[d]			0.00149	136.393	-0.480	2.275
Polynomial Degree 4[d]			0.00149	136.393	-0.480	2.275
Polynomial Degree 3[d]			0.00149	136.393	-0.480	2.275
Polynomial Degree 2[d]			0.00149	136.393	-0.480	2.275
Power[d]			0.00149	136.393	-0.480	2.275
Linear			0.00149	-58.509	-0.879	0.566

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Recommended model. There was an adequate fit to the variance when assuming constant variance. Of the models providing adequate fit, the BMDLs were sufficiently close (differed by <3-fold); therefore, the model with the lowest AIC was selected (Hill)

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control)

Figure A-4. Fit of Hill Model (with Nonconstant Variance) for Serum Total T4 Levels in Female Rats Administered 2,3,4,7,8-Pentachlorodibenzofuran

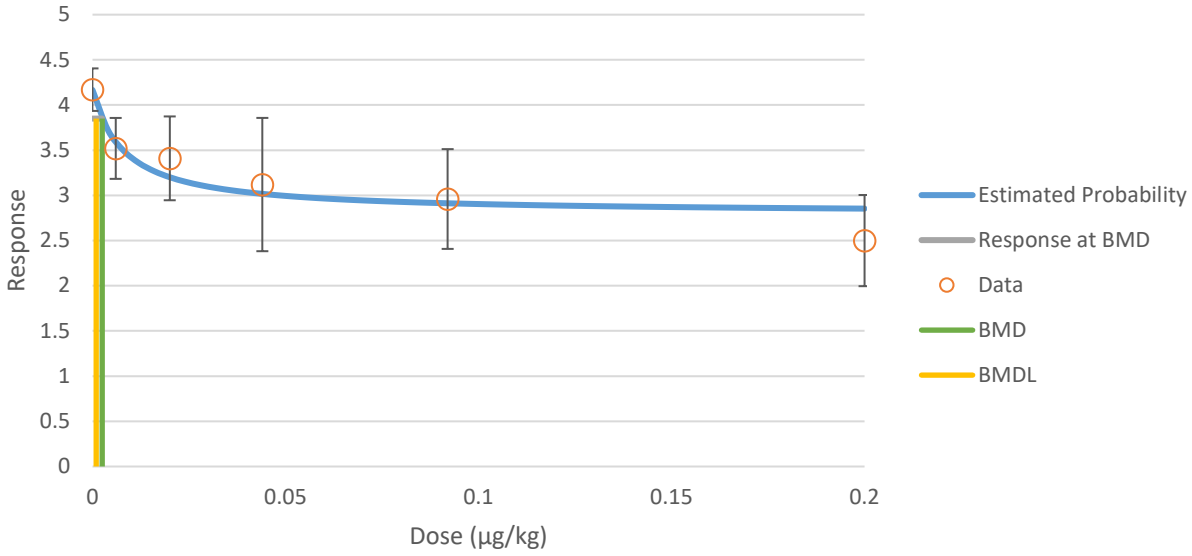


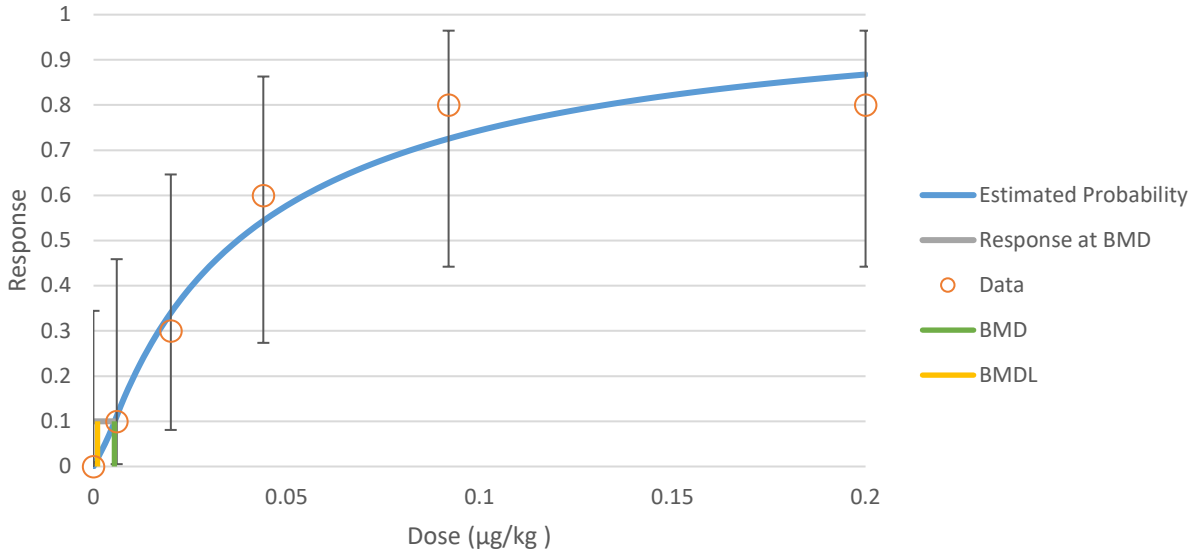
Table A-16. Results from BMD Analysis of Hepatocellular Hypertrophy Incidence in Female Rats Administered 2,3,4,7,8-Pentachlorodibenzofuran 5 Days/Week for 31 Weeks (NTP 2006)

Model	BMD_{1SD}[a] (µg/kg)	$BMDL_{1SD}$[a] (µg/kg)	p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Dichotomous Hill	0.00703	0.00203	0.862	60.494	0.2301	-0.0007
Gamma[d]	0.00756	0.00535	0.325	59.695	0.2296	-0.0004
Log-Logistic[e]	0.00522	0.00240	0.936	56.977	-0.1473	-0.0004
Multistage Degree 5[f]	0.00756	0.00535	0.459	57.695	0.2296	-0.0004
Multistage Degree 4[f]	0.00756	0.00535	0.459	57.695	0.2296	-0.0004
Multistage Degree 3[f]	0.00756	0.00535	0.459	57.695	0.2296	-0.0004
Multistage Degree 2[f]	0.00756	0.00535	0.459	57.695	0.2296	-0.0004
Multistage Degree 1[f]	0.00756	0.00535	0.325	59.695	0.2296	-0.0004
Weibull[f]	0.00756	0.00535	0.325	59.695	0.2296	-0.0016
Logistic			0.041	67.242	0.2337	-1.5569
Log-Probit[g]	**0.00541**	**0.00105**	**0.926**	**57.060**	**-0.1258**	**-0.0004**
Probit			0.042	67.658	0.2379	-1.5698

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals for dose group near the BMD and for the control dose group.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. Most models provided adequate fit to the data. BMDLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMDL was selected (Log-Probit model).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure dose associated with 10% extra risk)

Figure A-5. Fit of LogProbit Model for Hepatocellular Hypertrophy Incidence in Female Rats Administered 2,3,4,7,8-Pentachlorodibenzofuran



Intermittent Exposure: The $BMDL_{1SD}$ of 0.00095 µg/kg was adjusted for intermittent exposure.

$BMDL_{ADJ}$ = 0.00095 µg/kg x 5 days/7 days = 0.00068 µg/kg/day.

Uncertainty Factor: The $BMDL_{ADJ}$ is divided by a total uncertainty factor (UF) of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = $BMDL_{ADJ}$ ÷ UF
MRL = 0.00068 µg/kg/day ÷ 100 = 0.000007 µg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Decreases in serum total T4 levels have been reported in rats following 4 days of exposure to ≥27.5 µg/kg/day (Crofton et al. 2005; Ross et al. 2000), following 14 weeks of exposure to 0.092 µg/kg (NTP 2006), 31 weeks of exposure to ≥0.006 µg/kg (NTP 2006), and 53 weeks of exposure to 0.044 µg/kg (NTP 2006). Increases in serum total T3 levels have also been reported following 31 or 53 weeks of exposure. No alterations in serum TSH levels have been reported (NTP 2006). The lack of change in serum TSH levels is consistent with the findings of other chemicals which induce uridine 5′-diphospho-glucuronosyltransferase such as PCB and 3-methylcholanthrene (Hood and Klaassen 2000; Hood et al. 2003; Richardson and Klaassen 2010). Epidemiological studies on the potential thyroid toxicity of CDFs are inconclusive. However, occupational exposure studies involving CDDs (ATSDR 1998, 2012) and PCBs (ATSDR 2000) have found alterations in thyroid hormone levels.

Agency Contacts (Chemical Managers): Hana R. Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 2,3,4,7,8-Pentachlorodibenzofuran
CAS Numbers: 57117-31-4
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Chronic
MRL: 0.000004 µg/kg/day ($4x10^{-6}$ µg/kg/day)
Critical Effect: Hepatocellular hypertrophy and cystic degeneration in adrenal cortex
Reference: NTP 2006
Point of Departure: LOAEL of 0.006 µg/kg/day ($LOAEL_{ADJ}$ of 0.0043 µg/kg/day)
Uncertainty Factor: 1,000
LSE Graph Key: 45
Species: Rat

MRL Summary: A chronic-duration oral MRL of 0.000004 µg/kg/day ($4x10^{-6}$ µg/kg/day) was derived for 2,3,4,7,8-pentaCDF based on increased incidences of hepatocellular hypertrophy and cystic degeneration in adrenal cortex of female rats administered via gavage 0.006 µg/kg 2,3,4,7,8-pentaCDF 5 days/week for 2 years (NTP 2006). The MRL is based on a LOAEL of 0.006 µg/kg adjusted for continuous duration to a $LOAEL_{ADJ}$ of 0.0043 µg/kg/day and a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: One study (NTP 2006) evaluated the chronic oral toxicity of 2,3,4,7,8-pentaCDF; the results of this study are summarized in Table A-17. The hepatocellular hypertrophy and cystic degeneration in the adrenal gland were selected as the co-critical effects because these endpoints had the lowest LOAEL values (0.006 µg/kg).

Table A-17. Summary of Health Effects in Female Rats Administered 2,3,4,7,8-Pentachlorodibenzofuran 5 Days/week for 2 Years

	NOAEL (µg/kg)	LOAEL (µg/kg)	Effect
Hepatic		0.006	Minimal hepatocellular hypertrophy
		0.02	Diffuse fatty changes in liver
		0.2	Minimal to mild necrosis in liver Bile duct hyperplasia, bile duct fibrosis, and cholangiofibrosis
Endocrine		0.006	Cystic degeneration in adrenal cortex
		0.02	Follicular cell hypertrophy in thyroid gland
		0.044	Decreased serum total T4 levels (22%) and serum free T4 levels (17%) (measured at 53 weeks)
		0.092	Increased serum total T3 levels (23%) (measured at 53 weeks)
		0.2	Arterial chronic active inflammation in pancreas
Renal	0.02	0.044	Nephropathy
Reproductive	0.02	0.044	Squamous metaplasia in uterus
Other noncancer	0.02	0.044	Gingival squamous hyperplasia
Cardiovascular	0.092	0.2	Cardiomyopathy

Table A-17. Summary of Health Effects in Female Rats Administered 2,3,4,7,8-Pentachlorodibenzofuran 5 Days/week for 2 Years

	NOAEL (µg/kg)	LOAEL (µg/kg)	Effect
Respiratory	0.044	0.092	Bronchiolar metaplasia of alveolar epithelium
Gastrointestinal	0.092	0.2	Squamous hyperplasia of the forestomach
Immunological	0.092	0.2	Increased severity of thymic atrophy

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; T4 = thyroxine

Source: NTP 2006

Selection of the Principal Study: The NTP (2006) study was selected as the principal study.

Summary of the Principal Study:

NTP. 2006. Toxicology and carcinogenesis studies of 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) (CAS No. 57117-31-4) in female Harlan Sprague-Dawley rats (gavage studies). NTP TR 525.

Groups of 81 female Harlan Sprague-Dawley rats were administered via gavage 0, 6, 20, 44, 92, or 200 ng/kg (0, 0.006, 0.02, 0.044, 0.092, and 0.2 µg/kg) 2,3,4,7,8-pentaCDF in a corn oil:acetone vehicle 5 days/week for 105 weeks. Interim examinations were conducted in groups of 10 rats exposed for 53 weeks. Another group of 50 rats were exposed to 0.200 µg/kg for 30 weeks and held for the remainder of the 2-year study. The following parameters were used to assess toxicity in the core study groups and stop-exposure group: clinical observations, body weight, and complete histopathological examination. In rats exposed for 53 weeks, the following parameters were used to assess toxicity: clinical observations, body weight, organ weights (kidney, liver, lung, ovary, spleen, thymus, and thyroid), thyroid hormone levels (TSH, T3, T4), cell proliferation measured in liver and duodenum samples, cytochrome P450 activities in liver and lung samples, and histopathological examination of the adrenal gland, liver, lung, mammary gland, ovary, pancreas, pituitary gland, spleen, stomach, thymus, thyroid gland, uterus, and vagina in the 0 and 0.2 µg/kg groups; liver; thymus, and uterus in all groups.

No significant alterations in survival were observed. Some decreases in body weight were observed; however, throughout the study, body weights were within 10% of controls. After 53 weeks of exposure to 0.044, 0.092, and 0.2 µg/kg, decreased serum total T4 levels (22, 35, and 34%, respectively) and decreased free T4 levels (17, 22, and 9%, respectively) were observed; increased total T3 levels were observed at 0.092 and 0.2 µg/kg (16 and 19%). After 53 weeks of exposure, an increase in the incidence of hepatocellular hypertrophy was observed at 0.2 µg/kg and an increase in liver pigmentation was observed at ≥0.044 µg/kg.

Nonneoplastic lesions were also observed in the lungs, heart, forestomach, liver, kidneys, pancreas, thyroid, adrenal gland, thymus, uterus, and gingiva of rats exposed for 2 years:

- Lungs: Bronchiolar metaplasia of alveolar epithelium was observed in rats exposed to ≥0.092 µg/kg for 2 years.
- Heart: Increased incidences of cardiomyopathy at 0.2 µg/kg.
- Forestomach: Increased incidences of squamous hyperplasia in the forestomach at 0.2 µg/kg.
- Liver: Minimal hepatocellular hypertrophy at ≥0.006 µg/kg; minimal diffuse fatty changes, pigmentation, and multinucleated hepatocytes at ≥0.02 µg/kg; minimal to mild toxic hepatopathy (includes all nonneoplastic liver alterations under one term) at ≥0.044 µg/kg; and mild necrosis,

mild bile duct hyperplasia, minimal bile duct fibrosis, and mild cholangiofibrosis at 0.2 μg/kg. Most of the effects observed in the 0.2 μg/kg group were also observed in the 0.2 μg/kg stop exposure group, although the incidences were lower than in the rats exposed to 0.2 μg/kg for 2 years.

- Kidney: Increased incidence of nephropathy in the 0.044 and 0.2 μg/kg groups.
- Pancreas: Minimal acinar cytoplasmic vacuolization and moderate arterial chronic active inflammation in the 0.2 μg/kg groups.
- Thyroid: Follicular cell hypertrophy in the thyroid of rats exposed to ≥0.02 μg/kg.
- Adrenal gland: Mild cystic degeneration in the adrenal cortex of rats exposed to ≥0.006 μg/kg; also observed in the 0.2 μg/kg stop exposure group.
- Thymus: Dose-related increases in the severity of the thymic atrophy; the severity was mild in the control group compared to moderate to marked in the 0.2 μg/kg group. No significant increases in the incidence of thymus atrophy.
- Uterus: Cystic endometrial hyperplasia at ≥0.092 μg/kg and squamous metaplasia at ≥0.044 μg/kg; increased incidences of chronic active inflammation and squamous metaplasia were also observed in the 0.2 μg/kg stop exposure group.
- Gingiva: A nonsignificant increase in the incidence of gingival squamous hyperplasia was observed at 0.044 μg/kg; the investigators considered this to be treatment related.

A dose-related increase in the incidence of hepatocellular adenoma was observed; however, the incidence was not significantly increased at any dose level. A nonsignificant increase in the incidence of cholangiocarcinoma was observed at 0.2 μg/kg; the investigators noted that the observed cholangiocarcinoma differed morphologically from spontaneous cholangiocarcinoma and was considered treatment related. A nonsignificant increase in the incidence of gingival squamous cell carcinomas was observed in the 0.2 μg/kg group; the investigators considered these lesions to be treatment related. Nonsignificant increases in neoplastic lesions were also observed in the lungs, pancreas, and uterus; the incidence of some of these lesions was higher than historical controls and the investigators concluded that these lesions may be treatment related. The lesions included cystic keratinizing epithelioma in the lung of one rat in the 0.2 μg/kg group; acinus adenoma or carcinoma in the pancreas in the 0.092 μg/kg group and in the 0.2 μg/kg stop exposure group; and uterine carcinoma in the 0.092 and 0.2 μg/kg groups.

Selection of the Point of Departure for the MRL: The LOAEL of 0.006 μg/kg was selected as the POD.

BMD modeling was conducted to identify a potential POD using the incidence data for hepatocellular hypertrophy and cystic degeneration in the adrenal cortex, which are summarized in Table A-18. These two endpoints were selected for BMD analysis because they identified the lowest LOAEL values. The data were fit to all available dichotomous models in EPA's BMDS (version 3.1.2) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. A BMR of 10% was used. None of the available BMD models provided adequate fit for the liver or adrenal data. Thus, a NOAEL/LOAEL approach was used to select the POD.

Table A-18. Incidence of Nonneoplastic Lesions in the Liver and Adrenal Gland of Female Rats Administered 2,3,4,7,8-Pentachlorodibenzofuran 5 Days/Week for 2 Years

Dose level (µg/kg)	Hepatocellular hypertrophy	Cystic degeneration in adrenal cortex
0	2/53	4/53
0.006	13/53[a]	17/53[a]
0.02	17/53[a]	14/53[a]
0.044	17/52[a]	18/52[a]
0.092	24/53[a]	12/53[a]
0.2	34/53[a]	14/53[a]

[a]Significantly different from vehicle control, p<0.01.

Source: NTP 2006

Intermittent Exposure: The LOAEL of 0.006 µg/kg/day was adjusted for intermittent exposure.

$LOAEL_{ADJ}$ = 0.006 µg/kg/day x 5 days/7 days = 0.0043 µg/kg/day.

Uncertainty Factor: The $LOAEL_{ADJ}$ is divided by a total uncertainty factor (UF) of 1,000:

- 10 for the use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = $LOAEL_{ADJ}$ ÷ UF
MRL = 0.0043 µg/kg/day ÷ 1000 = 0.000004 µg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Although only one study evaluated the chronic toxicity of 2,3,4,7,8-pentaCDF; 14- and 31-week studies conducted by NTP (2006) provide support for the selection of the critical effects and POD.

Agency Contacts (Chemical Managers): Hana R. Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,7,8-Hexachlorodibenzofuran
CAS Numbers: 70648-26-9
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of acute-, intermediate-, or chronic-duration inhalation MRLs for 1,2,3,4,7,8-hexaCDF 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-hexaCDF following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,7,8-Hexachlorodibenzofuran
CAS Numbers: 70648-26-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of an acute-duration oral MRL for 1,2,3,4,7,8-hexaCDF due to the limited scope of the available studies evaluating toxicity following acute oral exposure.

Rationale for Not Deriving an MRL: Two developmental toxicity studies have evaluated the toxicity of 1,2,3,4,7,8-hexaCDF following acute-duration oral exposure. Both studies identified a LOAEL of 100 μg/kg/day (lowest dose tested) for hydronephrosis in the offspring of mice administered 1,2,3,4,7,8-hexaCDF on GDs 10–13 (Birnbaum et al. 1987a, 1987b); an increased incidence of cleft palate was also observed at ≥300 μg/kg/day. Studies with other 2,3,7,8-substituted CDFs confirm that hydronephrosis is a sensitive endpoint of CDF toxicity. However, there are other sensitive targets, such as the liver and thymus, which were not fully examined in the Birnbaum et al. (1987a, 1987b) studies; both studies reported increases in maternal relative liver weight at ≥100 μg/kg/day.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,7,8-Hexachlorodibenzofuran
CAS Numbers: 70648-26-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of an intermediate-duration oral MRL for 1,2,3,4,7,8-hexaCDF due to the lack of studies evaluating intermediate toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,4,7,8-hexaCDF following intermediate-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,7,8-Hexachlorodibenzofuran
CAS Numbers: 70648-26-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for 1,2,3,4,7,8-hexaCDF due to the lack of studies evaluating chronic toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,4,7,8-hexaCDF following chronic-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,6,7,8-Hexachlorodibenzofuran
CAS Numbers: 57117-44-9
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of acute-, intermediate-, or chronic-duration inhalation MRLs for 1,2,3,6,7,8-hexaCDF 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-hexaCDF following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,6,7,8-Hexachlorodibenzofuran
CAS Numbers: 57117-44-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of an acute-duration oral MRL for 1,2,3,6,7,8-hexaCDF due to the lack of studies evaluating acute toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,6,7,8-hexaCDF following acute-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,6,7,8-Hexachlorodibenzofuran
CAS Numbers: 57117-44-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.005 µg/kg/day
Critical Effect: Increased liver weight and decreased thymus weight
Reference: Pluess et al. 1988a
Point of Departure: $BMDL_{1SD}$ of 0.48 µg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 41
Species: Rat

MRL Summary: An intermediate-duration oral MRL of 0.005 µg/kg/day was derived for 1,2,3,6,7,8-hexaCDF based on increases in relative liver weight and decreases in absolute thymus weight in rats exposed to 2 µg/kg/day 1,2,3,6,7,8-hexaCDF in the diet for 13 weeks (Pluess et al. 1988a). The MRL is based on a $BMDL_{1SD}$ of 0.48 µg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: One study evaluated the toxicity of 1,2,3,6,7,8-hexaCDF following intermediate-duration oral exposure (Pluess et al. 1988a). The results of this study are summarized in Table A-19. The study identified several targets of toxicity including the liver, thymus, and body weight. The increases in liver weight, histological alterations in the liver, and decreases in thymus weight were selected as co-critical effects.

Table A-19. Summary of Health Effects Following Intermediate-Duration Oral Exposure to 1,2,3,6,7,8-Hexachlorodibenzofuran

Species, duration	NOAEL (µg/kg/day)	LOAEL (µg/kg/day)	Effect	Reference
Rat 13 weeks	0.2	2	• Increased relative liver weight (15% in males), vacuolization with lipid accumulation, single cell necrosis • Decreased absolute thymus weight (40–42%)	Pluess et al. 1988a
		20	• Decreased body weight gain (14–20%) • Thymic atrophy[a]	

[a]Considered a serious health effect.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: The Pluess et al. (1988a) (data also reported in Poiger et al. 1989) study is the only study evaluating intermediate-duration toxicity of 1,2,3,6,7,8-hexaCDF and was selected as the principal study.

Summary of the Principal Study:

Pluess N, Poiger H, Hohbach C, et al. 1988a. Subchronic toxicity of some chlorinated dibenzofurans (PCDFs) and a mixture of PCDFs and chlorinated dibenzodioxins (PCDDs) in rats. Chemosphere. 17:973-984.

Groups of six male and six female Iva:SIV 50(SD) rats were exposed to 0, 2, 20, or 200 μg/kg 1,2,3,6,7,8-hexaCDF in the diet for 13 weeks. Doses were calculated using a reference food intake of 0.016 kg/day and reference body weight of 0.152 kg (EPA 1989b); estimated doses were 0, 0.2, 2, and 20 μg/kg/day in the 0, 2, 20, and 200 μg/kg groups, respectively. The following parameters were used to evaluate toxicity: weekly body weight and food consumption measurements, hematological parameters (red blood cells, total and differential white blood cells, reticulocyte and thrombocyte counts, hemoglobin levels, and packed cell volume) and serum clinical chemistry indices (bilirubin, triglycerides, urea, cholesterol, alkaline phosphatase, ALT), organ weights (liver, thymus, spleen, kidneys, heart, and testes), and histopathology (lungs, liver, thymus, spleen, kidneys, heart, thyroid/parathyroids, adrenals, mesenteric and submandibular lymph nodes, uterus, ovaries, and testes).

No deaths occurred in either sex and there were no treatment-related effects on body weight or food consumption. Significant decreases in hemoglobin (9%) in both sexes and thrombocyte count (40%) in females were observed at 20 μg/kg/day. No significant effects on white blood cell count, red blood cell count, or packed cell volume were observed. Significant increases in serum alkaline phosphatase (18%) were observed in females at 2 μg/kg/day and increased serum cholesterol (26 and 33%) and decreased triglycerides (35 and 48%) were observed in both sexes at 20 μg/kg/day. No significant alterations in serum bilirubin, ALT, or urea were observed. Significant increases in relative liver weight were observed at 2 μg/kg/day in males (15%) and at 20 μg/kg/day in females (32%). Histological alterations were observed in the liver at 2 μg/kg/day and were more pronounced at 20 μg/kg/day; lesions included vacuolization with increased lipid content, single cell necrosis, and slight Kupffer cell hyperplasia. Significant decreases in relative thymus weight (40–42%) and histologic evidence of possible initial thymic atrophy were observed at 2 μg/kg/day. Marked thymic atrophy was observed at 20 μg/kg/day. The investigators did not provide incidence data for the liver or thymus histological alterations. No histological alterations were observed in the heart, kidneys, adrenal glands, spleen, lymph nodes, testes, uterus, or ovaries.

Selection of the Point of Departure for the MRL: A $BMDL_{1SD}$ of 0.48 μg/kg/day for increases in relative liver weight and decreases in absolute thymus weight was selected as the POD.

BMD modeling was conducted to identify a potential POD using the data for increases in relative liver weight in males and decreases in absolute thymus weight in males and females, which are summarized in Table A-20. Relative liver weight data for females was not modeled because it was only significantly increased at 20 μg/kg/day. The investigators did not provide incidence data for the liver or thymus histological alterations, which precluded BMD analyses of these data. The organ weight data were fit to all available continuous models in EPA's BMDS (version 3.1.2) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. A BMR of 1 standard deviation from the control mean was selected in the absence of a biologically based BMR.

Table A-20. Relative Liver and Absolute Thymus Weights in Male and Female Rats Exposed to 1,2,3,6,7,8-Hexachlorodibenzofuran in the Diet for 13 Weeks

Dose level (µg/kg/day)	Relative liver weight (mean±SD) (g)		Absolute thymus weight (mean±SD) (g)	
	Males	Females	Males	Females
0	3.35±0.26	3.37±0.23	0.48±0.02	0.48±0.09
0.2	3.27±0.26	3.56±0.26	0.45±0.08	0.41±0.08
2	3.85±0.21[a]	3.57±0.07	0.28±0.07[a]	0.29±0.04[a]
20	4.83±0.28[a]	4.45±0.27[a]	0.12±0.02[a]	0.10±0.02[a]

[a]Significantly different from control, $p<0.05$.

SD = standard deviation

Source: Pluess et al. 1988a

Only one model (with constant variance) provided adequate fit to the increases in relative liver weight in male rats. The Exponential 4-degree model estimated a BMD_{1SD} and $BMDL_{1SD}$ of 0.75 and 0.48 µg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-21 and the Exponential 4 model is illustrated in Figure A-6. None of the BMD models (with constant variance or nonconstant variance) provided adequate fit to the absolute thymus weights in male rats. Two models provided adequate fit for the absolute thymus weight in female rats, summarized in Table A-22. Both models identified a BMD_{1SD} of 0.73 µg/kg/day and $BMDL_{1SD}$ of 0.48 µg/kg/day. The Exponential 5-degree model (with nonconstant variance) is illustrated in Figure A-7.

Table A-21. Results from BMD Analysis (Constant Variance) of Relative Liver Weight in Male Rats Exposed to 1,2,3,6,7,8-Hexachlorodibenzofuran in the Diet for 13 Weeks (Pluess et al. 1988a)

Model	BMD_{1SD}[a] (µg/kg/day)	$BMDL_{1SD}$[a] (µg/kg/day)	Test 4 p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Exponential 2[d]			0.004	14.97	2.44	-0.754
Exponential 3[d]			0.004	14.97	2.44	-0.754
Exponential 4[d,e]	**0.75**	**0.48**	**0.273**	**7.12**	**-0.82**	**0.702**
Exponential 5[d]			NA	8.27	0.00	0.420
Hill[c]			NA	8.27	0.00	0.420
Polynomial Degree 3[d]			0.006	14.17	2.38	-0.674
Polynomial Degree 2[d]			0.006	14.17	2.38	-0.674
Power[d]			0.006	14.17	2.38	-0.674
Linear			0.006	14.17	2.38	-0.674

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Recommended model. There was an adequate fit to the variance when assuming constant variance. Only one model (Exponential 4) provided adequate fit.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control); NA = not applicable, goodness-of-fit test could not be performed

Figure A-6. Fit of Exponential 4 Model (with Constant Variance) to Relative Liver Weight in Male Rats Exposed to 1,2,3,6,7,8-Hexachlorodibenzofuran

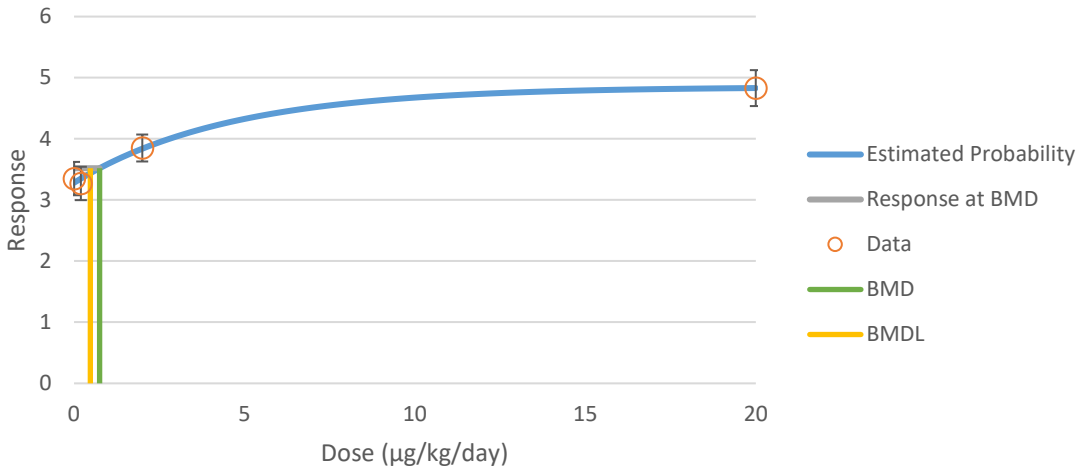


Table A-22. Results from BMD Analysis (Nonconstant Variance) of Absolute Thymus Weight in Female Rats Exposed to 1,2,3,6,7,8-Hexachlorodibenzofuran in the Diet for 13 Weeks (Pluess et al. 1988a)

Model	BMD_{1SD}[a] (µg/kg/day)	$BMDL_{1SD}$[a] (µg/kg/day)	Test 4 p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMD	Dose above BMD
Exponential 2[d]			0.003	-60.23	-2.11	1.828
Exponential 3[d]			0.003	-60.23	-2.11	1.828
Exponential 4[d]	0.73	0.48	0.265	-68.91	-0.86	0.656
Exponential 5[d,e]	**0.73**	**0.48**	**0.265**	**-68.91**	**-0.87**	**0.653**
Hill[c]			NA	-65.55	0.21	1.005
Polynomial Degree 3[d]			0.001	-57.26	-2.28	1.972
Polynomial Degree 2[d]			0.001	-57.26	-2.28	1.972
Power[d]			0.001	-57.26	-2.28	1.972
Linear			0.001	-57.26	-2.28	1.972

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet adequate fit.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Restricted model.
[e]Recommended model. There was an adequate fit to the variance when assuming constant variance. Of the models providing adequate fit, the BMDLs were sufficiently close (differed by <3-fold); therefore, the model with the lowest AIC was selected (Exponential 5).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control); NA = not applicable, goodness-of-fit test could not be performed

Figure A-7. Fit of Exponential 5 Model (with Nonconstant Variance) to Absolute Thymus Weight in Female Rats Exposed to 1,2,3,6,7,8-Hexachlorodibenzofuran

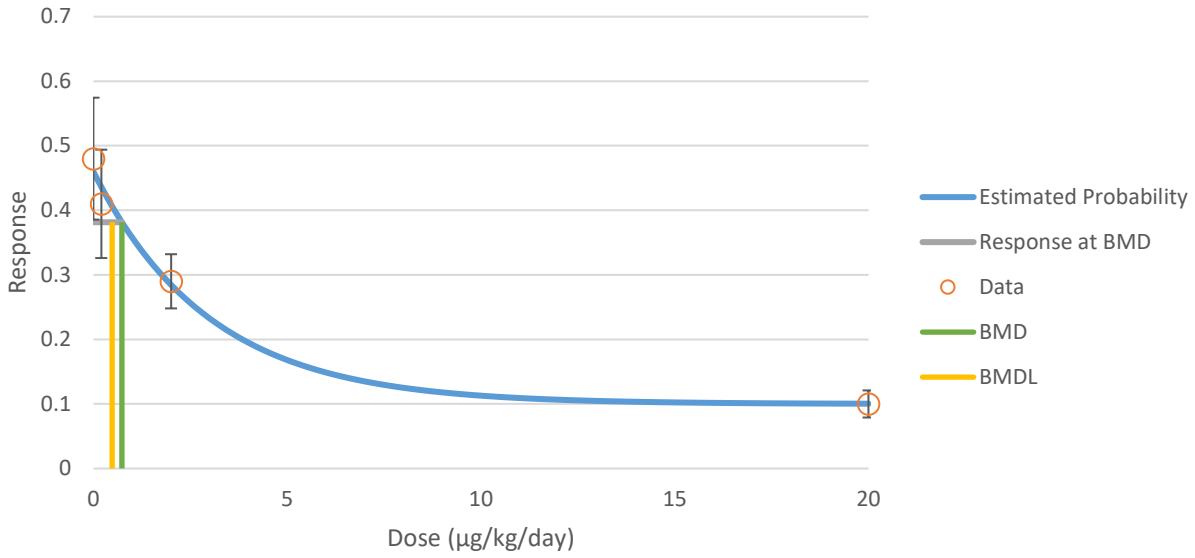


Table A-23 summarizes the potential candidate PODs for 1,2,3,6,7,8-hexaCDF. The lowest candidate POD was 0.48 µg/kg/day for increases in relative liver weight in males and decreases in absolute thymus weight in females; the $BMDL_{1SD}$ for these endpoints was selected as the POD.

Table A-23. Candidate Points of Departure 1,2,3,6,7,8-Hexachlorodibenzofuran Intermediate-Duration Oral MRL

Endpoint	NOAEL (µg/kg/day)	BMD_{1SD} (µg/kg/day)	$BMDL_{1SD}$ (µg/kg/day)
Increases in relative liver weight in males		0.75	0.48
Histological alterations in the liver (vacuolization with increased lipid content, single cell necrosis and slight Kupffer cell hyperplasia)	2		
Decrease in absolute thymus weight in males	2		
Decrease in absolute thymus weight in females		0.73	0.48

BMD = benchmark dose; BMDL = 95% lower confidence limit on the BMD; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; SD = standard deviation

Uncertainty Factor: The $BMDL_{1SD}$ is divided by a total uncertainty factor (UF) of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = $BMDL_{1SD}$ ÷ UF
0.48 µg/kg/day ÷ (10 x 10) = 0.0048 µg/kg/day ≈ 0.005 µg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Although there are limited data on the toxicity of 12,3,6,7,8-hexaCDF, identification of the liver and thymus as sensitive

targets is supported by other studies of 2,3,7,8-substituted CDF congeners. The liver and/or thymus were the most sensitive targets following intermediate-duration exposure to 2,3,7,8-tetraCDF (McNulty et al. 1981), 1,2,3,7,8-penta CDF (Pluess et al. 1988a), 2,3,4,7,8-pentaCDF (NTP 2006), and following chronic exposure to 2,3,4,7,8-pentaCDF (NTP 2006).

Agency Contacts (Chemical Managers): Hana R. Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,6,7,8-Hexachlorodibenzofuran
CAS Numbers: 57117-44-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for 1,2,3,6,7,8-hexaCDF due to the lack of studies evaluating chronic toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,6,7,8-hexaCDF following chronic-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,6,7,8-Heptachlorodibenzofuran
CAS Numbers: 67562-39-4
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of acute-, intermediate-, or chronic-duration inhalation MRLs for 1,2,3,4,6,7,8-heptaCDF 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-heptaCDF following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,6,7,8-Heptachlorodibenzofuran
CAS Numbers: 67562-39-4
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of an acute-duration oral MRL for 1,2,3,4,6,7,8-heptaCDF because the only available acute-duration oral study examined a limited number of endpoints.

Rationale for Not Deriving an MRL: One study evaluated the oral toxicity of 1,2,3,4,6,7,8-heptaCDF in laboratory animals. In this study, an ED_{50} of 208 µg/kg was identified for decreased antibody response to SRBC in mice administered a single gavage dose of 1,2,3,4,6,7,8-heptaCDF (Kerkvliet et al. 1985). Although studies on other 2,3,7,8-substituted CDFs identify the immune system as a target of toxicity, there are inadequate data to evaluate whether this would be the most sensitive effect for 1,2,3,4,6,7,8-heptaCDF. Thus, the database was not considered adequate to support derivation of an acute-duration oral MRL.

***Agency Contacts (Chemical Managers*):** Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,6,7,8-Heptachlorodibenzofuran
CAS Numbers: 67562-39-4
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of an intermediate-duration oral MRL for 1,2,3,4,6,7,8-heptaCDF due to the lack of studies evaluating intermediate toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,4,6,7,8-heptaCDF following intermediate-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,6,7,8-Heptachlorodibenzofuran
CAS Numbers: 67562-39-4
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for 1,2,3,4,6,7,8-heptaCDF due to the lack of studies evaluating chronic toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of 1,2,3,4,6,7,8-heptaCDF following chronic-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,6,7,8,9-Octachlorodibenzofuran
CAS Numbers: 39001-02-0
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Acute, Intermediate, Chronic

MRL Summary: There are insufficient data for the derivation of acute-, intermediate-, or chronic-duration inhalation MRLs for octaCDF 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 octaCDF following inhalation exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,6,7,8,9-Octachlorodibenzofuran
CAS Numbers: 39001-02-0
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of an acute-duration oral MRL for octaCDF because the only available study did not report adverse effects at the highest dose tested.

Rationale for Not Deriving an MRL: One animal study evaluated the toxicity of octaCDF following acute-duration oral exposure. In this study, no alterations in serum total T4 levels were observed in rats administered doses as high as 300 µg/kg/day for 4 days (Crofton et al. 2005).

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,6,7,8,9-Octachlorodibenzofuran
CAS Numbers: 39001-02-0
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of an intermediate-duration oral MRL for octaCDF due to the lack of studies evaluating chronic toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of octaCDF following intermediate-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,6,7,8,9-Octachlorodibenzofuran
CAS Numbers: 39001-02-0
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for octaCDF due to the lack of studies evaluating chronic toxicity.

Rationale for Not Deriving an MRL: No human or animal studies have evaluated the toxicity of octaCDF following chronic-duration oral exposure.

Agency Contacts (Chemical Managers): Hana Pohl

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR CDFS

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 CDFs.

B.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 CDFs. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of CDFs 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 CDFs are presented in Table B-1.

Table B-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
Developmental effects
Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

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

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for CDFs released for public comment in 2022; thus, the literature search was restricted to studies published between January 2018 and June 2022. The following main databases were searched in June 2022:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for CDFs. The query strings used for the literature search are presented in Table B-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 B-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 CDFs 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 B-2. Database Query Strings

Database search date	Query string
PubMed	
06/2022	(("Dibenzofurans, Polychlorinated/toxicity"[mh] OR "Dibenzofurans, Polychlorinated/adverse effects"[mh] OR "Dibenzofurans, Polychlorinated/poisoning"[mh] OR "Dibenzofurans, Polychlorinated/pharmacokinetics"[mh]) OR ("Dibenzofurans, Polychlorinated"[mh] AND ("environmental exposure"[mh] OR "occupational groups"[mh] OR ci[sh])) OR ("Dibenzofurans, Polychlorinated"[mh] AND toxicokinetics[mh:noexp]) OR ("Dibenzofurans, Polychlorinated/blood"[mh] OR "Dibenzofurans, Polychlorinated/cerebrospinal fluid"[mh] OR "Dibenzofurans, Polychlorinated/urine"[mh]) OR ("Dibenzofurans, Polychlorinated"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Dibenzofurans, Polychlorinated"[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 ("Dibenzofurans, Polychlorinated/antagonists and inhibitors"[mh]) OR ("Dibenzofurans, Polychlorinated/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Dibenzofurans, Polychlorinated/pharmacology"[majr])) AND (2019/06/01:3000[mhda] OR 2019/06/01:3000[crdat] OR 2019/06/01:3000[edat] OR 2019:3000[dp]) (("Dibenzofurans, Polychlorinated"[mh]) OR (39001-02-0[rn] OR 51207-31-9[rn] OR 55673-89-7[rn] OR 57117-31-4[rn] OR 57117-35-8[rn] OR 57117-37-0[rn] OR 57117-41-6[rn] OR 57117-44-9[rn] OR 60851-34-5[rn] OR 67517-48-0[rn] OR 67562-39-4[rn] OR 69698-58-4[rn] OR 70648-25-8[rn] OR 70648-26-9[rn] OR 72918-21-9[rn] OR 75627-02-0[rn] OR 42934-53-2[rn] OR 30402-14-3[rn] OR 30402-15-4[rn] OR 55684-94-1[rn] OR 38998-75-3[rn] OR "1,2,3,4,6,7,8-heptachlorodibenzofuran"[nm] OR "1,2,3,4-tetrachlorodibenzofuran"[nm] OR "polychlorodibenzofuran"[nm]) OR (136677-10-6[rn] OR 43047-99-0[rn] OR 51230-49-0[rn] OR 25074-67-3[rn] OR 74992-96-4[rn] OR 94538-00-8[rn] OR 5409-83-6[rn] OR 64560-14-1[rn] OR 54589-71-8[rn] OR 24478-72-6[rn] OR 58802-19-0[rn] OR 58802-20-3[rn] OR 71998-72-6[rn] OR 74992-98-6[rn] OR 43048-00-6[rn] OR 57117-39-2[rn] OR 57117-40-5[rn] OR 57117-43-8[rn] OR 75198-38-8[rn] OR 79060-60-9[rn] OR 91538-83-9[rn] OR 91538-84-0[rn] OR 92341-05-4[rn] OR 92341-06-5[rn] OR 92341-07-6[rn]) OR ("DCDF"[tw] OR "diCDF"[tw] OR "di-CDF"[tw] OR "HCDF"[tw]

Table B-2. Database Query Strings

Database search date	Query string
	OR "heptaCDF"[tw] OR "hepta-CDF"[tw] OR "hexaCDF"[tw] OR "hexa-CDF"[tw] OR "HpCDF"[tw] OR "HxCDF"[tw] OR "moCDF"[tw] OR "monoCDF"[tw] OR "mono-CDF"[tw] OR "OCDF"[tw] OR "octaCDF"[tw] OR "octa-CDF"[tw] OR "PCDF"[tw] OR "PeCDF"[tw] OR "pentaCDF"[tw] OR "penta-CDF"[tw] OR "Tcdbf"[tw] OR "TCDF"[tw] OR "tetraCDF"[tw] OR "tetra-CDF"[tw] OR "triCDF"[tw] OR "tri-CDF"[tw]) OR ("DCDFs"[tw] OR "diCDFs"[tw] OR "di-CDFs"[tw] OR "HCDFs"[tw] OR "heptaCDFs"[tw] OR "hepta-CDFs"[tw] OR "hexaCDFs"[tw] OR "hexa-CDFs"[tw] OR "HpCDFs"[tw] OR "HxCDFs"[tw] OR "moCDFs"[tw] OR "monoCDFs"[tw] OR "mono-CDFs"[tw] OR "OCDFs"[tw] OR "octaCDFs"[tw] OR "octa-CDFs"[tw] OR "PCDFs"[tw] OR "PeCDFs"[tw] OR "pentaCDFs"[tw] OR "penta-CDFs"[tw] OR "Tcdbfs"[tw] OR "TCDFs"[tw] OR "tetraCDFs"[tw] OR "tetra-CDFs"[tw] OR "triCDFs"[tw] OR "tri-CDFs"[tw]) OR ("CDF"[tw] AND "Benzofurans"[mh]) OR ("CDFs"[tw] AND "Benzofurans"[mh]) OR ("chlorodibenzofuran"[tw] OR "polychlorodibenzofuran"[tw] OR "monochlorodibenzofuran"[tw] OR "dichlorodibenzofuran"[tw] OR "trichlorodibenzofuran"[tw] OR "tetrachlorodibenzofuran"[tw] OR "pentachlorodibenzofuran"[tw] OR "hexachlorodibenzofuran"[tw] OR "heptachlorodibenzofuran"[tw] OR "octachlorodibenzofuran"[tw] OR "perchlorodibenzofuran"[tw] OR "chlorinated dibenzofuran"[tw] OR "polychlorinated dibenzofuran"[tw]) OR ("chlorodibenzofurans"[tw] OR "polychlorodibenzofurans"[tw] OR "monochlorodibenzofurans"[tw] OR "dichlorodibenzofurans"[tw] OR "trichlorodibenzofurans"[tw] OR "tetrachlorodibenzofurans"[tw] OR "pentachlorodibenzofurans"[tw] OR "hexachlorodibenzofurans"[tw] OR "heptachlorodibenzofurans"[tw] OR "octachlorodibenzofurans"[tw] OR "perchlorodibenzofurans"[tw] OR "chlorinated dibenzofurans"[tw] OR "polychlorinated dibenzofurans"[tw]) OR ("chloro dibenzofuran"[tw] OR "polychloro dibenzofuran"[tw] OR "monochloro dibenzofuran"[tw] OR "dichloro dibenzofuran"[tw] OR "trichloro dibenzofuran"[tw] OR "tetrachloro dibenzofuran"[tw] OR "pentachloro dibenzofuran"[tw] OR "hexachloro dibenzofuran"[tw] OR "heptachloro dibenzofuran"[tw] OR "octachloro dibenzofuran"[tw] OR "perchloro dibenzofuran"[tw]) OR ("chloro dibenzofurans"[tw] OR "polychloro dibenzofurans"[tw] OR "monochloro dibenzofurans"[tw] OR "dichloro dibenzofurans"[tw] OR "trichloro dibenzofurans"[tw] OR "tetrachloro dibenzofurans"[tw] OR "pentachloro dibenzofurans"[tw] OR "hexachloro dibenzofurans"[tw] OR "heptachloro dibenzofurans"[tw] OR "octachloro dibenzofurans"[tw] OR "perchloro dibenzofurans") OR ("dibenzofuran, chloro-"[tw] OR "dibenzofuran, dichloro-"[tw] OR "dibenzofuran, trichloro-"[tw] OR "dibenzofuran, tetrachloro-"[tw] OR "dibenzofuran, pentachloro-"[tw] OR "dibenzofuran, hexachloro-"[tw] OR "dibenzofuran, heptachloro-"[tw] OR "Dibenzofuran, octachloro-"[tw] OR "monochlordibenzofuran"[tw] OR "chlorinated dibenzo-furan"[tw] OR "polychlorinated dibenzo-furan"[tw]) OR ("chlorinated dibenzo-furans"[tw] OR "dibenzofurans, chlorinated"[tw] OR "hepta chloro furans"[tw] OR "heptachlorofurans"[tw] OR "penta chloro furans"[tw] OR "polychlorinated dibenzo-furans"[tw]) OR (("chlorinated"[tw] AND "dibenzofuran"[tw]) OR ("polychlorinated"[tw] AND "dibenzofuran"[tw]) OR (("monochlorinated"[tw] OR "dichlorinated"[tw] OR "trichlorinated"[tw] OR "tetrachlorinated"[tw] OR "pentachlorinated"[tw] OR "hexachlorinated"[tw] OR "heptachlorinated"[tw] OR "octachlorinated"[tw] OR "perchlorinated") AND "dibenzofuran"[tw]) OR (("dipolychlorinated"[tw] OR "tripolychlorinated"[tw] OR "tetrapolychlorinated"[tw] OR "pentapolychlorinated"[tw] OR "hexapolychlorinated"[tw] OR "heptapolychlorinated"[tw] OR "octapolychlorinated"[tw] OR "perpolychlorinated"[tw] OR "polypolychlorinated"[tw]) AND "dibenzofuran"[tw])) OR (("chlorinated"[tw] AND "dibenzofurans"[tw]) OR ("polychlorinated"[tw] AND "dibenzofurans"[tw]) OR (("monochlorinated"[tw] OR "dichlorinated"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"trichlorinated"[tw] OR "tetrachlorinated"[tw] OR "pentachlorinated"[tw] OR "hexachlorinated"[tw] OR "heptachlorinated"[tw] OR "octachlorinated"[tw] OR "perchlorinated") AND "dibenzofurans"[tw]) OR (("dipolychlorinated"[tw] OR "tripolychlorinated"[tw] OR "tetrapolychlorinated"[tw] OR "pentapolychlorinated"[tw] OR "hexapolychlorinated"[tw] OR "heptapolychlorinated"[tw] OR "octapolychlorinated"[tw] OR "perpolychlorinated"[tw] OR "polypolychlorinated"[tw]) AND "dibenzofurans"[tw])) OR ("CDD/F"[tw] OR "DCDD/F"[tw] OR "diCDD/F"[tw] OR "HCDD/F"[tw] OR "HpCDD/F"[tw] OR "HxCDD/F"[tw] OR "MCDD/F"[tw] OR "moCDD/F"[tw] OR "monoCDD/F"[tw] OR "OCDD/F"[tw] OR "PCDD/F"[tw] OR "PeCDD/F"[tw] OR "TCDD/F"[tw] OR "triCDD/F"[tw] OR "CDD/Fs"[tw] OR "DCDD/Fs"[tw] OR "diCDD/Fs"[tw] OR "HCDD/Fs"[tw] OR "HpCDD/Fs"[tw] OR "HxCDD/Fs"[tw] OR "MCDD/Fs"[tw] OR "moCDD/Fs"[tw] OR "monoCDD/Fs"[tw] OR "OCDD/Fs"[tw] OR "PCDD/Fs"[tw] OR "PeCDD/Fs"[tw] OR "TCDD/Fs"[tw] OR "triCDD/Fs"[tw]) OR ("chlorodiphenylene oxide"[tw] OR "monochlorodiphenylene oxide"[tw] OR "dichlorodiphenylene oxide"[tw] OR "trichlorodiphenylene oxide"[tw] OR "tetrachlorodiphenylene oxide"[tw] OR "pentachlorodiphenylene oxide"[tw] OR "hexachlorodiphenylene oxide"[tw] OR "heptachlorodiphenylene oxide"[tw] OR "octachlorodiphenylene oxide"[tw] OR "perchlorodiphenylene oxide"[tw] OR "polychlorodiphenylene oxide"[tw] OR "chlorodiphenylene oxides"[tw] OR "monochlorodiphenylene oxides"[tw] OR "dichlorodiphenylene oxides"[tw] OR "trichlorodiphenylene oxides"[tw] OR "tetrachlorodiphenylene oxides"[tw] OR "pentachlorodiphenylene oxides"[tw] OR "hexachlorodiphenylene oxides"[tw] OR "heptachlorodiphenylene oxides"[tw] OR "octachlorodiphenylene oxides"[tw] OR "perchlorodiphenylene oxides"[tw] OR "polychlorodiphenylene oxides"[tw]) OR ("12378 PeCDFuran"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,8,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,8,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,8-pentachloro-"[tw] OR "Dibenzofuran, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzofuran, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,4,6,7,8-hexachloro-"[tw] OR "Dibenzofuran, 2,3,4,7,8-pentachloro-"[tw] OR "Dibenzofuran, 2,3,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetra-chloro-"[tw]) OR ("Dibenzofuran, 3-chloro-"[tw] OR "Dibenzofuran, 2-chloro-"[tw] OR "Dibenzofuran, 2,4,8-trichloro-"[tw] OR "Dibenzofuran, 1,3-dichloro-"[tw] OR "Dibenzofuran, 2,4,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzofuran, 2,8-dichloro-"[tw] OR "Dibenzofuran, 1,4,8-trichloro-"[tw] OR "Dibenzofuran, 2,3,6,7-tetrachloro-"[tw] OR "Dibenzofuran, 3,4,6,7-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,4,6,7-pentachloro-"[tw] OR "Dibenzofuran, 2,7-dichloro-"[tw] OR "Dibenzofuran, 1,2,3,6,8,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,3,4,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,8,9-hexachloro-"[tw])) AND (("Benzofurans/toxicity"[mh] OR "Benzofurans/adverse effects"[mh] OR "Benzofurans/poisoning"[mh] OR "Benzofurans/pharmacokinetics"[mh]) OR ("Benzofurans"[mh] AND ("environmental exposure"[mh] OR "occupational groups"[mh] OR ci[sh])) OR ("Benzofurans"[mh] AND toxicokinetics[mh:noexp]) OR ("Benzofurans/blood"[mh] OR "Benzofurans/cerebrospinal fluid"[mh] OR "Benzofurans/urine"[mh]) OR ("Benzofurans"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	"endocrine disruptors"[mh])) OR ("Benzofurans"[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 ("Benzofurans/antagonists and inhibitors"[mh]) OR ("Benzofurans/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Benzofurans/pharmacology"[majr])) AND (2019/06/01:3000[mhda] OR 2019/06/01:3000[crdat] OR 2019/06/01:3000[edat] OR 2019:3000[dp]) (("Dibenzofurans, Polychlorinated"[mh]) OR (39001-02-0[rn] OR 51207-31-9[rn] OR 55673-89-7[rn] OR 57117-31-4[rn] OR 57117-35-8[rn] OR 57117-37-0[rn] OR 57117-41-6[rn] OR 57117-44-9[rn] OR 60851-34-5[rn] OR 67517-48-0[rn] OR 67562-39-4[rn] OR 69698-58-4[rn] OR 70648-25-8[rn] OR 70648-26-9[rn] OR 72918-21-9[rn] OR 75627-02-0[rn] OR 42934-53-2[rn] OR 30402-14-3[rn] OR 30402-15-4[rn] OR 55684-94-1[rn] OR 38998-75-3[rn] OR "1,2,3,4,6,7,8-heptachlorodibenzofuran"[nm] OR "1,2,3,4-tetrachlorodibenzofuran"[nm] OR "polychlorodibenzofuran"[nm]) OR (136677-10-6[rn] OR 43047-99-0[rn] OR 51230-49-0[rn] OR 25074-67-3[rn] OR 74992-96-4[rn] OR 94538-00-8[rn] OR 5409-83-6[rn] OR 64560-14-1[rn] OR 54589-71-8[rn] OR 24478-72-6[rn] OR 58802-19-0[rn] OR 58802-20-3[rn] OR 71998-72-6[rn] OR 74992-98-6[rn] OR 43048-00-6[rn] OR 57117-39-2[rn] OR 57117-40-5[rn] OR 57117-43-8[rn] OR 75198-38-8[rn] OR 79060-60-9[rn] OR 91538-83-9[rn] OR 91538-84-0[rn] OR 92341-05-4[rn] OR 92341-06-5[rn] OR 92341-07-6[rn]) OR ("DCDF"[tw] OR "diCDF"[tw] OR "di-CDF"[tw] OR "HCDF"[tw] OR "heptaCDF"[tw] OR "hepta-CDF"[tw] OR "hexaCDF"[tw] OR "hexa-CDF"[tw] OR "HpCDF"[tw] OR "HxCDF"[tw] OR "moCDF"[tw] OR "monoCDF"[tw] OR "mono-CDF"[tw] OR "OCDF"[tw] OR "octaCDF"[tw] OR "octa-CDF"[tw] OR "PCDF"[tw] OR "PeCDF"[tw] OR "pentaCDF"[tw] OR "penta-CDF"[tw] OR "Tcdbf"[tw] OR "TCDF"[tw] OR "tetraCDF"[tw] OR "tetra-CDF"[tw] OR "triCDF"[tw] OR "tri-CDF"[tw]) OR ("DCDFs"[tw] OR "diCDFs"[tw] OR "di-CDFs"[tw] OR "HCDFs"[tw] OR "heptaCDFs"[tw] OR "hepta-CDFs"[tw] OR "hexaCDFs"[tw] OR "hexa-CDFs"[tw] OR "HpCDFs"[tw] OR "HxCDFs"[tw] OR "moCDFs"[tw] OR "monoCDFs"[tw] OR "mono-CDFs"[tw] OR "OCDFs"[tw] OR "octaCDFs"[tw] OR "octa-CDFs"[tw] OR "PCDFs"[tw] OR "PeCDFs"[tw] OR "pentaCDFs"[tw] OR "penta-CDFs"[tw] OR "Tcdbfs"[tw] OR "TCDFs"[tw] OR "tetraCDFs"[tw] OR "tetra-CDFs"[tw] OR "triCDFs"[tw] OR "tri-CDFs"[tw]) OR ("CDF"[tw] AND "Benzofurans"[mh]) OR ("CDFs"[tw] AND "Benzofurans"[mh]) OR ("chlorodibenzofuran"[tw] OR "polychlorodibenzofuran"[tw] OR "monochlorodibenzofuran"[tw] OR "dichlorodibenzofuran"[tw] OR "trichlorodibenzofuran"[tw] OR "tetrachlorodibenzofuran"[tw] OR "pentachlorodibenzofuran"[tw] OR "hexachlorodibenzofuran"[tw] OR "heptachlorodibenzofuran"[tw] OR "octachlorodibenzofuran"[tw] OR "perchlorodibenzofuran"[tw] OR "chlorinated dibenzofuran"[tw] OR "polychlorinated dibenzofuran"[tw]) OR ("chlorodibenzofurans"[tw] OR "polychlorodibenzofurans"[tw] OR "monochlorodibenzofurans"[tw] OR "dichlorodibenzofurans"[tw] OR "trichlorodibenzofurans"[tw] OR "tetrachlorodibenzofurans"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"pentachlorodibenzofurans"[tw] OR "hexachlorodibenzofurans"[tw] OR "heptachlorodibenzofurans"[tw] OR "octachlorodibenzofurans"[tw] OR "perchlorodibenzofurans"[tw] OR "chlorinated dibenzofurans"[tw] OR "polychlorinated dibenzofurans"[tw]) OR ("chloro dibenzofuran"[tw] OR "polychloro dibenzofuran"[tw] OR "monochloro dibenzofuran"[tw] OR "dichloro dibenzofuran"[tw] OR "trichloro dibenzofuran"[tw] OR "tetrachloro dibenzofuran"[tw] OR "pentachloro dibenzofuran"[tw] OR "hexachloro dibenzofuran"[tw] OR "heptachloro dibenzofuran"[tw] OR "octachloro dibenzofuran"[tw] OR "perchloro dibenzofuran"[tw]) OR ("chloro dibenzofurans"[tw] OR "polychloro dibenzofurans"[tw] OR "monochloro dibenzofurans"[tw] OR "dichloro dibenzofurans"[tw] OR "trichloro dibenzofurans"[tw] OR "tetrachloro dibenzofurans"[tw] OR "pentachloro dibenzofurans"[tw] OR "hexachloro dibenzofurans"[tw] OR "heptachloro dibenzofurans"[tw] OR "octachloro dibenzofurans"[tw] OR "perchloro dibenzofurans") OR ("dibenzofuran, chloro-"[tw] OR "dibenzofuran, dichloro-"[tw] OR "dibenzofuran, trichloro-"[tw] OR "dibenzofuran, tetrachloro-"[tw] OR "dibenzofuran, pentachloro-"[tw] OR "dibenzofuran, hexachloro-"[tw] OR "dibenzofuran, heptachloro-"[tw] OR "Dibenzofuran, octachloro-"[tw] OR "monochlordibenzofuran"[tw] OR "chlorinated dibenzo-furan"[tw] OR "polychlorinated dibenzo-furan"[tw]) OR ("chlorinated dibenzo-furans"[tw] OR "dibenzofurans, chlorinated"[tw] OR "hepta chloro furans"[tw] OR "heptachlorofurans"[tw] OR "penta chloro furans"[tw] OR "polychlorinated dibenzo-furans"[tw]) OR (("chlorinated"[tw] AND "dibenzofuran"[tw]) OR ("polychlorinated"[tw] AND "dibenzofuran"[tw]) OR (("monochlorinated"[tw] OR "dichlorinated"[tw] OR "trichlorinated"[tw] OR "tetrachlorinated"[tw] OR "pentachlorinated"[tw] OR "hexachlorinated"[tw] OR "heptachlorinated"[tw] OR "octachlorinated"[tw] OR "perchlorinated") AND "dibenzofuran"[tw]) OR (("dipolychlorinated"[tw] OR "tripolychlorinated"[tw] OR "tetrapolychlorinated"[tw] OR "pentapolychlorinated"[tw] OR "hexapolychlorinated"[tw] OR "heptapolychlorinated"[tw] OR "octapolychlorinated"[tw] OR "perpolychlorinated"[tw] OR "polypolychlorinated"[tw]) AND "dibenzofuran"[tw])) OR (("chlorinated"[tw] AND "dibenzofurans"[tw]) OR ("polychlorinated"[tw] AND "dibenzofurans"[tw]) OR (("monochlorinated"[tw] OR "dichlorinated"[tw] OR "trichlorinated"[tw] OR "tetrachlorinated"[tw] OR "pentachlorinated"[tw] OR "hexachlorinated"[tw] OR "heptachlorinated"[tw] OR "octachlorinated"[tw] OR "perchlorinated") AND "dibenzofurans"[tw]) OR (("dipolychlorinated"[tw] OR "tripolychlorinated"[tw] OR "tetrapolychlorinated"[tw] OR "pentapolychlorinated"[tw] OR "hexapolychlorinated"[tw] OR "heptapolychlorinated"[tw] OR "octapolychlorinated"[tw] OR "perpolychlorinated"[tw] OR "polypolychlorinated"[tw]) AND "dibenzofurans"[tw])) OR ("CDD/F"[tw] OR "DCDD/F"[tw] OR "diCDD/F"[tw] OR "HCDD/F"[tw] OR "HpCDD/F"[tw] OR "HxCDD/F"[tw] OR "MCDD/F"[tw] OR "moCDD/F"[tw] OR "monoCDD/F"[tw] OR "OCDD/F"[tw] OR "PCDD/F"[tw] OR "PeCDD/F"[tw] OR "TCDD/F"[tw] OR "triCDD/F"[tw] OR "CDD/Fs"[tw] OR "DCDD/Fs"[tw] OR "diCDD/Fs"[tw] OR "HCDD/Fs"[tw] OR "HpCDD/Fs"[tw] OR "HxCDD/Fs"[tw] OR "MCDD/Fs"[tw] OR "moCDD/Fs"[tw] OR "monoCDD/Fs"[tw] OR "OCDD/Fs"[tw] OR "PCDD/Fs"[tw] OR "PeCDD/Fs"[tw] OR "TCDD/Fs"[tw] OR "triCDD/Fs"[tw]) OR ("chlorodiphenylene oxide"[tw] OR "monochlorodiphenylene oxide"[tw] OR "dichlorodiphenylene oxide"[tw] OR "trichlorodiphenylene oxide"[tw] OR "tetrachlorodiphenylene oxide"[tw] OR "pentachlorodiphenylene oxide"[tw] OR "hexachlorodiphenylene oxide"[tw] OR "heptachlorodiphenylene oxide"[tw] OR "octachlorodiphenylene oxide"[tw] OR "perchlorodiphenylene oxide"[tw] OR "polychlorodiphenylene oxide"[tw] OR "chlorodiphenylene oxides"[tw] OR "monochlorodiphenylene oxides"[tw] OR "dichlorodiphenylene oxides"[tw] OR "trichlorodiphenylene oxides"[tw] OR "tetrachlorodiphenylene oxides"[tw] OR "pentachlorodiphenylene oxides"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"hexachlorodiphenylene oxides"[tw] OR "heptachlorodiphenylene oxides"[tw] OR "octachlorodiphenylene oxides"[tw] OR "perchlorodiphenylene oxides"[tw] OR "polychlorodiphenylene oxides"[tw]) OR ("12378 PeCDFuran"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,8,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,8,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,8-pentachloro-"[tw] OR "Dibenzofuran, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzofuran, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,4,6,7,8-hexachloro-"[tw] OR "Dibenzofuran, 2,3,4,7,8-pentachloro-"[tw] OR "Dibenzofuran, 2,3,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetra-chloro-"[tw]) OR ("Dibenzofuran, 3-chloro-"[tw] OR "Dibenzofuran, 2-chloro-"[tw] OR "Dibenzofuran, 2,4,8-trichloro-"[tw] OR "Dibenzofuran, 1,3-dichloro-"[tw] OR "Dibenzofuran, 2,4,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzofuran, 2,8-dichloro-"[tw] OR "Dibenzofuran, 1,4,8-trichloro-"[tw] OR "Dibenzofuran, 2,3,6,7-tetrachloro-"[tw] OR "Dibenzofuran, 3,4,6,7-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,4,6,7-pentachloro-"[tw] OR "Dibenzofuran, 2,7-dichloro-"[tw] OR "Dibenzofuran, 1,2,3,6,8,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,3,4,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,8,9-hexachloro-"[tw])) 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 "occupational groups"[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/pharmacology"[majr])) AND (2019/06/01:3000[mhda] OR 2019/06/01:3000[crdat] OR 2019/06/01:3000[edat] OR 2019:3000[dp]) ((((("DCDF"[tw] OR "diCDF"[tw] OR "di-CDF"[tw] OR "HCDF"[tw] OR "heptaCDF"[tw] OR "hepta-CDF"[tw] OR "hexaCDF"[tw] OR "hexa-CDF"[tw] OR "HpCDF"[tw] OR "HxCDF"[tw] OR "moCDF"[tw] OR "monoCDF"[tw] OR "mono-CDF"[tw] OR "OCDF"[tw] OR "octaCDF"[tw] OR "octa-CDF"[tw] OR "PCDF"[tw] OR "PeCDF"[tw] OR "pentaCDF"[tw] OR "penta-CDF"[tw] OR "Tcdbf"[tw] OR "TCDF"[tw] OR "tetraCDF"[tw] OR "tetra-CDF"[tw] OR "triCDF"[tw] OR "tri-CDF"[tw]) OR ("DCDFs"[tw] OR "diCDFs"[tw] OR "di-CDFs"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"HCDFs"[tw] OR "heptaCDFs"[tw] OR "hepta-CDFs"[tw] OR "hexaCDFs"[tw] OR "hexa-CDFs"[tw] OR "HpCDFs"[tw] OR "HxCDFs"[tw] OR "moCDFs"[tw] OR "monoCDFs"[tw] OR "mono-CDFs"[tw] OR "OCDFs"[tw] OR "octaCDFs"[tw] OR "octa-CDFs"[tw] OR "PCDFs"[tw] OR "PeCDFs"[tw] OR "pentaCDFs"[tw] OR "penta-CDFs"[tw] OR "Tcdbfs"[tw] OR "TCDFs"[tw] OR "tetraCDFs"[tw] OR "tetra-CDFs"[tw] OR "triCDFs"[tw] OR "tri-CDFs"[tw]) OR ("CDF"[tw] AND "Benzofurans"[mh]) OR ("CDFs"[tw] AND "Benzofurans"[mh]) OR ("chlorodibenzofuran"[tw] OR "polychlorodibenzofuran"[tw] OR "monochlorodibenzofuran"[tw] OR "dichlorodibenzofuran"[tw] OR "trichlorodibenzofuran"[tw] OR "tetrachlorodibenzofuran"[tw] OR "pentachlorodibenzofuran"[tw] OR "hexachlorodibenzofuran"[tw] OR "heptachlorodibenzofuran"[tw] OR "octachlorodibenzofuran"[tw] OR "perchlorodibenzofuran"[tw] OR "chlorinated dibenzofuran"[tw] OR "polychlorinated dibenzofuran"[tw]) OR ("chlorodibenzofurans"[tw] OR "polychlorodibenzofurans"[tw] OR "monochlorodibenzofurans"[tw] OR "dichlorodibenzofurans"[tw] OR "trichlorodibenzofurans"[tw] OR "tetrachlorodibenzofurans"[tw] OR "pentachlorodibenzofurans"[tw] OR "hexachlorodibenzofurans"[tw] OR "heptachlorodibenzofurans"[tw] OR "octachlorodibenzofurans"[tw] OR "perchlorodibenzofurans"[tw] OR "chlorinated dibenzofurans"[tw] OR "polychlorinated dibenzofurans"[tw]) OR ("chloro dibenzofuran"[tw] OR "polychloro dibenzofuran"[tw] OR "monochloro dibenzofuran"[tw] OR "dichloro dibenzofuran"[tw] OR "trichloro dibenzofuran"[tw] OR "tetrachloro dibenzofuran"[tw] OR "pentachloro dibenzofuran"[tw] OR "hexachloro dibenzofuran"[tw] OR "heptachloro dibenzofuran"[tw] OR "octachloro dibenzofuran"[tw] OR "perchloro dibenzofuran"[tw]) OR ("chloro dibenzofurans"[tw] OR "polychloro dibenzofurans"[tw] OR "monochloro dibenzofurans"[tw] OR "dichloro dibenzofurans"[tw] OR "trichloro dibenzofurans"[tw] OR "tetrachloro dibenzofurans"[tw] OR "pentachloro dibenzofurans"[tw] OR "hexachloro dibenzofurans"[tw] OR "heptachloro dibenzofurans"[tw] OR "octachloro dibenzofurans"[tw] OR "perchloro dibenzofurans") OR ("dibenzofuran, chloro-"[tw] OR "dibenzofuran, dichloro-"[tw] OR "dibenzofuran, trichloro-"[tw] OR "dibenzofuran, tetrachloro-"[tw] OR "dibenzofuran, pentachloro-"[tw] OR "dibenzofuran, hexachloro-"[tw] OR "dibenzofuran, heptachloro-"[tw] OR "Dibenzofuran, octachloro-"[tw] OR "monochlordibenzofuran"[tw] OR "chlorinated dibenzo-furan"[tw] OR "polychlorinated dibenzo-furan"[tw]) OR ("chlorinated dibenzo-furans"[tw] OR "dibenzofurans, chlorinated"[tw] OR "hepta chloro furans"[tw] OR "heptachlorofurans"[tw] OR "penta chloro furans"[tw] OR "polychlorinated dibenzo-furans"[tw]) OR (("chlorinated"[tw] AND "dibenzofuran"[tw]) OR ("polychlorinated"[tw] AND "dibenzofuran"[tw]) OR (("monochlorinated"[tw] OR "dichlorinated"[tw] OR "trichlorinated"[tw] OR "tetrachlorinated"[tw] OR "pentachlorinated"[tw] OR "hexachlorinated"[tw] OR "heptachlorinated"[tw] OR "octachlorinated"[tw] OR "perchlorinated") AND "dibenzofuran"[tw]) OR (("dipolychlorinated"[tw] OR "tripolychlorinated"[tw] OR "tetrapolychlorinated"[tw] OR "pentapolychlorinated"[tw] OR "hexapolychlorinated"[tw] OR "heptapolychlorinated"[tw] OR "octapolychlorinated"[tw] OR "perpolychlorinated"[tw] OR "polypolychlorinated"[tw]) AND "dibenzofuran"[tw])) OR (("chlorinated"[tw] AND "dibenzofurans"[tw]) OR ("polychlorinated"[tw] AND "dibenzofurans"[tw]) OR (("monochlorinated"[tw] OR "dichlorinated"[tw] OR "trichlorinated"[tw] OR "tetrachlorinated"[tw] OR "pentachlorinated"[tw] OR "hexachlorinated"[tw] OR "heptachlorinated"[tw] OR "octachlorinated"[tw] OR "perchlorinated") AND "dibenzofurans"[tw]) OR (("dipolychlorinated"[tw] OR "tripolychlorinated"[tw] OR "tetrapolychlorinated"[tw] OR "pentapolychlorinated"[tw] OR "hexapolychlorinated"[tw] OR "heptapolychlorinated"[tw] OR "octapolychlorinated"[tw] OR "perpolychlorinated"[tw] OR "polypolychlorinated"[tw]) AND "dibenzofurans"[tw])) OR

Table B-2. Database Query Strings

Database search date	Query string
	("CDD/F"[tw] OR "DCDD/F"[tw] OR "diCDD/F"[tw] OR "HCDD/F"[tw] OR "HpCDD/F"[tw] OR "HxCDD/F"[tw] OR "MCDD/F"[tw] OR "moCDD/F"[tw] OR "monoCDD/F"[tw] OR "OCDD/F"[tw] OR "PCDD/F"[tw] OR "PeCDD/F"[tw] OR "TCDD/F"[tw] OR "triCDD/F"[tw] OR "CDD/Fs"[tw] OR "DCDD/Fs"[tw] OR "diCDD/Fs"[tw] OR "HCDD/Fs"[tw] OR "HpCDD/Fs"[tw] OR "HxCDD/Fs"[tw] OR "MCDD/Fs"[tw] OR "moCDD/Fs"[tw] OR "monoCDD/Fs"[tw] OR "OCDD/Fs"[tw] OR "PCDD/Fs"[tw] OR "PeCDD/Fs"[tw] OR "TCDD/Fs"[tw] OR "triCDD/Fs"[tw]) OR ("chlorodiphenylene oxide"[tw] OR "monochlorodiphenylene oxide"[tw] OR "dichlorodiphenylene oxide"[tw] OR "trichlorodiphenylene oxide"[tw] OR "tetrachlorodiphenylene oxide"[tw] OR "pentachlorodiphenylene oxide"[tw] OR "hexachlorodiphenylene oxide"[tw] OR "heptachlorodiphenylene oxide"[tw] OR "octachlorodiphenylene oxide"[tw] OR "perchlorodiphenylene oxide"[tw] OR "polychlorodiphenylene oxide"[tw] OR "chlorodiphenylene oxides"[tw] OR "monochlorodiphenylene oxides"[tw] OR "dichlorodiphenylene oxides"[tw] OR "trichlorodiphenylene oxides"[tw] OR "tetrachlorodiphenylene oxides"[tw] OR "pentachlorodiphenylene oxides"[tw] OR "hexachlorodiphenylene oxides"[tw] OR "heptachlorodiphenylene oxides"[tw] OR "octachlorodiphenylene oxides"[tw] OR "perchlorodiphenylene oxides"[tw] OR "polychlorodiphenylene oxides"[tw]) OR ("12378 PeCDFuran"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,8,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,8,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,8-pentachloro-"[tw] OR "Dibenzofuran, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzofuran, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,4,6,7,8-hexachloro-"[tw] OR "Dibenzofuran, 2,3,4,7,8-pentachloro-"[tw] OR "Dibenzofuran, 2,3,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetra-chloro-"[tw]) OR ("Dibenzofuran, 3-chloro-"[tw] OR "Dibenzofuran, 2-chloro-"[tw] OR "Dibenzofuran, 2,4,8-trichloro-"[tw] OR "Dibenzofuran, 1,3-dichloro-"[tw] OR "Dibenzofuran, 2,4,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzofuran, 2,8-dichloro-"[tw] OR "Dibenzofuran, 1,4,8-trichloro-"[tw] OR "Dibenzofuran, 2,3,6,7-tetrachloro-"[tw] OR "Dibenzofuran, 3,4,6,7-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,4,6,7-pentachloro-"[tw] OR "Dibenzofuran, 2,7-dichloro-"[tw] OR "Dibenzofuran, 1,2,3,6,8,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,3,4,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,8,9-hexachloro-"[tw]))) NOT medline[sb]) AND (2019/06/01:3000[mhda] OR 2019/06/01:3000[crdat] OR 2019/06/01:3000[edat] OR 2019:3000[dp]) ((((("Dibenzofurans, Polychlorinated"[mh]) OR (39001-02-0[rn] OR 51207-31-9[rn] OR 55673-89-7[rn] OR 57117-31-4[rn] OR 57117-35-8[rn] OR 57117-37-0[rn] OR 57117-41-6[rn] OR 57117-44-9[rn] OR 60851-34-5[rn] OR 67517-48-0[rn] OR 67562-39-4[rn] OR 69698-58-4[rn] OR 70648-25-8[rn] OR 70648-26-9[rn] OR 72918-21-9[rn] OR 75627-02-0[rn] OR 42934-53-2[rn] OR 30402-14-3[rn] OR 30402-15-4[rn] OR 55684-94-1[rn] OR 38998-75-3[rn] OR "1,2,3,4,6,7,8-heptachlorodibenzofuran"[nm] OR "1,2,3,4-tetrachlorodibenzofuran"[nm] OR "polychlorodibenzofuran"[nm]) OR (136677-10-6[rn] OR 43047-99-0[rn] OR 51230-49-0[rn] OR 25074-67-3[rn] OR 74992-96-4[rn] OR 94538-00-8[rn] OR 5409-83-6[rn] OR 64560-14-1[rn] OR 54589-71-8[rn] OR 24478-72-6[rn] OR

Table B-2. Database Query Strings

Database search date	Query string
	58802-19-0[rn] OR 58802-20-3[rn] OR 71998-72-6[rn] OR 74992-98-6[rn] OR 43048-00-6[rn] OR 57117-39-2[rn] OR 57117-40-5[rn] OR 57117-43-8[rn] OR 75198-38-8[rn] OR 79060-60-9[rn] OR 91538-83-9[rn] OR 91538-84-0[rn] OR 92341-05-4[rn] OR 92341-06-5[rn] OR 92341-07-6[rn]) OR ("DCDF"[tw] OR "diCDF"[tw] OR "di-CDF"[tw] OR "HCDF"[tw] OR "heptaCDF"[tw] OR "hepta-CDF"[tw] OR "hexaCDF"[tw] OR "hexa-CDF"[tw] OR "HpCDF"[tw] OR "HxCDF"[tw] OR "moCDF"[tw] OR "monoCDF"[tw] OR "mono-CDF"[tw] OR "OCDF"[tw] OR "octaCDF"[tw] OR "octa-CDF"[tw] OR "PCDF"[tw] OR "PeCDF"[tw] OR "pentaCDF"[tw] OR "penta-CDF"[tw] OR "Tcdbf"[tw] OR "TCDF"[tw] OR "tetraCDF"[tw] OR "tetra-CDF"[tw] OR "triCDF"[tw] OR "tri-CDF"[tw]) OR ("DCDFs"[tw] OR "diCDFs"[tw] OR "di-CDFs"[tw] OR "HCDFs"[tw] OR "heptaCDFs"[tw] OR "hepta-CDFs"[tw] OR "hexaCDFs"[tw] OR "hexa-CDFs"[tw] OR "HpCDFs"[tw] OR "HxCDFs"[tw] OR "moCDFs"[tw] OR "monoCDFs"[tw] OR "mono-CDFs"[tw] OR "OCDFs"[tw] OR "octaCDFs"[tw] OR "octa-CDFs"[tw] OR "PCDFs"[tw] OR "PeCDFs"[tw] OR "pentaCDFs"[tw] OR "penta-CDFs"[tw] OR "Tcdbfs"[tw] OR "TCDFs"[tw] OR "tetraCDFs"[tw] OR "tetra-CDFs"[tw] OR "triCDFs"[tw] OR "tri-CDFs"[tw]) OR ("CDF"[tw] AND "Benzofurans"[mh]) OR ("CDFs"[tw] AND "Benzofurans"[mh]) OR ("chlorodibenzofuran"[tw] OR "polychlorodibenzofuran"[tw] OR "monochlorodibenzofuran"[tw] OR "dichlorodibenzofuran"[tw] OR "trichlorodibenzofuran"[tw] OR "tetrachlorodibenzofuran"[tw] OR "pentachlorodibenzofuran"[tw] OR "hexachlorodibenzofuran"[tw] OR "heptachlorodibenzofuran"[tw] OR "octachlorodibenzofuran"[tw] OR "perchlorodibenzofuran"[tw] OR "chlorinated dibenzofuran"[tw] OR "polychlorinated dibenzofuran"[tw]) OR ("chlorodibenzofurans"[tw] OR "polychlorodibenzofurans"[tw] OR "monochlorodibenzofurans"[tw] OR "dichlorodibenzofurans"[tw] OR "trichlorodibenzofurans"[tw] OR "tetrachlorodibenzofurans"[tw] OR "pentachlorodibenzofurans"[tw] OR "hexachlorodibenzofurans"[tw] OR "heptachlorodibenzofurans"[tw] OR "octachlorodibenzofurans"[tw] OR "perchlorodibenzofurans"[tw] OR "chlorinated dibenzofurans"[tw] OR "polychlorinated dibenzofurans"[tw]) OR ("chloro dibenzofuran"[tw] OR "polychloro dibenzofuran"[tw] OR "monochloro dibenzofuran"[tw] OR "dichloro dibenzofuran"[tw] OR "trichloro dibenzofuran"[tw] OR "tetrachloro dibenzofuran"[tw] OR "pentachloro dibenzofuran"[tw] OR "hexachloro dibenzofuran"[tw] OR "heptachloro dibenzofuran"[tw] OR "octachloro dibenzofuran"[tw] OR "perchloro dibenzofuran"[tw]) OR ("chloro dibenzofurans"[tw] OR "polychloro dibenzofurans"[tw] OR "monochloro dibenzofurans"[tw] OR "dichloro dibenzofurans"[tw] OR "trichloro dibenzofurans"[tw] OR "tetrachloro dibenzofurans"[tw] OR "pentachloro dibenzofurans"[tw] OR "hexachloro dibenzofurans"[tw] OR "heptachloro dibenzofurans"[tw] OR "octachloro dibenzofurans"[tw] OR "perchloro dibenzofurans") OR ("dibenzofuran, chloro-"[tw] OR "dibenzofuran, dichloro-"[tw] OR "dibenzofuran, trichloro-"[tw] OR "dibenzofuran, tetrachloro-"[tw] OR "dibenzofuran, pentachloro-"[tw] OR "dibenzofuran, hexachloro-"[tw] OR "dibenzofuran, heptachloro-"[tw] OR "Dibenzofuran, octachloro-"[tw] OR "monochlordibenzofuran"[tw] OR "chlorinated dibenzo-furan"[tw] OR "polychlorinated dibenzo-furan"[tw]) OR ("chlorinated dibenzo-furans"[tw] OR "dibenzofurans, chlorinated"[tw] OR "hepta chloro furans"[tw] OR "heptachlorofurans"[tw] OR "penta chloro furans"[tw] OR "polychlorinated dibenzo-furans"[tw]) OR (("chlorinated"[tw] AND "dibenzofuran"[tw]) OR ("polychlorinated"[tw] AND "dibenzofuran"[tw]) OR (("monochlorinated"[tw] OR "dichlorinated"[tw] OR "trichlorinated"[tw] OR "tetrachlorinated"[tw] OR "pentachlorinated"[tw] OR "hexachlorinated"[tw] OR "heptachlorinated"[tw] OR "octachlorinated"[tw] OR "perchlorinated") AND "dibenzofuran"[tw]) OR (("dipolychlorinated"[tw] OR "tripolychlorinated"[tw] OR "tetrapolychlorinated"[tw] OR "pentapolychlorinated"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"hexapolychlorinated"[tw] OR "heptapolychlorinated"[tw] OR "octapolychlorinated"[tw] OR "perpolychlorinated"[tw] OR "polypolychlorinated"[tw]) AND "dibenzofuran"[tw])) OR (("chlorinated"[tw] AND "dibenzofurans"[tw]) OR ("polychlorinated"[tw] AND "dibenzofurans"[tw]) OR (("monochlorinated"[tw] OR "dichlorinated"[tw] OR "trichlorinated"[tw] OR "tetrachlorinated"[tw] OR "pentachlorinated"[tw] OR "hexachlorinated"[tw] OR "heptachlorinated"[tw] OR "octachlorinated"[tw] OR "perchlorinated") AND "dibenzofurans"[tw]) OR (("dipolychlorinated"[tw] OR "tripolychlorinated"[tw] OR "tetrapolychlorinated"[tw] OR "pentapolychlorinated"[tw] OR "hexapolychlorinated"[tw] OR "heptapolychlorinated"[tw] OR "octapolychlorinated"[tw] OR "perpolychlorinated"[tw] OR "polypolychlorinated"[tw]) AND "dibenzofurans"[tw])) OR ("CDD/F"[tw] OR "DCDD/F"[tw] OR "diCDD/F"[tw] OR "HCDD/F"[tw] OR "HpCDD/F"[tw] OR "HxCDD/F"[tw] OR "MCDD/F"[tw] OR "moCDD/F"[tw] OR "monoCDD/F"[tw] OR "OCDD/F"[tw] OR "PCDD/F"[tw] OR "PeCDD/F"[tw] OR "TCDD/F"[tw] OR "triCDD/F"[tw] OR "CDD/Fs"[tw] OR "DCDD/Fs"[tw] OR "diCDD/Fs"[tw] OR "HCDD/Fs"[tw] OR "HpCDD/Fs"[tw] OR "HxCDD/Fs"[tw] OR "MCDD/Fs"[tw] OR "moCDD/Fs"[tw] OR "monoCDD/Fs"[tw] OR "OCDD/Fs"[tw] OR "PCDD/Fs"[tw] OR "PeCDD/Fs"[tw] OR "TCDD/Fs"[tw] OR "triCDD/Fs"[tw]) OR ("chlorodiphenylene oxide"[tw] OR "monochlorodiphenylene oxide"[tw] OR "dichlorodiphenylene oxide"[tw] OR "trichlorodiphenylene oxide"[tw] OR "tetrachlorodiphenylene oxide"[tw] OR "pentachlorodiphenylene oxide"[tw] OR "hexachlorodiphenylene oxide"[tw] OR "heptachlorodiphenylene oxide"[tw] OR "octachlorodiphenylene oxide"[tw] OR "perchlorodiphenylene oxide"[tw] OR "polychlorodiphenylene oxide"[tw] OR "chlorodiphenylene oxides"[tw] OR "monochlorodiphenylene oxides"[tw] OR "dichlorodiphenylene oxides"[tw] OR "trichlorodiphenylene oxides"[tw] OR "tetrachlorodiphenylene oxides"[tw] OR "pentachlorodiphenylene oxides"[tw] OR "hexachlorodiphenylene oxides"[tw] OR "heptachlorodiphenylene oxides"[tw] OR "octachlorodiphenylene oxides"[tw] OR "perchlorodiphenylene oxides"[tw] OR "polychlorodiphenylene oxides"[tw]) OR ("12378 PeCDFuran"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,8,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,8,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,8-pentachloro-"[tw] OR "Dibenzofuran, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzofuran, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,4,6,7,8-hexachloro-"[tw] OR "Dibenzofuran, 2,3,4,7,8-pentachloro-"[tw] OR "Dibenzofuran, 2,3,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetra-chloro-"[tw]) OR ("Dibenzofuran, 3-chloro-"[tw] OR "Dibenzofuran, 2-chloro-"[tw] OR "Dibenzofuran, 2,4,8-trichloro-"[tw] OR "Dibenzofuran, 1,3-dichloro-"[tw] OR "Dibenzofuran, 2,4,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzofuran, 2,8-dichloro-"[tw] OR "Dibenzofuran, 1,4,8-trichloro-"[tw] OR "Dibenzofuran, 2,3,6,7-tetrachloro-"[tw] OR "Dibenzofuran, 3,4,6,7-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,4,6,7-pentachloro-"[tw] OR "Dibenzofuran, 2,7-dichloro-"[tw] OR "Dibenzofuran, 1,2,3,6,8,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,3,4,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,8,9-hexachloro-"[tw])) AND ("Dibenzofurans, Polychlorinated"[mh] OR "Benzofurans"[mh] OR "Dioxins"[mh]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR ci[sh] OR bl[sh]

Table B-2. Database Query Strings

Database search date	Query string
	OR cf[sh] OR ur[sh] OR "environmental exposure"[mh] OR "occupational groups"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR (("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 "pharmacology"[sh:noexp] OR toxicokinetics[mh:noexp] OR "Polychlorinated Dibenzodioxins/antagonists and inhibitors"[MeSH Terms] OR "Benzofurans/antagonists and inhibitors"[MeSH Terms] OR "Dioxins/antagonists and inhibitors"[MeSH Terms])) AND (2019/06/01:3000[mhda] OR 2019/06/01:3000[crdat] OR 2019/06/01:3000[edat] OR 2019:3000[dp])) OR ((dioxin human toxicity) AND (2020/05/20:3000[mhda] OR 2020/05/20:3000[crdat] OR 2020/05/20:3000[edat])) (((("Dibenzofurans, Polychlorinated"[mh]) OR (39001-02-0[rn] OR 51207-31-9[rn] OR 55673-89-7[rn] OR 57117-31-4[rn] OR 57117-35-8[rn] OR 57117-37-0[rn] OR 57117-41-6[rn] OR 57117-44-9[rn] OR 60851-34-5[rn] OR 67517-48-0[rn] OR 67562-39-4[rn] OR 69698-58-4[rn] OR 70648-25-8[rn] OR 70648-26-9[rn] OR 72918-21-9[rn] OR 75627-02-0[rn] OR 42934-53-2[rn] OR 30402-14-3[rn] OR 30402-15-4[rn] OR 55684-94-1[rn] OR 38998-75-3[rn] OR "1,2,3,4,6,7,8-heptachlorodibenzofuran"[nm] OR "1,2,3,4-tetrachlorodibenzofuran"[nm] OR "polychlorodibenzofuran"[nm]) OR (136677-10-6[rn] OR 43047-99-0[rn] OR 51230-49-0[rn] OR 25074-67-3[rn] OR 74992-96-4[rn] OR 94538-00-8[rn] OR 5409-83-6[rn] OR 64560-14-1[rn] OR 54589-71-8[rn] OR 24478-72-6[rn] OR 58802-19-0[rn] OR 58802-20-3[rn] OR 71998-72-6[rn] OR 74992-98-6[rn] OR 43048-00-6[rn] OR 57117-39-2[rn] OR 57117-40-5[rn] OR 57117-43-8[rn] OR 75198-38-8[rn] OR 79060-60-9[rn] OR 91538-83-9[rn] OR 91538-84-0[rn] OR 92341-05-4[rn] OR 92341-06-5[rn] OR 92341-07-6[rn]) OR ("DCDF"[tw] OR "diCDF"[tw] OR "di-CDF"[tw] OR "HCDF"[tw] OR "heptaCDF"[tw] OR "hepta-CDF"[tw] OR "hexaCDF"[tw] OR "hexa-CDF"[tw] OR "HpCDF"[tw] OR "HxCDF"[tw] OR "moCDF"[tw] OR "monoCDF"[tw] OR "mono-CDF"[tw] OR "OCDF"[tw] OR "octaCDF"[tw] OR "octa-CDF"[tw] OR "PCDF"[tw] OR "PeCDF"[tw] OR "pentaCDF"[tw] OR "penta-CDF"[tw] OR "Tcdbf"[tw] OR "TCDF"[tw] OR "tetraCDF"[tw] OR "tetra-CDF"[tw] OR "triCDF"[tw] OR "tri-CDF"[tw]) OR ("DCDFs"[tw] OR "diCDFs"[tw] OR "di-CDFs"[tw] OR "HCDFs"[tw] OR "heptaCDFs"[tw] OR "hepta-CDFs"[tw] OR "hexaCDFs"[tw] OR "hexa-CDFs"[tw] OR "HpCDFs"[tw] OR "HxCDFs"[tw] OR "moCDFs"[tw] OR "monoCDFs"[tw] OR "mono-CDFs"[tw] OR "OCDFs"[tw] OR "octaCDFs"[tw] OR "octa-CDFs"[tw] OR "PCDFs"[tw] OR "PeCDFs"[tw] OR "pentaCDFs"[tw] OR "penta-CDFs"[tw] OR "Tcdbfs"[tw] OR "TCDFs"[tw] OR "tetraCDFs"[tw] OR "tetra-CDFs"[tw] OR "triCDFs"[tw] OR "tri-CDFs"[tw]) OR ("CDF"[tw] AND "Benzofurans"[mh]) OR ("CDFs"[tw] AND "Benzofurans"[mh]) OR ("chlorodibenzofuran"[tw] OR "polychlorodibenzofuran"[tw] OR "monochlorodibenzofuran"[tw] OR "dichlorodibenzofuran"[tw] OR "trichlorodibenzofuran"[tw] OR "tetrachlorodibenzofuran"[tw] OR "pentachlorodibenzofuran"[tw] OR "hexachlorodibenzofuran"[tw] OR "heptachlorodibenzofuran"[tw] OR "octachlorodibenzofuran"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"perchlorodibenzofuran"[tw] OR "chlorinated dibenzofuran"[tw] OR "polychlorinated dibenzofuran"[tw]) OR ("chlorodibenzofurans"[tw] OR "polychlorodibenzofurans"[tw] OR "monochlorodibenzofurans"[tw] OR "dichlorodibenzofurans"[tw] OR "trichlorodibenzofurans"[tw] OR "tetrachlorodibenzofurans"[tw] OR "pentachlorodibenzofurans"[tw] OR "hexachlorodibenzofurans"[tw] OR "heptachlorodibenzofurans"[tw] OR "octachlorodibenzofurans"[tw] OR "perchlorodibenzofurans"[tw] OR "chlorinated dibenzofurans"[tw] OR "polychlorinated dibenzofurans"[tw]) OR ("chloro dibenzofuran"[tw] OR "polychloro dibenzofuran"[tw] OR "monochloro dibenzofuran"[tw] OR "dichloro dibenzofuran"[tw] OR "trichloro dibenzofuran"[tw] OR "tetrachloro dibenzofuran"[tw] OR "pentachloro dibenzofuran"[tw] OR "hexachloro dibenzofuran"[tw] OR "heptachloro dibenzofuran"[tw] OR "octachloro dibenzofuran"[tw] OR "perchloro dibenzofuran"[tw]) OR ("chloro dibenzofurans"[tw] OR "polychloro dibenzofurans"[tw] OR "monochloro dibenzofurans"[tw] OR "dichloro dibenzofurans"[tw] OR "trichloro dibenzofurans"[tw] OR "tetrachloro dibenzofurans"[tw] OR "pentachloro dibenzofurans"[tw] OR "hexachloro dibenzofurans"[tw] OR "heptachloro dibenzofurans"[tw] OR "octachloro dibenzofurans"[tw] OR "perchloro dibenzofurans") OR ("dibenzofuran, chloro-"[tw] OR "dibenzofuran, dichloro-"[tw] OR "dibenzofuran, trichloro-"[tw] OR "dibenzofuran, tetrachloro-"[tw] OR "dibenzofuran, pentachloro-"[tw] OR "dibenzofuran, hexachloro-"[tw] OR "dibenzofuran, heptachloro-"[tw] OR "Dibenzofuran, octachloro-"[tw] OR "monochlordibenzofuran"[tw] OR "chlorinated dibenzo-furan"[tw] OR "polychlorinated dibenzo-furan"[tw]) OR ("chlorinated dibenzo-furans"[tw] OR "dibenzofurans, chlorinated"[tw] OR "hepta chloro furans"[tw] OR "heptachlorofurans"[tw] OR "penta chloro furans"[tw] OR "polychlorinated dibenzo-furans"[tw]) OR (("chlorinated"[tw] AND "dibenzofuran"[tw]) OR ("polychlorinated"[tw] AND "dibenzofuran"[tw]) OR (("monochlorinated"[tw] OR "dichlorinated"[tw] OR "trichlorinated"[tw] OR "tetrachlorinated"[tw] OR "pentachlorinated"[tw] OR "hexachlorinated"[tw] OR "heptachlorinated"[tw] OR "octachlorinated"[tw] OR "perchlorinated") AND "dibenzofuran"[tw]) OR (("dipolychlorinated"[tw] OR "tripolychlorinated"[tw] OR "tetrapolychlorinated"[tw] OR "pentapolychlorinated"[tw] OR "hexapolychlorinated"[tw] OR "heptapolychlorinated"[tw] OR "octapolychlorinated"[tw] OR "perpolychlorinated"[tw] OR "polypolychlorinated"[tw]) AND "dibenzofuran"[tw])) OR (("chlorinated"[tw] AND "dibenzofurans"[tw]) OR ("polychlorinated"[tw] AND "dibenzofurans"[tw]) OR (("monochlorinated"[tw] OR "dichlorinated"[tw] OR "trichlorinated"[tw] OR "tetrachlorinated"[tw] OR "pentachlorinated"[tw] OR "hexachlorinated"[tw] OR "heptachlorinated"[tw] OR "octachlorinated"[tw] OR "perchlorinated") AND "dibenzofurans"[tw]) OR (("dipolychlorinated"[tw] OR "tripolychlorinated"[tw] OR "tetrapolychlorinated"[tw] OR "pentapolychlorinated"[tw] OR "hexapolychlorinated"[tw] OR "heptapolychlorinated"[tw] OR "octapolychlorinated"[tw] OR "perpolychlorinated"[tw] OR "polypolychlorinated"[tw]) AND "dibenzofurans"[tw])) OR ("CDD/F"[tw] OR "DCDD/F"[tw] OR "diCDD/F"[tw] OR "HCDD/F"[tw] OR "HpCDD/F"[tw] OR "HxCDD/F"[tw] OR "MCDD/F"[tw] OR "moCDD/F"[tw] OR "monoCDD/F"[tw] OR "OCDD/F"[tw] OR "PCDD/F"[tw] OR "PeCDD/F"[tw] OR "TCDD/F"[tw] OR "triCDD/F"[tw] OR "CDD/Fs"[tw] OR "DCDD/Fs"[tw] OR "diCDD/Fs"[tw] OR "HCDD/Fs"[tw] OR "HpCDD/Fs"[tw] OR "HxCDD/Fs"[tw] OR "MCDD/Fs"[tw] OR "moCDD/Fs"[tw] OR "monoCDD/Fs"[tw] OR "OCDD/Fs"[tw] OR "PCDD/Fs"[tw] OR "PeCDD/Fs"[tw] OR "TCDD/Fs"[tw] OR "triCDD/Fs"[tw]) OR ("chlorodiphenylene oxide"[tw] OR "monochlorodiphenylene oxide"[tw] OR "dichlorodiphenylene oxide"[tw] OR "trichlorodiphenylene oxide"[tw] OR "tetrachlorodiphenylene oxide"[tw] OR "pentachlorodiphenylene oxide"[tw] OR "hexachlorodiphenylene oxide"[tw] OR "heptachlorodiphenylene oxide"[tw] OR "octachlorodiphenylene oxide"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"perchlorodiphenylene oxide"[tw] OR "polychlorodiphenylene oxide"[tw] OR "chlorodiphenylene oxides"[tw] OR "monochlorodiphenylene oxides"[tw] OR "dichlorodiphenylene oxides"[tw] OR "trichlorodiphenylene oxides"[tw] OR "tetrachlorodiphenylene oxides"[tw] OR "pentachlorodiphenylene oxides"[tw] OR "hexachlorodiphenylene oxides"[tw] OR "heptachlorodiphenylene oxides"[tw] OR "octachlorodiphenylene oxides"[tw] OR "perchlorodiphenylene oxides"[tw] OR "polychlorodiphenylene oxides"[tw]) OR ("12378 PeCDFuran"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,8,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,8,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,8-pentachloro-"[tw] OR "Dibenzofuran, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzofuran, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,4,6,7,8-hexachloro-"[tw] OR "Dibenzofuran, 2,3,4,7,8-pentachloro-"[tw] OR "Dibenzofuran, 2,3,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetra-chloro-"[tw]) OR ("Dibenzofuran, 3-chloro-"[tw] OR "Dibenzofuran, 2-chloro-"[tw] OR "Dibenzofuran, 2,4,8-trichloro-"[tw] OR "Dibenzofuran, 1,3-dichloro-"[tw] OR "Dibenzofuran, 2,4,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzofuran, 2,8-dichloro-"[tw] OR "Dibenzofuran, 1,4,8-trichloro-"[tw] OR "Dibenzofuran, 2,3,6,7-tetrachloro-"[tw] OR "Dibenzofuran, 3,4,6,7-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,4,6,7-pentachloro-"[tw] OR "Dibenzofuran, 2,7-dichloro-"[tw] OR "Dibenzofuran, 1,2,3,6,8,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,3,4,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,8,9-hexachloro-"[tw])) AND ("Dibenzofurans, Polychlorinated"[mh] OR "Benzofurans"[mh] OR "Dioxins"[mh]) AND (("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]))) AND (2019/06/01:3000[mhda] OR 2019/06/01:3000[crdat] OR 2019/06/01:3000[edat] OR 2019:3000[dp]) (((("Dibenzofuran, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzofuran, octachloro-"[tw] OR "OCDF"[tw] OR "Octachlorodibenzofuran"[tw] OR "Octapolychlorinated dibenzofuran"[tw] OR "PCDF 135"[tw] OR "Perchlorodibenzofuran"[tw] OR "2,3,7,8-Chlorodibenzofuran"[tw] OR "2,3,7,8-Tetrapolychlorinated dibenzofuran"[tw] OR "Dibenzofuran, 2,3,7,8-tetra-chloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetrachloro-"[tw] OR "PCDF 83"[tw] OR "Tcdbf"[tw] OR "TCDF"[tw] OR "Tetrachlorodibenzofuran"[tw] OR "Tetrachlorodibenzofurans"[tw] OR "1,2,3,4,7,8,9-Heptachloro-dibenzofuran"[tw] OR "1,2,3,4,7,8,9-Heptachlorodibenzofluran"[tw] OR "1,2,3,4,7,8,9-Heptachlorodibenzofuran"[tw] OR "1,2,3,4,7,8,9-HpCDF"[tw] OR "Dibenzofuran, 1,2,3,4,7,8,9-heptachloro-"[tw] OR "Heptachlorodibenzofuran, 1,2,3,4,7,8,9-"[tw] OR "HpCDF, 1,2,3,4,7,8,9-"[tw] OR "PCDF 134"[tw] OR "2,3,4,7,8-PeCDF"[tw] OR "2,3,4,7,8-pentachloro-dibenzofuran"[tw] OR "2,3,4,7,8-Pentachlorodibenzofuran"[tw] OR "2,3,4,7,8-Pentapolychlorinated

Table B-2. Database Query Strings

Database search date	Query string
	dibenzofuran"[tw] OR "4-PeCDF"[tw] OR "Dibenzofuran, 2,3,4,7,8-pentachloro-"[tw] OR "PCDF"[tw] OR "PeCDF, 2,3,4,7,8-"[tw] OR "Pentachlorodibenzofuran, 2,3,4,7,8-"[tw] OR "1,3,7,8-Tetrachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,3,7,8-tetrachloro-"[tw] OR "2,3,6,8-Tetrachlorodibenzofuran"[tw] OR "Dibenzofuran, 2,3,6,8-tetrachloro-"[tw] OR "1,2,3,7,8-PeCDF"[tw] OR "1,2,3,7,8-Pentachlorodibenzofuran"[tw] OR "12378 PeCDFuran"[tw] OR "Dibenzofuran, 1,2,3,7,8-pentachloro-"[tw] OR "PCDF 94"[tw] OR "PeCDF, 1,2,3,7,8-"[tw] OR "Pentachlorodibenzofuran, 1,2,3,7,8-"[tw] OR "1,2,3,6,7,8-Hexa polychlorinated dibenzofuran"[tw] OR "1,2,3,6,7,8-Hexachloro- dibenzofuran"[tw] OR "1,2,3,6,7,8-Hexachlorodibenzofuran"[tw] OR "1,2,3,6,7,8-HxCDF"[tw] OR "2,3,4,7,8,9-Hexachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,2,3,6,7,8-hexachloro-"[tw] OR "PCDF 121"[tw] OR "2,3,4,6,7,8-Hexachloro-dibenzofuran"[tw] OR "2,3,4,6,7,8-Hexachlorodibenzofuran"[tw] OR "2,3,4,6,7,8-HxCDF"[tw] OR "Dibenzofuran, 2,3,4,6,7,8-hexachloro-"[tw] OR "Hexachlorodibenzofuran, 2,3,4,6,7,8-"[tw] OR "HxCDF, 2,3,4,6,7,8-"[tw] OR "PCDF 130"[tw] OR "1,2,3,4,8-Pentachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,2,3,4,8-pentachloro-"[tw] OR "1,2,3,4,6,7,8-Hepta polychlorinated dibenzofuran"[tw] OR "1,2,3,4,6,7,8-Heptachloro-dibenzofuran"[tw] OR "1,2,3,4,6,7,8-Heptachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Heptachlorodibenzofuran, 1,2,3,4,6,7,8-"[tw] OR "HpCDF"[tw] OR "PCDF 131"[tw] OR "1,2,3,4,6,8,9-Heptachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,2,3,4,6,8,9-heptachloro-"[tw] OR "1,2,3,4,6,7,9-Heptachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "1,2,3,4,7,8-HCDF"[tw] OR "1,2,3,4,7,8-Hexa polychlorinated dibenzofuran"[tw] OR "1,2,3,4,7,8-Hexachloro-dibenzofuran"[tw] OR "1,2,3,4,7,8-Hexachlorodibenzofuran"[tw] OR "1,2,3,4,7,8-HxCDF"[tw] OR "Dibenzofuran, 1,2,3,4,7,8-hexachloro-"[tw] OR "HCDF"[tw] OR "Hexachlorodibenzofuran, 1,2,3,4,7,8-"[tw] OR "HXCDF, 1,2,3,4,7,8-"[tw] OR "PCDF 118"[tw] OR "1,2,3,7,8,9-Hexachloro-dibenzofuran"[tw] OR "1,2,3,7,8,9-Hexachlorodibenzofuran"[tw] OR "1,2,3,7,8,9-HxCDF"[tw] OR "Dibenzofuran, 1,2,3,7,8,9-hexachloro-"[tw] OR "Hexachlorodibenzofuran, 1,2,3,7,8,9-"[tw] OR "HxCDF, 1,2,3,7,8,9-"[tw] OR "PCDF 124"[tw] OR "1,2,4,6,7,9-Hexachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,2,4,6,7,9-hexachloro-"[tw]) OR ("3-Chlorodibenzofuran"[tw] OR "3-Monochlorodibenzofuran"[tw] OR "Dibenzofuran, 3-chloro-"[tw] OR "2-Chlorodibenzofuran"[tw] OR "2-Monochlorodibenzofuran"[tw] OR "Dibenzofuran, 2-chloro-"[tw] OR "2,4,8-Trichlorodibenzofuran"[tw] OR "Dibenzofuran, 2,4,8-trichloro-"[tw] OR "4-Chlorodibenzofuran"[tw] OR "1,3-Dichlorodibenzofuran"[tw] OR "Dibenzofuran, 1,3-dichloro-"[tw] OR "2,4,6,8-Tcdf"[tw] OR "2,4,6,8-Tetrachlorodibenzofuran"[tw] OR "Dibenzofuran, 2,4,6,8-tetrachloro-"[tw] OR "1,2,7,8-Tcdf"[tw] OR "1,2,7,8-Tetrachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,2,7,8-tetrachloro-"[tw] OR "1,3,6,8-Tcdf"[tw] OR "1,3,6,8-Tetrachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,3,6,8-tetrachloro-"[tw] OR "1,2,3,4-Tetrachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,2,3,4-tetrachloro-"[tw] OR "2,8-Dichlorodibenzofuran"[tw] OR "Dibenzofuran, 2,8-dichloro-"[tw] OR "1,4,8-Trichlorodibenzofuran"[tw] OR "Dibenzofuran, 1,4,8-trichloro-"[tw] OR "Dibenzofuran, trichloro-Trichlorodibenzofuran"[tw] OR "Dibenzofuran, 2,3,6,7-tetrachloro-"[tw] OR "2,3,6,7-Tetrachlorodibenzofuran"[tw] OR "Dibenzofuran, 3,4,6,7-tetrachloro-"[tw] OR "3,4,6,7-Tetrachlorodibenzofuran"[tw] OR "Dibenzofuran, 2,3,4,6,7-pentachloro-"[tw] OR "2,3,4,6,7-PeCDF"[tw] OR "2,3,4,6,7-Pentachlorodibenzofuran"[tw] OR "Dibenzofuran, 2,7-dichloro-"[tw] OR "2,7-Dichlorodibenzofuran"[tw] OR "1,2,3,6,8,9-Hexachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,2,3,6,8,9-hexachloro-"[tw] OR "1,2,3,4,6,7-Hexachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,2,3,4,6,7-hexachloro-"[tw] OR "1,2,3,4,6,9-Hexachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,2,3,4,6,9-hexachloro-"[tw] OR "1,2,3,4,7,9-Hexachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,2,3,4,7,9-hexachloro-"[tw] OR "1,3,4,6,7,9-Hexachlorodibenzofuran"[tw] OR "Dibenzofuran,

Table B-2. Database Query Strings

Database search date	Query string
	1,3,4,6,7,9-hexachloro-"[tw] OR "1,2,3,6,7,9-Hexachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,2,3,6,7,9-hexachloro-"[tw] OR "1,2,3,4,8,9-Hexachlorodibenzofuran"[tw] OR "Dibenzofuran, 1,2,3,4,8,9-hexachloro"[tw])) OR ("Chlorinated dibenzo-furans"[tw] OR "Chlorinated dibenzofurans"[tw] OR "Chlorodibenzofuran"[tw] OR "Chlorodibenzofurans"[tw] OR "Dibenzofuran, chloro derivs."[tw] OR "Dibenzofuran, chloro-"[tw] OR "Dibenzofuran, dichloro-"[tw] OR "Dibenzofuran, heptachloro-"[tw] OR "Dibenzofuran, hexachloro-"[tw] OR "Dibenzofuran, pentachloro-"[tw] OR "Dibenzofuran, tetrachloro-"[tw] OR "Dibenzofurans, chlorinated"[tw] OR "Dichlorodibenzofuran"[tw] OR "HCDF"[tw] OR "Hepta chloro furans"[tw] OR "Heptachlordibenzofuran"[tw] OR "HEPTACHLORODIBENZOFURAN"[tw] OR "Heptachlorodibenzofurans"[tw] OR "Heptachlorofurans"[tw] OR "Hexachlorodibenzofuran"[tw] OR "Hexachlorodibenzofurans"[tw] OR "HpCDF"[tw] OR "HpCDFs"[tw] OR "HxCDF"[tw] OR "Monochlordibenzofuran"[tw] OR "Monochlorodibenzofuran"[tw] OR "PCDFs"[tw] OR "PeCDF"[tw] OR "PeCDFs"[tw] OR "Penta chloro furans"[tw] OR "Pentachlorodibenzofuran"[tw] OR "Pentachlorodibenzofurans"[tw] OR "Polychlorinated dibenzo-furans"[tw] OR "Polychlorinated Dibenzofurans, Total"[tw] OR "Polychlorodibenzofurans"[tw] OR "TCDF"[tw] OR "TCDFs"[tw] OR "Tetrachlorodibenzofuran"[tw] OR "Tetrachlorodibenzofurans"[tw])) NOT (("DCDF"[tw] OR "diCDF"[tw] OR "di-CDF"[tw] OR "HCDF"[tw] OR "heptaCDF"[tw] OR "hepta-CDF"[tw] OR "hexaCDF"[tw] OR "hexa-CDF"[tw] OR "HpCDF"[tw] OR "HxCDF"[tw] OR "moCDF"[tw] OR "monoCDF"[tw] OR "mono-CDF"[tw] OR "OCDF"[tw] OR "octaCDF"[tw] OR "octa-CDF"[tw] OR "PCDF"[tw] OR "PeCDF"[tw] OR "pentaCDF"[tw] OR "penta-CDF"[tw] OR "Tcdbf"[tw] OR "TCDF"[tw] OR "tetraCDF"[tw] OR "tetra-CDF"[tw] OR "triCDF"[tw] OR "tri-CDF"[tw]) OR ("DCDFs"[tw] OR "diCDFs"[tw] OR "di-CDFs"[tw] OR "HCDFs"[tw] OR "heptaCDFs"[tw] OR "hepta-CDFs"[tw] OR "hexaCDFs"[tw] OR "hexa-CDFs"[tw] OR "HpCDFs"[tw] OR "HxCDFs"[tw] OR "moCDFs"[tw] OR "monoCDFs"[tw] OR "mono-CDFs"[tw] OR "OCDFs"[tw] OR "octaCDFs"[tw] OR "octa-CDFs"[tw] OR "PCDFs"[tw] OR "PeCDFs"[tw] OR "pentaCDFs"[tw] OR "penta-CDFs"[tw] OR "Tcdbfs"[tw] OR "TCDFs"[tw] OR "tetraCDFs"[tw] OR "tetra-CDFs"[tw] OR "triCDFs"[tw] OR "tri-CDFs"[tw]) OR ("CDF"[tw] AND "Benzofurans"[mh]) OR ("CDFs"[tw] AND "Benzofurans"[mh]) OR ("chlorodibenzofuran"[tw] OR "polychlorodibenzofuran"[tw] OR "monochlorodibenzofuran"[tw] OR "dichlorodibenzofuran"[tw] OR "trichlorodibenzofuran"[tw] OR "tetrachlorodibenzofuran"[tw] OR "pentachlorodibenzofuran"[tw] OR "hexachlorodibenzofuran"[tw] OR "heptachlorodibenzofuran"[tw] OR "octachlorodibenzofuran"[tw] OR "perchlorodibenzofuran"[tw] OR "chlorinated dibenzofuran"[tw] OR "polychlorinated dibenzofuran"[tw]) OR ("chlorodibenzofurans"[tw] OR "polychlorodibenzofurans"[tw] OR "monochlorodibenzofurans"[tw] OR "dichlorodibenzofurans"[tw] OR "trichlorodibenzofurans"[tw] OR "tetrachlorodibenzofurans"[tw] OR "pentachlorodibenzofurans"[tw] OR "hexachlorodibenzofurans"[tw] OR "heptachlorodibenzofurans"[tw] OR "octachlorodibenzofurans"[tw] OR "perchlorodibenzofurans"[tw] OR "chlorinated dibenzofurans"[tw] OR "polychlorinated dibenzofurans"[tw]) OR ("chloro dibenzofuran"[tw] OR "polychloro dibenzofuran"[tw] OR "monochloro dibenzofuran"[tw] OR "dichloro dibenzofuran"[tw] OR "trichloro dibenzofuran"[tw] OR "tetrachloro dibenzofuran"[tw] OR "pentachloro dibenzofuran"[tw] OR "hexachloro dibenzofuran"[tw] OR "heptachloro dibenzofuran"[tw] OR "octachloro dibenzofuran"[tw] OR "perchloro dibenzofuran"[tw]) OR ("chloro dibenzofurans"[tw] OR "polychloro dibenzofurans"[tw] OR "monochloro dibenzofurans"[tw] OR "dichloro dibenzofurans"[tw] OR "trichloro dibenzofurans"[tw] OR "tetrachloro dibenzofurans"[tw] OR "pentachloro dibenzofurans"[tw] OR "hexachloro dibenzofurans"[tw] OR "heptachloro

Table B-2. Database Query Strings

Database search date	Query string
	dibenzofurans"[tw] OR "octachloro dibenzofurans"[tw] OR "perchloro dibenzofurans") OR ("dibenzofuran, chloro-"[tw] OR "dibenzofuran, dichloro-"[tw] OR "dibenzofuran, trichloro-"[tw] OR "dibenzofuran, tetrachloro-"[tw] OR "dibenzofuran, pentachloro-"[tw] OR "dibenzofuran, hexachloro-"[tw] OR "dibenzofuran, heptachloro-"[tw] OR "Dibenzofuran, octachloro-"[tw] OR "monochlordibenzofuran"[tw] OR "chlorinated dibenzo-furan"[tw] OR "polychlorinated dibenzo-furan"[tw]) OR ("dibenzofuran, chloro-"[tw] OR "dibenzofuran, dichloro-"[tw] OR "dibenzofuran, trichloro-"[tw] OR "dibenzofuran, tetrachloro-"[tw] OR "dibenzofuran, pentachloro-"[tw] OR "dibenzofuran, hexachloro-"[tw] OR "dibenzofuran, heptachloro-"[tw] OR "Dibenzofuran, octachloro-"[tw] OR "monochlordibenzofuran"[tw] OR "chlorinated dibenzo-furan"[tw] OR "polychlorinated dibenzo-furan"[tw]) OR ("chlorinated dibenzo-furans"[tw] OR "dibenzofurans, chlorinated"[tw] OR "hepta chloro furans"[tw] OR "heptachlorofurans"[tw] OR "penta chloro furans"[tw] OR "polychlorinated dibenzo-furans"[tw]) OR (("chlorinated"[tw] AND "dibenzofuran"[tw]) OR ("polychlorinated"[tw] AND "dibenzofuran"[tw]) OR (("monochlorinated"[tw] OR "dichlorinated"[tw] OR "trichlorinated"[tw] OR "tetrachlorinated"[tw] OR "pentachlorinated"[tw] OR "hexachlorinated"[tw] OR "heptachlorinated"[tw] OR "octachlorinated"[tw] OR "perchlorinated") AND "dibenzofuran"[tw]) OR (("dipolychlorinated"[tw] OR "tripolychlorinated"[tw] OR "tetrapolychlorinated"[tw] OR "pentapolychlorinated"[tw] OR "hexapolychlorinated"[tw] OR "heptapolychlorinated"[tw] OR "octapolychlorinated"[tw] OR "perpolychlorinated"[tw] OR "polypolychlorinated"[tw]) AND "dibenzofuran"[tw])) OR (("chlorinated"[tw] AND "dibenzofurans"[tw]) OR ("polychlorinated"[tw] AND "dibenzofurans"[tw]) OR (("monochlorinated"[tw] OR "dichlorinated"[tw] OR "trichlorinated"[tw] OR "tetrachlorinated"[tw] OR "pentachlorinated"[tw] OR "hexachlorinated"[tw] OR "heptachlorinated"[tw] OR "octachlorinated"[tw] OR "perchlorinated") AND "dibenzofurans"[tw]) OR (("dipolychlorinated"[tw] OR "tripolychlorinated"[tw] OR "tetrapolychlorinated"[tw] OR "pentapolychlorinated"[tw] OR "hexapolychlorinated"[tw] OR "heptapolychlorinated"[tw] OR "octapolychlorinated"[tw] OR "perpolychlorinated"[tw] OR "polypolychlorinated"[tw]) AND "dibenzofurans"[tw])) OR ("CDD/F"[tw] OR "DCDD/F"[tw] OR "diCDD/F"[tw] OR "HCDD/F"[tw] OR "HpCDD/F"[tw] OR "HxCDD/F"[tw] OR "MCDD/F"[tw] OR "moCDD/F"[tw] OR "monoCDD/F"[tw] OR "OCDD/F"[tw] OR "PCDD/F"[tw] OR "PeCDD/F"[tw] OR "TCDD/F"[tw] OR "triCDD/F"[tw] OR "CDD/Fs"[tw] OR "DCDD/Fs"[tw] OR "diCDD/Fs"[tw] OR "HCDD/Fs"[tw] OR "HpCDD/Fs"[tw] OR "HxCDD/Fs"[tw] OR "MCDD/Fs"[tw] OR "moCDD/Fs"[tw] OR "monoCDD/Fs"[tw] OR "OCDD/Fs"[tw] OR "PCDD/Fs"[tw] OR "PeCDD/Fs"[tw] OR "TCDD/Fs"[tw] OR "triCDD/Fs"[tw]) OR ("chlorodiphenylene oxide"[tw] OR "monochlorodiphenylene oxide"[tw] OR "dichlorodiphenylene oxide"[tw] OR "trichlorodiphenylene oxide"[tw] OR "tetrachlorodiphenylene oxide"[tw] OR "pentachlorodiphenylene oxide"[tw] OR "hexachlorodiphenylene oxide"[tw] OR "heptachlorodiphenylene oxide"[tw] OR "octachlorodiphenylene oxide"[tw] OR "perchlorodiphenylene oxide"[tw] OR "polychlorodiphenylene oxide"[tw] OR "chlorodiphenylene oxides"[tw] OR "monochlorodiphenylene oxides"[tw] OR "dichlorodiphenylene oxides"[tw] OR "trichlorodiphenylene oxides"[tw] OR "tetrachlorodiphenylene oxides"[tw] OR "pentachlorodiphenylene oxides"[tw] OR "hexachlorodiphenylene oxides"[tw] OR "heptachlorodiphenylene oxides"[tw] OR "octachlorodiphenylene oxides"[tw] OR "perchlorodiphenylene oxides"[tw] OR "polychlorodiphenylene oxides"[tw]) OR ("chlorodiphenylene oxide"[tw] OR "monochlorodiphenylene oxide"[tw] OR "dichlorodiphenylene oxide"[tw] OR "trichlorodiphenylene oxide"[tw] OR "tetrachlorodiphenylene oxide"[tw] OR "pentachlorodiphenylene oxide"[tw] OR "hexachlorodiphenylene oxide"[tw] OR "heptachlorodiphenylene oxide"[tw] OR "octachlorodiphenylene oxide"[tw] OR

Table B-2. Database Query Strings

Database search date	Query string
	"perchlorodiphenylene oxide"[tw] OR "polychlorodiphenylene oxide"[tw] OR "chlorodiphenylene oxides"[tw] OR "monochlorodiphenylene oxides"[tw] OR "dichlorodiphenylene oxides"[tw] OR "trichlorodiphenylene oxides"[tw] OR "tetrachlorodiphenylene oxides"[tw] OR "pentachlorodiphenylene oxides"[tw] OR "hexachlorodiphenylene oxides"[tw] OR "heptachlorodiphenylene oxides"[tw] OR "octachlorodiphenylene oxides"[tw] OR "perchlorodiphenylene oxides"[tw] OR "polychlorodiphenylene oxides"[tw]) OR ("12378 PeCDFuran"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,8,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,8,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,8-pentachloro-"[tw] OR "Dibenzofuran, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzofuran, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,4,6,7,8-hexachloro-"[tw] OR "Dibenzofuran, 2,3,4,7,8-pentachloro-"[tw] OR "Dibenzofuran, 2,3,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetra-chloro-"[tw]) OR ("12378 PeCDFuran"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8,9-octachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,8-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,8,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,8,9-heptachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,8-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,8-pentachloro-"[tw] OR "Dibenzofuran, 1,2,3,6,7,8-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,7,8,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,7,8-pentachloro-"[tw] OR "Dibenzofuran, 1,2,4,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,3,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,4,6,7,8-hexachloro-"[tw] OR "Dibenzofuran, 2,3,4,7,8-pentachloro-"[tw] OR "Dibenzofuran, 2,3,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,7,8-tetra-chloro-"[tw]) OR ("Dibenzofuran, 3-chloro-"[tw] OR "Dibenzofuran, 2-chloro-"[tw] OR "Dibenzofuran, 2,4,8-trichloro-"[tw] OR "Dibenzofuran, 1,3-dichloro-"[tw] OR "Dibenzofuran, 2,4,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzofuran, 2,8-dichloro-"[tw] OR "Dibenzofuran, 1,4,8-trichloro-"[tw] OR "Dibenzofuran, 2,3,6,7-tetrachloro-"[tw] OR "Dibenzofuran, 3,4,6,7-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,4,6,7-pentachloro-"[tw] OR "Dibenzofuran, 2,7-dichloro-"[tw] OR "Dibenzofuran, 1,2,3,6,8,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,3,4,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,8,9-hexachloro-"[tw]) OR ("Dibenzofuran, 3-chloro-"[tw] OR "Dibenzofuran, 2-chloro-"[tw] OR "Dibenzofuran, 2,4,8-trichloro-"[tw] OR "Dibenzofuran, 1,3-dichloro-"[tw] OR "Dibenzofuran, 2,4,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,2,7,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,3,6,8-tetrachloro-"[tw] OR "Dibenzofuran, 1,2,3,4-tetrachloro-"[tw] OR "Dibenzofuran, 2,8-dichloro-"[tw] OR "Dibenzofuran, 1,4,8-trichloro-"[tw] OR "Dibenzofuran, 2,3,6,7-tetrachloro-"[tw] OR "Dibenzofuran, 3,4,6,7-tetrachloro-"[tw] OR "Dibenzofuran, 2,3,4,6,7-pentachloro-"[tw] OR "Dibenzofuran, 2,7-dichloro-"[tw] OR "Dibenzofuran, 1,2,3,6,8,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,7-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,6,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,3,4,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,6,7,9-hexachloro-"[tw] OR "Dibenzofuran, 1,2,3,4,8,9-hexachloro-"[tw]))
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06/2022	Date Published 2018 to 2022

Table B-2. Database Query Strings

Database search date	Query string
	"DCDF" OR "diCDF" OR "di-CDF" OR "HCDF" OR "heptaCDF" OR "hepta-CDF" OR "hexaCDF" OR "hexa-CDF" OR "HpCDF" OR "HxCDF" OR "moCDF" OR "monoCDF" OR "mono-CDF" OR "OCDF" OR "octaCDF" OR "octa-CDF" OR "PCDF" OR "PeCDF" OR "pentaCDF" OR "penta-CDF" OR "Tcdbf" OR "TCDF" OR "tetraCDF" OR "tetra-CDF" OR "triCDF" OR "tri-CDF" OR "DCDFs" OR "diCDFs" OR "di-CDFs" OR "HCDFs" OR "heptaCDFs" OR "hepta-CDFs" OR "hexaCDFs" OR "hexa-CDFs" OR "HpCDFs" OR "HxCDFs" OR "moCDFs" OR "monoCDFs" OR "mono-CDFs" OR "OCDFs" OR "octaCDFs" OR "octa-CDFs" OR "PCDFs" OR "PeCDFs" OR "pentaCDFs" OR "penta-CDFs" OR "Tcdbfs" OR "TCDFs" OR "tetraCDFs" OR "tetra-CDFs" OR "triCDFs" OR "tri-CDFs" OR "chlorodibenzofuran" OR "polychlorodibenzofuran" OR "monochlorodibenzofuran" OR "dichlorodibenzofuran" OR "trichlorodibenzofuran" OR "tetrachlorodibenzofuran" OR "pentachlorodibenzofuran" OR "hexachlorodibenzofuran" OR "heptachlorodibenzofuran" OR "octachlorodibenzofuran" OR "perchlorodibenzofuran" OR "chlorinated dibenzofuran" OR "polychlorinated dibenzofuran" OR "chlorodibenzofurans" OR "polychlorodibenzofurans" OR "monochlorodibenzofurans" OR "dichlorodibenzofurans" OR "trichlorodibenzofurans" OR "tetrachlorodibenzofurans" OR "pentachlorodibenzofurans" OR "hexachlorodibenzofurans" OR "heptachlorodibenzofurans" OR "octachlorodibenzofurans" OR "perchlorodibenzofurans" OR "chlorinated dibenzofurans" OR "polychlorinated dibenzofurans" Date Published 2018 to 2022 "chlorinated dibenzofuran" OR "polychlorinated dibenzofuran" OR "monochlorinated dibenzofuran" OR "dichlorinated dibenzofuran" OR "trichlorinated dibenzofuran" OR "tetrachlorinated dibenzofuran" OR "pentachlorinated dibenzofuran" OR "hexachlorinated dibenzofuran" OR "heptachlorinated dibenzofuran" OR "octachlorinated dibenzofuran" OR "perchlorinated dibenzofuran" OR "dipolychlorinated dibenzofuran" OR "tripolychlorinated dibenzofuran" OR "tetrapolychlorinated dibenzofuran" OR "pentapolychlorinated dibenzofuran" OR "hexapolychlorinated dibenzofuran" OR "heptapolychlorinated dibenzofuran" OR "octapolychlorinated dibenzofuran" OR "perpolychlorinated dibenzofuran" OR "polypolychlorinated dibenzofuran" OR "chlorinated dibenzofurans" OR "polychlorinated dibenzofurans" OR "monochlorinated dibenzofurans" OR "dichlorinated dibenzofurans" OR "trichlorinated dibenzofurans" OR "tetrachlorinated dibenzofurans" OR "pentachlorinated dibenzofurans" OR "hexachlorinated dibenzofurans" OR "heptachlorinated dibenzofurans" OR "octachlorinated dibenzofurans" OR "perchlorinated dibenzofurans" OR "dipolychlorinated dibenzofurans" OR "tripolychlorinated dibenzofurans" OR "tetrapolychlorinated dibenzofurans" OR "pentapolychlorinated dibenzofurans" OR "hexapolychlorinated dibenzofurans" OR "heptapolychlorinated dibenzofurans" OR "octapolychlorinated dibenzofurans" OR "perpolychlorinated dibenzofurans" OR "polypolychlorinated dibenzofurans" OR "chloro dibenzofuran" OR "polychloro dibenzofuran" OR "monochloro dibenzofuran" OR "dichloro dibenzofuran" OR "trichloro dibenzofuran" OR "tetrachloro dibenzofuran" OR "pentachloro dibenzofuran" OR "hexachloro dibenzofuran" OR "heptachloro dibenzofuran" OR "octachloro dibenzofuran" OR "perchloro dibenzofuran" OR "chloro dibenzofurans" OR "polychloro dibenzofurans" OR "monochloro dibenzofurans" OR "dichloro dibenzofurans" OR "trichloro dibenzofurans" OR "tetrachloro dibenzofurans" OR "pentachloro dibenzofurans" OR "hexachloro dibenzofurans" OR "heptachloro dibenzofurans" OR "octachloro dibenzofurans" OR "perchloro dibenzofurans" OR "dibenzofuran, chloro-" OR "dibenzofuran, dichloro-" OR "dibenzofuran, trichloro-" OR "dibenzofuran, tetrachloro-" OR "dibenzofuran, pentachloro-" OR "dibenzofuran, hexachloro-" OR "dibenzofuran, heptachloro-" OR "Dibenzofuran, octachloro-" OR "monochlordibenzofuran" OR "chlorinated dibenzo-furan" OR

Table B-2. Database Query Strings

Database search date	Query string
	"polychlorinated dibenzo-furan" OR "chlorinated dibenzo-furans" OR "dibenzofurans, chlorinated" OR "hepta chloro furans" OR "heptachlorofurans" OR "penta chloro furans" OR "polychlorinated dibenzo-furans" Date Published 2018 to 2022 "chlorodiphenylene oxide" OR "monochlorodiphenylene oxide" OR "dichlorodiphenylene oxide" OR "trichlorodiphenylene oxide" OR "tetrachlorodiphenylene oxide" OR "pentachlorodiphenylene oxide" OR "hexachlorodiphenylene oxide" OR "heptachlorodiphenylene oxide" OR "octachlorodiphenylene oxide" OR "perchlorodiphenylene oxide" OR "polychlorodiphenylene oxide" OR "chlorodiphenylene oxides" OR "monochlorodiphenylene oxides" OR "dichlorodiphenylene oxides" OR "trichlorodiphenylene oxides" OR "tetrachlorodiphenylene oxides" OR "pentachlorodiphenylene oxides" OR "hexachlorodiphenylene oxides" OR "heptachlorodiphenylene oxides" OR "octachlorodiphenylene oxides" OR "perchlorodiphenylene oxides" OR "polychlorodiphenylene oxides" OR "12378 PeCDFuran" OR "Dibenzofuran, 1,2,3,4,6,7,8,9-octachloro-" OR "Dibenzofuran, 1,2,3,4,6,7,8-heptachloro-" OR "Dibenzofuran, 1,2,3,4,6,7,9-heptachloro-" OR "Dibenzofuran, 1,2,3,4,6,8,9-heptachloro-" OR "Dibenzofuran, 1,2,3,4,7,8,9-heptachloro-" OR "Dibenzofuran, 1,2,3,4,7,8-hexachloro-" OR "Dibenzofuran, 1,2,3,4,8-pentachloro-" OR "Dibenzofuran, 1,2,3,6,7,8-hexachloro-" OR "Dibenzofuran, 1,2,3,7,8,9-hexachloro-" OR "Dibenzofuran, 1,2,3,7,8-pentachloro-" OR "Dibenzofuran, 1,2,4,6,7,9-hexachloro-" OR "Dibenzofuran, 1,3,7,8-tetrachloro-" OR "Dibenzofuran, 2,3,4,6,7,8-hexachloro-" OR "Dibenzofuran, 2,3,4,7,8-pentachloro-" OR "Dibenzofuran, 2,3,6,8-tetrachloro-" OR "Dibenzofuran, 2,3,7,8-tetrachloro-" OR "Dibenzofuran, 2,3,7,8-tetra-chloro-" OR "Dibenzofuran, 3-chloro-" OR "Dibenzofuran, 2-chloro-" OR "Dibenzofuran, 2,4,8-trichloro-" OR "Dibenzofuran, 1,3-dichloro-" OR "Dibenzofuran, 2,4,6,8-tetrachloro-" OR "Dibenzofuran, 1,2,7,8-tetrachloro-" OR "Dibenzofuran, 1,3,6,8-tetrachloro-" OR "Dibenzofuran, 1,2,3,4-tetrachloro-" OR "Dibenzofuran, 2,8-dichloro-" OR "Dibenzofuran, 1,4,8-trichloro-" OR "Dibenzofuran, 2,3,6,7-tetrachloro-" OR "Dibenzofuran, 3,4,6,7-tetrachloro-" OR "Dibenzofuran, 2,3,4,6,7-pentachloro-" OR "Dibenzofuran, 2,7-dichloro-" OR "Dibenzofuran, 1,2,3,6,8,9-hexachloro-" OR "Dibenzofuran, 1,2,3,4,6,7-hexachloro-" OR "Dibenzofuran, 1,2,3,4,6,9-hexachloro-" OR "Dibenzofuran, 1,2,3,4,7,9-hexachloro-" OR "Dibenzofuran, 1,3,4,6,7,9-hexachloro-" OR "Dibenzofuran, 1,2,3,6,7,9-hexachloro-" OR "Dibenzofuran, 1,2,3,4,8,9-hexachloro-"
Toxcenter	
06/2022	FILE 'TOXCENTER' ENTERED AT 16:55:43 ON 02 JUN 2022
	L1 8780 SEA FILE=TOXCENTER 39001-02-0 OR 51207-31-9 OR 55673-89-7 OR 57117-31-4 OR 57117-35-8 OR 57117-37-0 OR 57117-41-6 OR 57117-44-9 OR 60851-34-5 OR 67517-48-0 OR 67562-39-4 OR 69698-58-4 OR 70648-25-8 OR 70648-26-9 OR 72918-21-9 OR 75627-02-0 OR 42934-53-2 OR 30402-14-3 OR 30402-15-4 OR 55684-94-1 OR 38998-75-3
	L2 901 SEA FILE=TOXCENTER 136677-10-6 OR 43047-99-0 OR 51230-49-0 OR 25074-67-3 OR 74992-96-4 OR 94538-00-8 OR 5409-83-6 OR 64560-14-1 OR 54589-71-8 OR 24478-72-6 OR 58802-19-0 OR 58802-20-3 OR 71998-72-6 OR 74992-98-6 OR 43048-00-6
	L3 500 SEA FILE=TOXCENTER 57117-39-2 OR 57117-40-5 OR 57117-43-8 OR 75198-38-8 OR 79060-60-9 OR 91538-83-9 OR 91538-84-0 OR 92341-05-4 OR 92341-06-5 OR 92341-07-6
	L4 8203 SEA FILE=TOXCENTER 24478-72-6 OR 24478-73-7 OR 24478-74-8 OR

Table B-2. Database Query Strings

Database search date	Query string
	25074-67-3 OR 30402-14-3 OR 30402-15-4 OR 38998-75-3 OR 39001-02-0 OR 42934-53-2 OR 43047-99-0 OR 43048-00-6 OR 51207-31-9 OR 51230-49-0 OR 5409-83-6 OR 54589-71-8 OR 55673-89-7 OR 55684-94-1 OR 55722-27-5
	L5 6044 SEA FILE=TOXCENTER 57117-31-4 OR 57117-32-5 OR 57117-33-6 OR 57117-34-7 OR 57117-35-8 OR 57117-36-9 OR 57117-37-0 OR 57117-38-1 OR 57117-39-2 OR 57117-40-5 OR 57117-41-6 OR 57117-42-7 OR 57117-43-8 OR 57117-44-9 OR 58802-14-5 OR 58802-15-6 OR 58802-16-7 OR 58802-17-8
	L6 4489 SEA FILE=TOXCENTER 58802-18-9 OR 58802-19-0 OR 58802-20-3 OR 58802-21-4 OR 60390-27-4 OR 60851-34-5 OR 62615-08-1 OR 64126-85-8 OR 64126-86-9 OR 64126-87-0 OR 64560-13-0 OR 64560-14-1 OR 64560-15-2 OR 64560-16-3 OR 64560-17-4 OR 66794-59-0 OR 67481-22-5 OR 67517-48-0 DIS COST
	L7 4907 SEA FILE=TOXCENTER 67562-39-4 OR 67562-40-7 OR 67652-39-5 OR 69433-00-7 OR 69698-57-3 OR 69698-58-4 OR 69698-59-5 OR 69698-60-8 OR 70648-13-4 OR 70648-14-5 OR 70648-15-6 OR 70648-16-7 OR 70648-18-9 OR 70648-19-0 OR 70648-20-3 OR 70648-21-4 OR 70648-22-5 OR 70648-23-6
	L8 5141 SEA FILE=TOXCENTER 70648-24-7 OR 70648-25-8 OR 70648-26-9 OR 70872-82-1 OR 71998-72-6 OR 71998-73-7 OR 71998-74-8 OR 71998-75-9 OR 72918-21-9 OR 74423-73-7 OR 74918-40-4 OR 74992-96-4 OR 74992-97-5 OR 74992-98-6 OR 75198-38-8 OR 75627-02-0 OR 76621-12-0 OR 79060-60-9
	L9 273 SEA FILE=TOXCENTER 81638-37-1 OR 82911-58-8 OR 82911-59-9 OR 82911-60-2 OR 82911-61-3 OR 83636-47-9 OR 83690-98-6 OR 83704-21-6 OR 83704-22-7 OR 83704-23-8 OR 83704-24-9 OR 83704-25-0 OR 83704-26-1 OR 83704-27-2 OR 83704-28-3 OR 83704-29-4 OR 83704-30-7 OR 83704-31-8
	L10 286 SEA FILE=TOXCENTER 83704-32-9 OR 83704-33-0 OR 83704-34-1 OR 83704-35-2 OR 83704-36-3 OR 83704-37-4 OR 83704-38-5 OR 83704-39-6 OR 83704-40-9 OR 83704-41-0 OR 83704-42-1 OR 83704-43-2 OR 83704-44-3 OR 83704-45-4 OR 83704-46-5 OR 83704-47-6 OR 83704-48-7 OR 83704-49-8
	L11 531 SEA FILE=TOXCENTER 83704-50-1 OR 83704-51-2 OR 83704-52-3 OR 83704-53-4 OR 83704-54-5 OR 83704-55-6 OR 83710-07-0 OR 83719-40-8 OR 84761-86-4 OR 89059-46-1 OR 91538-83-9 OR 91538-84-0 OR 92341-04-3 OR 92341-05-4 OR 92341-06-5 OR 92341-07-6 OR 94538-00-8 OR 94538-01-9 OR 94538-02-0 OR 94570-83-9
	L14 9010 SEA FILE=TOXCENTER L1 OR L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11
	L16 8986 SEA FILE=TOXCENTER L14 NOT TSCATS/FS
	L17 8768 SEA FILE=TOXCENTER L16 NOT PATENT/DT
	L18 293 SEA FILE=TOXCENTER L17 AND ED>=20190701 ACTIVATE TOXQUERY/Q

	L19 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)

Table B-2. Database Query Strings

Database search date	Query string
	L20 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L21 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L22 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L23 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L24 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L25 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L26 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L27 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L28 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L29 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L30 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L31 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L32 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L33 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L34 QUE (ENDOCRIN? AND DISRUPT?)
	L35 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L36 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L37 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L38 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L39 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L40 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L41 QUE (NEPHROTOX? OR HEPATOTOX?)
	L42 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L43 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L44 QUE 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 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40 OR L41 OR L42 OR L43
	L45 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE

Table B-2. Database Query Strings

Database search date	Query string
	OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE
	OR PORCINE OR MONKEY? OR MACAQUE?)
	L46 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L47 QUE L44 OR L45 OR L46
	L48 QUE (NONHUMAN MAMMALS)/ORGN
	L49 QUE L47 OR L48
	L50 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L51 QUE L49 OR L50

	L52 141 SEA FILE=TOXCENTER L18 AND L51
	L53 5 SEA FILE=TOXCENTER L52 AND MEDLINE/FS
	L54 135 DUP REM L52 (6 DUPLICATES REMOVED)
	D SCAN L54

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via Chemview	
06/2022	39001-02-0; 51207-31-9; 55673-89-7; 57117-31-4; 57117-35-8; 57117-37-0; 57117-41-6; 57117-44-9; 60851-34-5; 67517-48-0; 67562-39-4; 69698-58-4; 70648-25-8; 70648-26-9; 72918-21-9; 75627-02-0; 42934-53-2; 30402-14-3; 30402-15-4; 55684-94-1; 38998-75-3; 136677-10-6; 43047-99-0; 51230-49-0; 25074-67-3; 74992-96-4; 94538-00-8; 5409-83-6; 64560-14-1; 54589-71-8; 24478-72-6; 58802-19-0; 58802-20-3; 71998-72-6; 74992-98-6; 43048-00-6; 57117-39-2; 57117-40-5; 57117-43-8; 75198-38-8; 79060-60-9; 91538-83-9; 91538-84-0; 92341-05-4; 92341-06-5; 92341-07-6
NTP	
06/2022	Date limited 2020-present or 2010-2019 (or Not Dated) "39001-02-0" "51207-31-9" "55673-89-7" "57117-31-4" "57117-35-8" "57117-37-0" "57117-41-6" "57117-44-9" "60851-34-5" "67517-48-0" "67562-39-4" "69698-58-4" "70648-25-8" "70648-26-9" "72918-21-9" "75627-02-0" "42934-53-2" "30402-14-3" "30402-15-4" "55684-94-1" "38998-75-3" "136677-10-6" "43047-99-0" "51230-49-0" "25074-67-3" "74992-96-4" "94538-00-8" "5409-83-6" "64560-14-1" "54589-71-8" "24478-72-6" "58802-19-0" "58802-20-3" "71998-72-6" "74992-98-6" "43048-00-6" "57117-39-2" "57117-40-5" "57117-43-8" "75198-38-8" "79060-60-9" "91538-83-9" "91538-84-0" "92341-05-4" "92341-06-5" "92341-07-6" "PCDFs" "CDFs" "chlorinated dibenzofurans" "polychlorinated dibenzofurans"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"chlorodibenzofuran" "polychlorodibenzofuran" "monochlorodibenzofuran" "dichlorodibenzofuran" "heptachlorodibenzofuran" "octachlorodibenzofuran" "perchlorodibenzofuran" "trichlorodibenzofuran" "tetrachlorodibenzofuran" "pentachlorodibenzofuran" "hexachlorodibenzofuran"
Regulations.gov	
06/2022	39001-02-0; 51207-31-9; 55673-89-7; 57117-31-4; 57117-35-8; 57117-37-0; 57117-41-6; 57117-44-9; 60851-34-5; 67517-48-0; 67562-39-4; 69698-58-4; 70648-25-8; 70648-26-9; 72918-21-9; 75627-02-0; 42934-53-2; 30402-14-3; 30402-15-4; 55684-94-1; 38998-75-3; 136677-10-6; 43047-99-0; 51230-49-0; 25074-67-3; 74992-96-4; 94538-00-8; 5409-83-6; 64560-14-1; 54589-71-8; 24478-72-6; 58802-19-0; 58802-20-3; 71998-72-6; 74992-98-6; 43048-00-6; 57117-39-2; 57117-40-5; 57117-43-8; 75198-38-8; 79060-60-9; 91538-83-9; 91538-84-0; 92341-05-4; 92341-06-5; 92341-07-6; PCDF; CDF; "chlorinated dibenzofuran"; "chlorinated dibenzofurans"; "polychlorinated dibenzofuran"; "polychlorinated dibenzofurans"; chlorodibenzofuran; polychlorodibenzofuran; monochlorodibenzofuran; dichlorodibenzofuran; heptachlorodibenzofuran; octachlorodibenzofuran; perchlorodibenzofuran; trichlorodibenzofuran; tetrachlorodibenzofuran; pentachlorodibenzofuran; hexachlorodibenzofuran
NIH RePORTER	
09/2022	Fiscal Year: Active Projects; Text Search: "DCDF" OR "diCDF" OR "di-CDF" OR "HCDF" OR "heptaCDF" OR "hepta-CDF" OR "hexaCDF" OR "hexa-CDF" OR "HpCDF" OR "HxCDF" OR "moCDF" OR "monoCDF" OR "mono-CDF" OR "OCDF" OR "octaCDF" OR "octa-CDF" OR "PCDF" OR "PeCDF" OR "pentaCDF" OR "penta-CDF" OR "Tcdbf" OR "TCDF" OR "tetraCDF" OR "tetra-CDF" OR "triCDF" OR "tri-CDF" OR "DCDFs" OR "diCDFs" OR "di-CDFs" OR "HCDFs" OR "heptaCDFs" OR "hepta-CDFs" OR "hexaCDFs" OR "hexa-CDFs" OR "HpCDFs" OR "HxCDFs" OR "moCDFs" OR "monoCDFs" OR "mono-CDFs" OR "OCDFs" OR "octaCDFs" OR "octa-CDFs" OR "PCDFs" OR "PeCDFs" OR "pentaCDFs" OR "penta-CDFs" OR "Tcdbfs" OR "TCDFs" OR "tetraCDFs" OR "tetra-CDFs" OR "triCDFs" OR "tri-CDFs" OR "chlorodibenzofuran" OR "polychlorodibenzofuran" OR "monochlorodibenzofuran" OR "dichlorodibenzofuran" OR "trichlorodibenzofuran" OR "tetrachlorodibenzofuran" OR "pentachlorodibenzofuran" OR "hexachlorodibenzofuran" OR "heptachlorodibenzofuran" OR "octachlorodibenzofuran" OR "perchlorodibenzofuran" OR "chlorinated dibenzofuran" OR "polychlorinated dibenzofuran" OR "chlorodibenzofurans" OR "polychlorodibenzofurans" OR "monochlorodibenzofurans" OR "dichlorodibenzofurans" OR "trichlorodibenzofurans" OR "tetrachlorodibenzofurans" OR "pentachlorodibenzofurans" OR "hexachlorodibenzofurans" OR "heptachlorodibenzofurans" OR "octachlorodibenzofurans" OR "perchlorodibenzofurans" OR "chlorinated dibenzofurans" OR "polychlorinated dibenzofurans" OR "chlorinated dibenzofuran" OR "polychlorinated dibenzofuran" OR "monochlorinated dibenzofuran" OR "dichlorinated dibenzofuran" OR "trichlorinated dibenzofuran" OR "tetrachlorinated dibenzofuran" OR "pentachlorinated dibenzofuran" OR "hexachlorinated dibenzofuran" OR "heptachlorinated dibenzofuran" OR "octachlorinated dibenzofuran" OR "perchlorinated dibenzofuran" OR "dipolychlorinated dibenzofuran" OR "tripolychlorinated dibenzofuran" OR "tetrapolychlorinated dibenzofuran" OR "pentapolychlorinated dibenzofuran" OR "hexapolychlorinated dibenzofuran" OR "heptapolychlorinated dibenzofuran" OR "octapolychlorinated dibenzofuran" OR "perpolychlorinated

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	dibenzofuran" OR "polypolychlorinated dibenzofuran" (advanced) Limit to: Project Title, Project Terms, Project Abstracts Fiscal Year: Active Projects; Text Search: "chlorinated dibenzofurans" OR "polychlorinated dibenzofurans" OR "monochlorinated dibenzofurans" OR "dichlorinated dibenzofurans" OR "trichlorinated dibenzofurans" OR "tetrachlorinated dibenzofurans" OR "pentachlorinated dibenzofurans" OR "hexachlorinated dibenzofurans" OR "heptachlorinated dibenzofurans" OR "octachlorinated dibenzofurans" OR "perchlorinated dibenzofurans" OR "dipolychlorinated dibenzofurans" OR "tripolychlorinated dibenzofurans" OR "tetrapolychlorinated dibenzofurans" OR "pentapolychlorinated dibenzofurans" OR "hexapolychlorinated dibenzofurans" OR "heptapolychlorinated dibenzofurans" OR "octapolychlorinated dibenzofurans" OR "perpolychlorinated dibenzofurans" OR "polypolychlorinated dibenzofurans" OR "chloro dibenzofuran" OR "polychloro dibenzofuran" OR "monochloro dibenzofuran" OR "dichloro dibenzofuran" OR "trichloro dibenzofuran" OR "tetrachloro dibenzofuran" OR "pentachloro dibenzofuran" OR "hexachloro dibenzofuran" OR "heptachloro dibenzofuran" OR "octachloro dibenzofuran" OR "perchloro dibenzofuran" OR "chloro dibenzofurans" OR "polychloro dibenzofurans" OR "monochloro dibenzofurans" OR "dichloro dibenzofurans" OR "trichloro dibenzofurans" OR "tetrachloro dibenzofurans" OR "pentachloro dibenzofurans" OR "hexachloro dibenzofurans" OR "heptachloro dibenzofurans" OR "octachloro dibenzofurans" OR "perchloro dibenzofurans" OR "dibenzofuran, chloro-" OR "dibenzofuran, dichloro-" OR "dibenzofuran, trichloro-" OR "dibenzofuran, tetrachloro-" OR "dibenzofuran, pentachloro-" OR "dibenzofuran, hexachloro-" OR "dibenzofuran, heptachloro-" OR "Dibenzofuran, octachloro-" OR "monochlordibenzofuran" OR "chlorinated dibenzo-furan" OR "polychlorinated dibenzo-furan" OR "chlorinated dibenzo-furans" OR "dibenzofurans, chlorinated" OR "hepta chloro furans" OR "heptachlorofurans" OR "penta chloro furans" OR "polychlorinated dibenzo-furans" (advanced) Limit to: Project Title, Project Terms, Project Abstracts Fiscal Year: Active Projects; Text Search: "chlorodiphenylene oxide" OR "monochlorodiphenylene oxide" OR "dichlorodiphenylene oxide" OR "trichlorodiphenylene oxide" OR "tetrachlorodiphenylene oxide" OR "pentachlorodiphenylene oxide" OR "hexachlorodiphenylene oxide" OR "heptachlorodiphenylene oxide" OR "octachlorodiphenylene oxide" OR "perchlorodiphenylene oxide" OR "polychlorodiphenylene oxide" OR "chlorodiphenylene oxides" OR "monochlorodiphenylene oxides" OR "dichlorodiphenylene oxides" OR "trichlorodiphenylene oxides" OR "tetrachlorodiphenylene oxides" OR "pentachlorodiphenylene oxides" OR "hexachlorodiphenylene oxides" OR "heptachlorodiphenylene oxides" OR "octachlorodiphenylene oxides" OR "perchlorodiphenylene oxides" OR "polychlorodiphenylene oxides" OR "12378 PeCDFuran" OR "Dibenzofuran, 1,2,3,4,6,7,8,9-octachloro-" OR "Dibenzofuran, 1,2,3,4,6,7,8-heptachloro-" OR "Dibenzofuran, 1,2,3,4,6,7,9-heptachloro-" OR "Dibenzofuran, 1,2,3,4,6,8,9-heptachloro-" OR "Dibenzofuran, 1,2,3,4,7,8,9-heptachloro-" OR "Dibenzofuran, 1,2,3,4,7,8-hexachloro-" OR "Dibenzofuran, 1,2,3,4,8-pentachloro-" OR "Dibenzofuran, 1,2,3,6,7,8-hexachloro-" OR "Dibenzofuran, 1,2,3,7,8,9-hexachloro-" OR "Dibenzofuran, 1,2,3,7,8-pentachloro-" OR "Dibenzofuran, 1,2,4,6,7,9-hexachloro-" OR "Dibenzofuran, 1,3,7,8-tetrachloro-" OR "Dibenzofuran, 2,3,4,6,7,8-hexachloro-" OR "Dibenzofuran, 2,3,4,7,8-pentachloro-" OR "Dibenzofuran, 2,3,6,8-tetrachloro-" OR "Dibenzofuran, 2,3,7,8-tetrachloro-" OR "Dibenzofuran, 2,3,7,8-tetra-chloro-" OR "Dibenzofuran, 3-chloro-" OR "Dibenzofuran, 2-chloro-" OR "Dibenzofuran, 2,4,8-

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	trichloro-" OR "Dibenzofuran, 1,3-dichloro-" OR "Dibenzofuran, 2,4,6,8-tetrachloro-" OR "Dibenzofuran, 1,2,7,8-tetrachloro-" OR "Dibenzofuran, 1,3,6,8-tetrachloro-" OR "Dibenzofuran, 1,2,3,4-tetrachloro-" OR "Dibenzofuran, 2,8-dichloro-" OR "Dibenzofuran, 1,4,8-trichloro-" OR "Dibenzofuran, 2,3,6,7-tetrachloro-" OR "Dibenzofuran, 3,4,6,7-tetrachloro-" OR "Dibenzofuran, 2,3,4,6,7-pentachloro-" OR "Dibenzofuran, 2,7-dichloro-" OR "Dibenzofuran, 1,2,3,6,8,9-hexachloro-" OR "Dibenzofuran, 1,2,3,4,6,7-hexachloro-" OR "Dibenzofuran, 1,2,3,4,6,9-hexachloro-" OR "Dibenzofuran, 1,2,3,4,7,9-hexachloro-" OR "Dibenzofuran, 1,3,4,6,7,9-hexachloro-" OR "Dibenzofuran, 1,2,3,6,7,9-hexachloro-" OR "Dibenzofuran, 1,2,3,4,8,9-hexachloro-" (advanced) Limit to: Project Title, Project Terms, Project Abstracts Fiscal Year: Active Projects; Text Search: "CDD/F" OR "DCDD/F" OR "diCDD/F" OR "HCDD/F" OR "HpCDD/F" OR "HxCDD/F" OR "MCDD/F" OR "moCDD/F" OR "monoCDD/F" OR "OCDD/F" OR "PCDD/F" OR "PeCDD/F" OR "TCDD/F" OR "triCDD/F" OR "CDD/Fs" OR "DCDD/Fs" OR "diCDD/Fs" OR "HCDD/Fs" OR "HpCDD/Fs" OR "HxCDD/Fs" OR "MCDD/Fs" OR "moCDD/Fs" OR "monoCDD/Fs" OR "OCDD/Fs" OR "PCDD/Fs" OR "PeCDD/Fs" OR "TCDD/Fs" OR "triCDD/Fs" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2022 results were:

- Number of records identified from PubMed, Toxline, and TOXCENTER (after duplicate removal): 663
- Number of records identified from other strategies: 30
- Total number of records to undergo literature screening: 693

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on CDFs:

- 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 B-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.

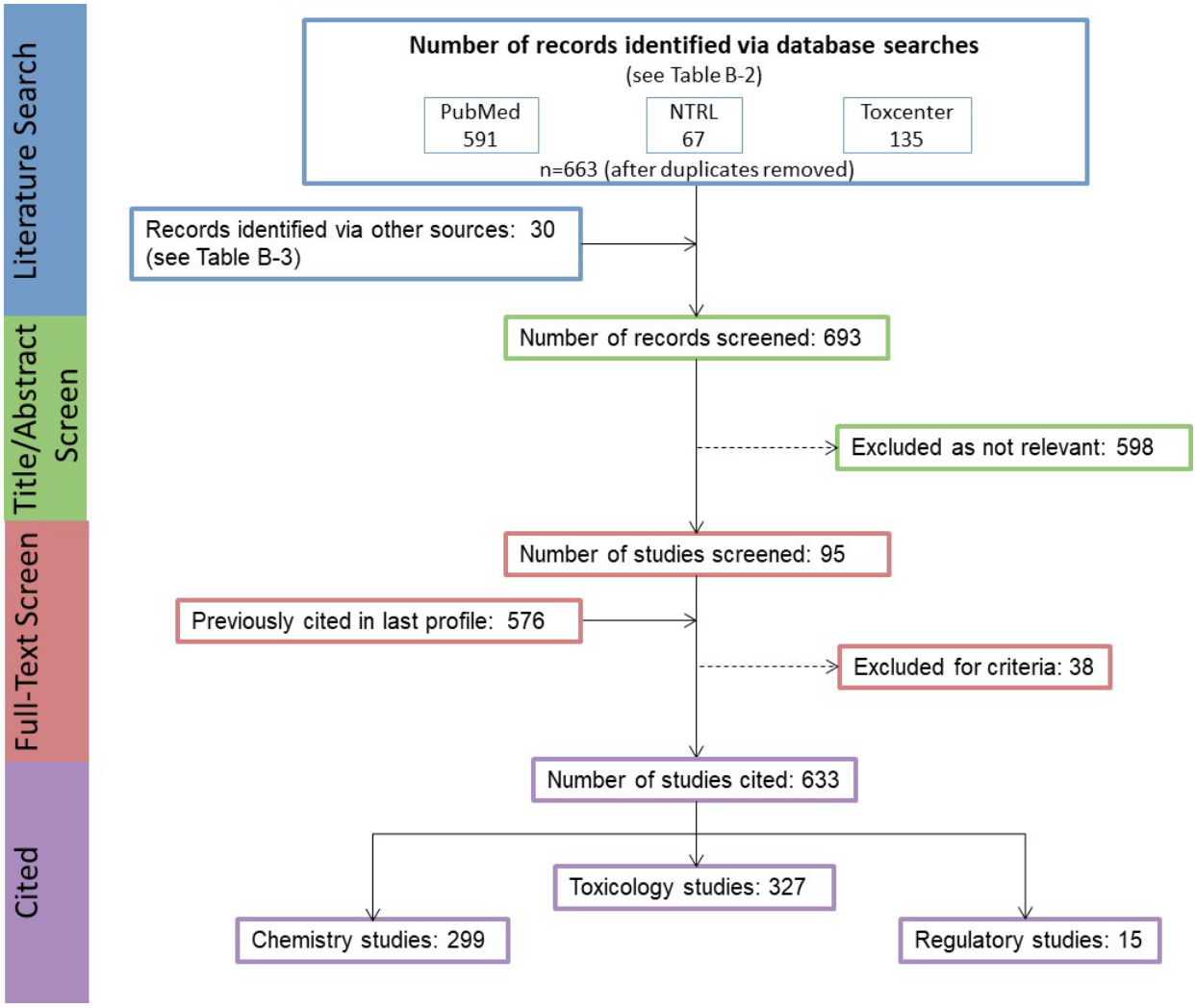
- Number of titles and abstracts screened: 693
- Number of studies considered relevant and moved to the next step: 95

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: 95
- Number of studies cited in the pre-public draft of the toxicological profile: 576
- Total number of studies cited in the profile: 633

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. July 2019 Literature Search Results and Screen for CDFs



APPENDIX C. 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 C-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 C-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.

APPENDIX C

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
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 (10)									
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									

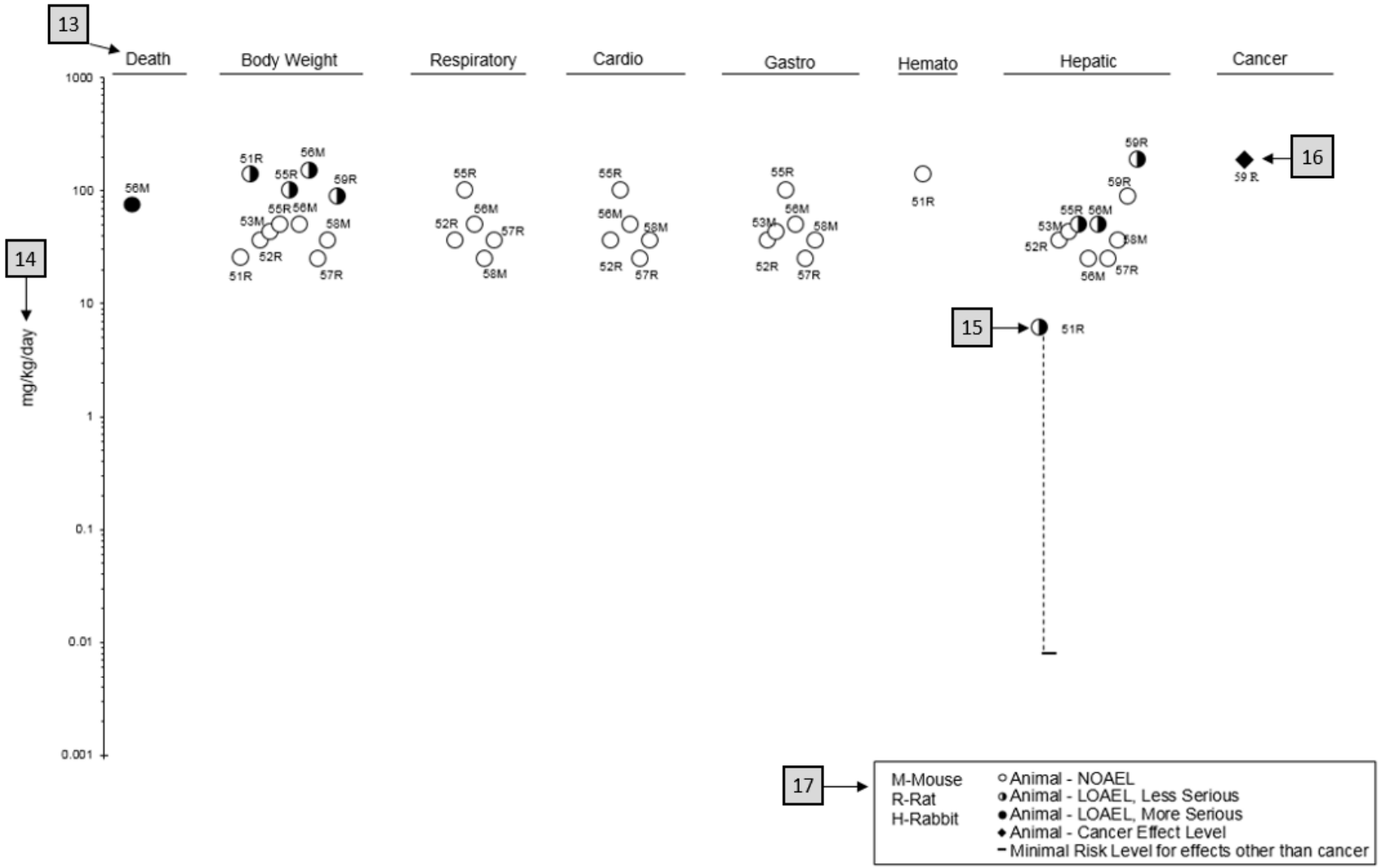
[a]The number corresponds to entries in Figure 2-x.

(11) [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).

APPENDIX C

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX D. 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:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.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, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • 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 E. 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.

Bioaccumulation—Intake and retention of a substance from all environmental sources, e.g., food and water.

Bioconcentration--Intake and retention of a substance in an aquatic organism entirely by respiration from water.

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 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 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 dose 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 dose, 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)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration 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.

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 F. 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
AHH	Aryl hydrocarbon hydrolase
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
EEG	electroencephalogram
EPA	Environmental Protection Agency
EROD	7-ethoxyresorufin 0-deethylhydrolase
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 Substance 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	lactic 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
MFO	mixed function oxydase
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
TEF	toxic equivalency factor
TEQ	total toxic equivalent
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