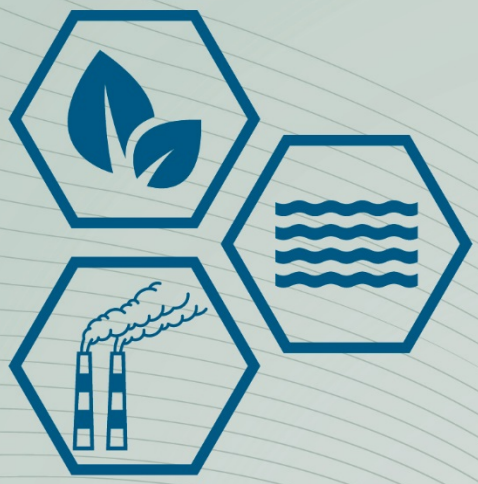

Toxicological Profile for Chlorodibenzofurans (CDFs)

Draft for Public Comment

January 2022

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

CS274127-A

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FOREWORD

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

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

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

Each profile includes the following:

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

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

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

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

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

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Office of Innovation and Analytics
Toxicology Section
1600 Clifton Road, N.E.
Mail Stop S102-1
Atlanta, Georgia 30329-4027

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

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

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

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

VERSION HISTORY

Date	Description
January 2022	Draft for public comment toxicological profile released
May 1994	Final toxicological profile released

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Hana R. Pohl, M.D., Ph.D. (Lead)
Breanna Alman, M.P.H.
Franco Scinicariello, M.D., M.P.H.

Lisa Ingerman, Ph.D., D.A.B.T.
Mario Citra, Ph.D.

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

SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:

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

Additional reviews for science and/or policy:

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

PEER REVIEWERS

1. Michael D. Collins, Ph.D., M.S.P.H., M.S., Professor; UCLA Fielding School of Public Health; Los Angeles, California

2. Charles J. Everett, Ph.D.; U.S. Department of Veterans Affairs; Ralph H. Johnson VA Medical Center; Charleston, South Carolina

3. Eric J. Reiner; University of Toronto; Toronto, Ontario, Canada

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

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

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

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

Chlorodibenzofurans (CDFs) are a class of structurally similar chlorinated hydrocarbons containing two benzene rings fused to a central furan ring (see chemical structure in Section 4.1). Based on the number of chlorine substituents (one to eight) on the benzene rings, there are eight homologues of CDFs (monochlorinated through octachlorinated). Each homologous group contains one or more isomers. There are 135 possible CDF isomers, including 4 monochlorinated dibenzofurans (monoCDFs), 16 dichlorinated dibenzofurans (diCDFs), 28 trichlorinated dibenzofurans (triCDFs), 38 tetrachlorinated dibenzofurans (tetraCDFs), 28 pentachlorinated dibenzofurans (pentaCDFs), 16 hexachlorinated dibenzofurans (hexaCDFs), 4 heptachlorinated dibenzofurans (heptaCDFs), and 1 octachlorinated dibenzofuran (octaCDF). The term congener is used to refer to any one particular isomer. Mono-, di-, and trichlorinated CDFs are not considered in this profile.

1.1 OVERVIEW AND U.S. EXPOSURES

CDFs are not manufactured commercially in the United States or any other country except on a laboratory scale for use in chemical laboratories or for toxicological studies. These compounds are undesired byproducts during the manufacture of various compounds or combustion mechanisms. There are several ways in which these substances are introduced to the environment, but there are three important processes that account for the majority of unintentional production of these substances: (1) thermal reactions such as releases from hazardous waste incineration facilities; (2) fires or accidents from polychlorinated biphenyl (PCB)-filled transformers and capacitors; and (3) high temperature industrial processes like copper smelting and electrical arc furnaces in steel mills or other similar practices. The manufacture of PCBs ceased in the late 1970s and improvements in engineering controls in industrial processes have resulted in a decrease in the release of CDFs into the environment. However, since these substances are persistent, they are still detected in environmental media.

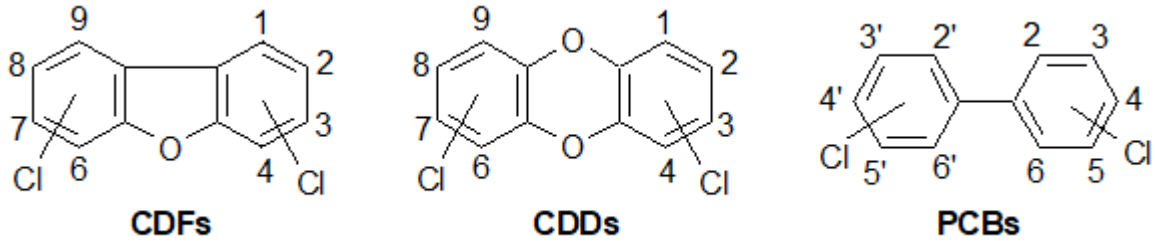
The higher chlorinated congeners of CDFs are particularly persistent in the environment and degrade slowly in air, water, and soil. They have been detected in remote areas far from their point of release and are subject to long-range transport. The higher chlorinated congeners are not highly volatile and have little mobility in soil. They are highly lipophilic and tend to accumulate in fat, liver, muscle, and kidney. They tend to bioconcentrate in aquatic organisms; however, their levels in fish and other aquatic species have been declining since the 1970s as environmental releases have decreased.

Humans are primarily exposed to CDFs through the ingestion of food items that are contaminated with these substances. Inhalation of ambient air, ingestion of drinking water, and use of certain consumer products that are contaminated with CDFs are also likely, but less important, exposure routes. More information regarding the unintentional production, environmental fate, and exposure to CDFs can be found in Chapter 5.

1.2 SUMMARY OF HEALTH EFFECTS

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

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



The dioxin-like compounds share a common mechanism of action that involves binding to the aryl hydrocarbon (Ah) receptor, which is a cellular protein. Epidemiological studies and experimental animal toxicological studies demonstrate that exposure to dioxin-like compounds can result in a wide range of adverse health outcomes including lethality, wasting syndrome, developmental toxicity, immunotoxicity, neurotoxicity, chloracne, liver toxicity, reproductive toxicity, and damage to teeth. The potencies of the different dioxin-like compounds vary with the substitution pattern, with 2,3,7,8-substituted CDDs and CDFs being more toxic than other congeners. Among the 2,3,7,8-substituted compounds, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) and 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin (1,2,3,7,8-pentaCDD) are the most toxic and octachlorodibenzo-*p*-dioxin (OCDD) and octachlorodibenzofuran (octaCDF) are the least toxic; 2,3,4,7,8-pentaCDF is the most toxic CDF congener (Van den Berg et al. 2006). Toxic equivalency factors (TEFs) have been developed, which use

2,3,7,8-TCDD as the reference chemical (see Section 2.1 for additional information). The TEFs allow for a comparison of the toxicity of the different dioxin-like compounds, and can also be used to estimate the overall toxicity of an environmental mixture of dioxin-like compounds. Using the TEFs, risk assessors can sum the risks associated with the individual dioxin-like compounds to calculate an overall risk.

Most of the information on human health effects that pertains to CDFs is from studies of people who ingested contaminated rice oil for up to 9–10 months during the Yusho and Yu-Cheng poisoning incidents in Japan and Taiwan, respectively. These health effects cannot be attributed solely to CDFs due to mixed chemical exposure and possible interactions between CDFs, PCBs, and other components of the contaminated rice oils, but there is sufficient evidence that CDFs are the main causal agents (see Section 2.1 for additional information). Although the Yusho and Yu-Cheng studies consist largely of observations on groups that are not very well defined and lack controls and exposure level information, they do provide a generally consistent picture of the health status of the affected people and an indication of potential effects for the general population who are exposed to low levels of CDFs. Manifestations of the Yusho and Yu-Cheng outbreaks include serious health effects such as severe skin lesions (e.g., persistent acneiform eruptions, hyperpigmentation) and ocular signs (e.g., hypersecretion of eyelid glands), increased susceptibility to respiratory infection (e.g., chronic bronchitis), and neurological symptoms and signs (e.g., limb numbness, reduced nerve conduction velocities, delayed neurobehavioral development). Less serious effects observed in Yusho and Yu-Cheng patients include mild hematological changes (e.g., anemia) and clinically insignificant hepatic alterations (e.g., changes in ultrastructure and serum triglycerides). Some of these effects, particularly dermal, ocular, and neurobehavioral manifestations, also occurred in children born of exposed mothers.

Most of the information on the toxicity of CDFs in laboratory animals comes from oral exposure studies; two studies involved dermal exposure and no inhalation studies were located. Laboratory animal studies have evaluated the toxicity of eight CDF congeners: 2,3,7,8-tetraCDF, 1,2,3,4,8-pentaCDF, 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,6,7,8-hexaCDF, 1,2,3,4,6,7,8-hepta-CDF, and octaCDF; several studies also evaluated a mixture of CDF congeners. The health effects associated with exposure of laboratory animals to CDFs are similar across congeners, although there are differences in relative toxicity. At lower doses, the primary targets are the liver, thymus, thyroid hormones, and developing organism following acute- or intermediate-duration exposure. In addition to these targets, chronic exposure also results in damage to the adrenal cortex, kidney, uterus, and gingiva. Cancer was observed following chronic oral exposure to 2,3,4,7,8-pentaCDF (the only congener with chronic exposure data).

The health effects associated with oral exposure to 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, and 1,2,3,6,7,8-hexaCDF in laboratory animals are illustrated in Figures 1-2, 1-3, 1-4, and 1-5, respectively. The other four congeners (1,2,3,4,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,4,6,7,8-heptaCDF, and octaCDF) had studies that only examined a single endpoint (1,2,3,4,7,8-hexaCDF and 1,2,3,4,6,7,8-heptaCDF) or there were no adverse effects identified at the highest dose levels (1,2,3,4,8-pentaCDF and octaCDF).

Hepatic Effects. Mild hepatic effects were reported among the Yusho and Yu-Cheng cohorts; the observed effects include increases in serum triglycerides (Okumura et al. 1979; Uzawa et al. 1969) and increases in serum aminotransferase levels (Rogan 1989). Hepatic effects have been observed in animals orally exposed to 2,3,7,8-substituted CDF congeners. The effects include increases in liver weight (NTP 2006; Pluess et al. 1988a, 1988b), lipid accumulation in the liver (Brewster et al. 1988; Pluess et al. 1988a, 1988b), and hepatocellular hypertrophy (NTP 2006). Histological alterations in the bile duct have also been observed in rats and monkeys exposed to 2,3,7,8-tetraCDF (McNulty et al. 1981; Moore et al. 1979) and 2,3,4,7,8-pentaCDF (NTP 2006). In the only study (Pluess et al. 1988a) evaluating a non-2,3,7,8-substituted congener, no liver effects were observed at doses at least 30 times higher than those resulting in liver effects for other congeners.

Immunological Effects. Studies of the Yusho and Yu-Cheng cohort have reported increases in the frequency and/or severity of skin and respiratory infections and lower resistance to illness (Kuratsune 1989; Rogan 1989). Increases in the prevalence of immune related diseases have also been reported (Akahane et al. 2018; Guo et al. 1999). Immunological effects observed in laboratory animals exposed to CDFs include decreases in thymus weight, thymic atrophy, and impaired immune responses. Decreases in thymus weight and/or thymic atrophy have been reported in several animal species exposed to 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, and 1,2,3,4,6,7,8-heptaCDF (McNulty et al. 1981; Moore et al. 1979; NTP 2006; Pluess et al. 1988a, 1988b; Taura et al. 2014). No alterations in thymus weight were observed in rats exposed to 1,2,3,4,8-pentaCDF (Pluess et al. 1988a). A small number of studies examined immune function. Decreases in lymphoproliferative responses to mitogens were observed in guinea pigs exposed to 2,3,7,8-tetraCDF (Luster et al. 1979a, 1979b) or 2,3,4,7,8-pentaCDF (Johnson et al. 2000).

Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 2,3,7,8-Tetrachlorodibenzofuran

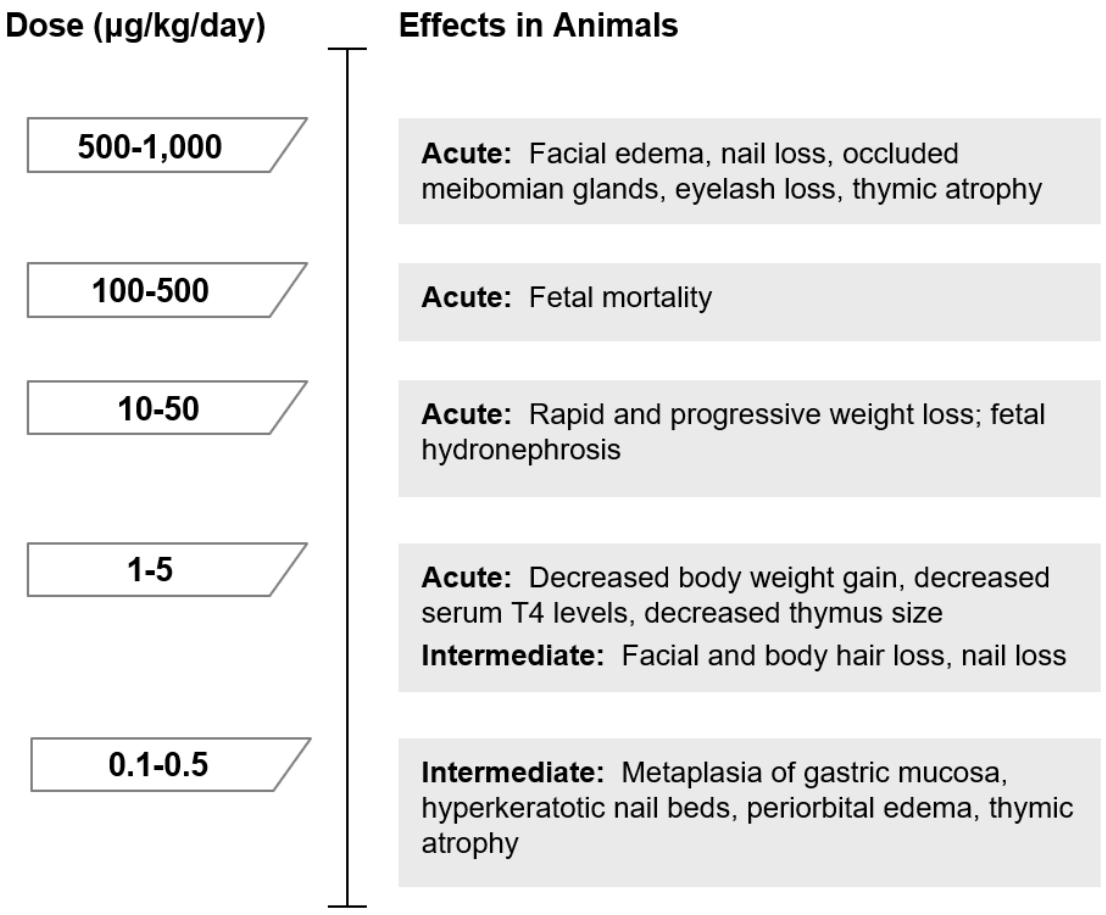


Figure 1-3. Health Effects Found in Animals Following Oral Exposure to 1,2,3,7,8-Pentachlorodibenzofuran

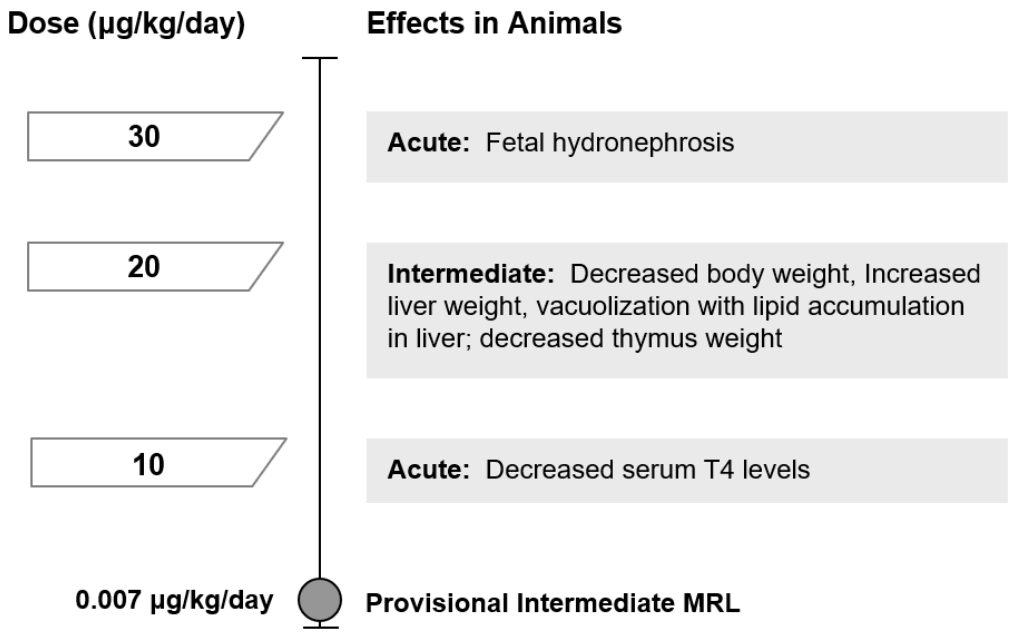


Figure 1-4. Health Effects Found in Animals Following Oral Exposure to 2,3,4,7,8-Pentachlorodibenzofuran

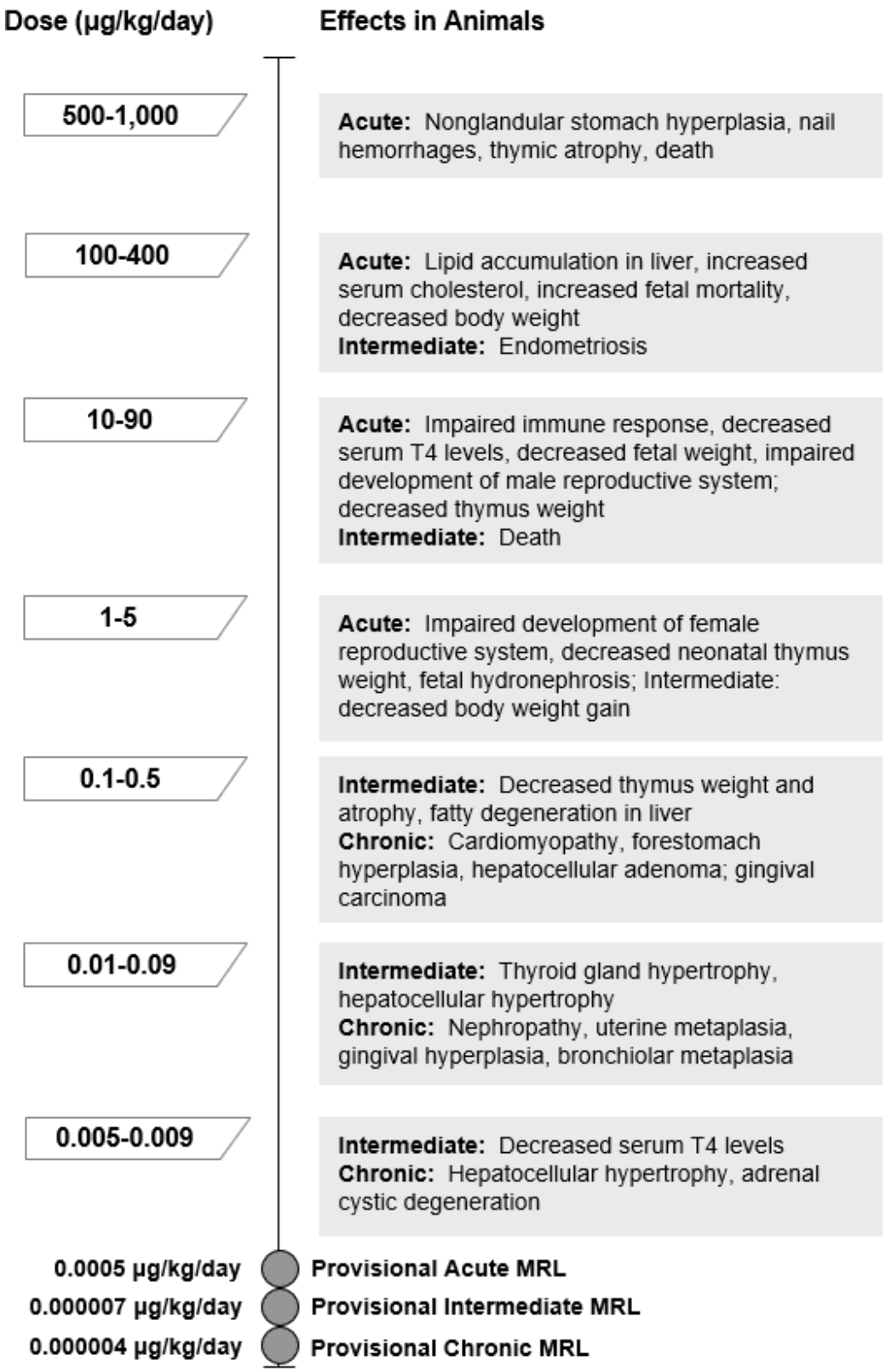
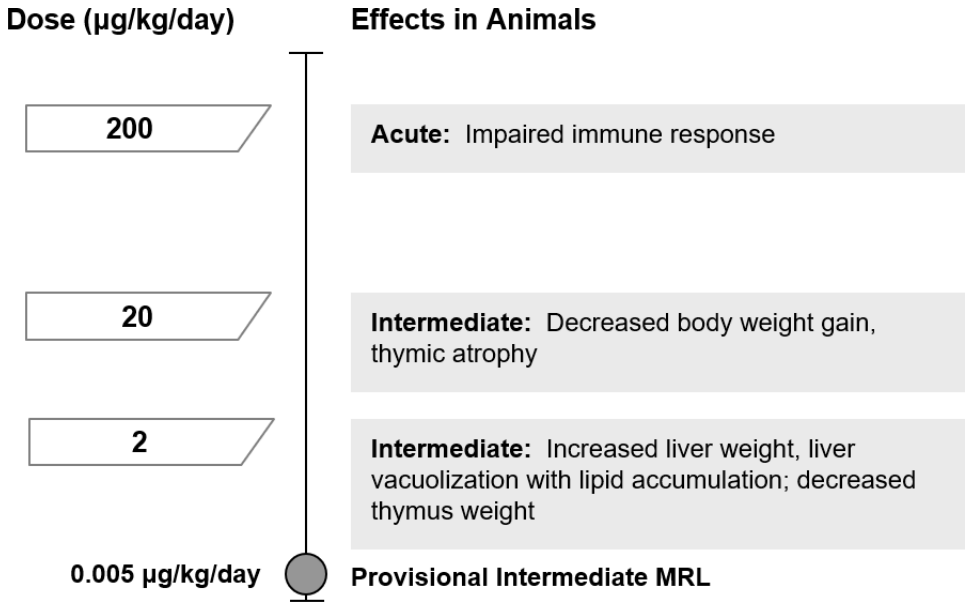


Figure 1-5. Health Effects Found in Animals Following Oral Exposure to 1,2,3,6,7,8-Hexachlorodibenzofuran



Thyroid Effects. There are limited data on potential thyroid effects in the Yusho and Yu-Cheng cohorts; effects include hypothyroidism and goiter (Akahane et al. 2018; Guo et al. 1999) and no alteration in thyroid hormone levels (Nagayama et al. 2001). These endpoints were evaluated many years after the incidents. In laboratory animals, decreases in serum total thyroxine (T4) were observed in acute-duration oral studies of 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, and 2,3,4,7,8-pentaCDF (Crofton et al. 2005; Ross et al. 2000) and in intermediate-duration studies of 2,3,4,7,8-pentaCDF (NTP 2006). No alterations in serum T4 levels were observed in rats acutely exposed to a relatively high dose of octaCDF (Crofton et al. 2005).

Developmental Effects. Developmental effects that were reported in the Yusho and Yu-Cheng cohort include skin lesions and hyperpigmentation, decreased birth weight, neurodevelopmental effects such a delays in developmental milestones and cognitive development, and higher prevalence of infections in children of exposed mothers (Chao et al. 1997; Chen et al. 1992; Funatsu et al. 1971; Guo et al. 1995; Hsu et al. 1985; Lan et al. 1987; Rogan et al. 1988; Taki et al. 1969; Yamaguchi et al. 1971; Yen et al. 1994; Yu et al. 1991). Developmental studies in laboratory animals primarily focused on evaluating the potential of CDF congeners to induce specific anomalies. Hydronephrosis and cleft palate were observed in mouse fetuses exposed to 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF (Birnbaum et al. 1987a, 1987b; Weber et al. 1984, 1985). Other developmental effects observed in animal studies include fetal mortality, decreases in fetal or offspring weights, and impaired development of the reproductive system (Birnbaum et al. 1987a; Couture et al. 1989; Salisbury and Marcinkiewicz 2002; Taura et al. 2014; Weber et al. 1984).

Cancer Effects. Several studies of the Yusho and Yu-Cheng cohorts evaluated carcinogenicity; the results appear to be inconsistent. A meta-analysis found an association with lung cancer, but not for other cancer types (Li et al. 2015a). There is limited information on the carcinogenicity of CDFs in laboratory animals. An oral exposure study of 2,3,4,7,8-pentaCDF in female rats concluded that there was some evidence of carcinogenicity (NTP 2006); increases in the incidence of hepatocellular adenoma, cholangiocarcinoma, and gingival squamous cell carcinoma were observed. Dermal exposure studies of 2,3,7,8-tetraCDF, 2,3,4,7,8-pentaCDF, and 1,2,3,4,7,8-hexaCDF found evidence of skin tumor promotion activity (Hebert et al. 1990; Poland et al. 1982).

The International Agency for Research on Cancer (IARC 2012) concluded that 2,3,4,7,8-pentaCDF is carcinogenic to humans; the agency also concluded that other CDF congeners are not classifiable as to their carcinogenicity to humans (Group 3) (IARC 1997). The Department of Health and Human Services

(HHS) (NTP 2016) and the U.S. Environmental Protection Agency (EPA) (IRIS 2020) have not conducted carcinogenicity assessments.

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation databases were not considered adequate for deriving inhalation MRLs for the eight CDF congeners (2,3,7,8-tetraCDF, 1,2,3,4,8-pentaCDF, 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, 1,2,3,6,7,8-hexaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,4,6,7,8-heptaCDF, or octaCDF) that had toxicity data. No inhalation studies were identified for any of these compounds.

The oral databases were considered adequate for derivation of a provisional intermediate-duration MRL for 1,2,3,7,8-pentaCDF; acute-, intermediate-, and chronic-duration provisional MRL for 2,3,4,7,8-pentaCDF; and a provisional intermediate-duration MRL for 1,2,3,6,7,8-hexaCDF. As illustrated in Figures 1-6, 1-7, and 1-8, the liver, thymus, thyroid, and developing organism are the most sensitive targets following acute and intermediate exposure; adrenal, liver, and reproductive effects were also observed at relatively low doses following chronic exposure to 2,3,4,7,8-pentaCDF (the only congener with chronic exposure data). The MRL values for 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, and 1,2,3,6,7,8-hexaCDF are summarized in Tables 1-1, 1-2, and 1-3, respectively, and discussed in greater detail in Appendix A. The oral databases for 2,3,7,8-tetraCDF, 1,2,3,4,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,4,6,7,8-heptaCDF, and octaCDF were not considered adequate for oral MRL derivations.

As discussed in Section 1.2, humans are typically exposed to a mixture of CDFs, CDDs, and PCBs in the environment. A TEF approach is often used to evaluate the toxicity associated with exposure to a mixture of dioxin-like compounds. In this application of the TEF approach, the relative effect potency of an individual congener in the mixture is expressed relative to the potency of the reference compound, 2,3,7,8-TCDD. An alternative approach for deriving MRLs for CDFs using empirical data is to use the MRLs for 2,3,7,8-TCDD adjusted by the TEF for the 2,3,7,8-substituted CDF congeners; a discussion of the use of TEFs to derive MRLs for CDFs is presented in Appendix A.

Figure 1-6. Summary of Sensitive Targets of 1,2,3,7,8-Pentachlorodibenzofuran – Oral

The thyroid, liver, thymus, body weight, and developing organisms are the most sensitive targets of 1,2,3,7,8-pentachlorodibenzofuran oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

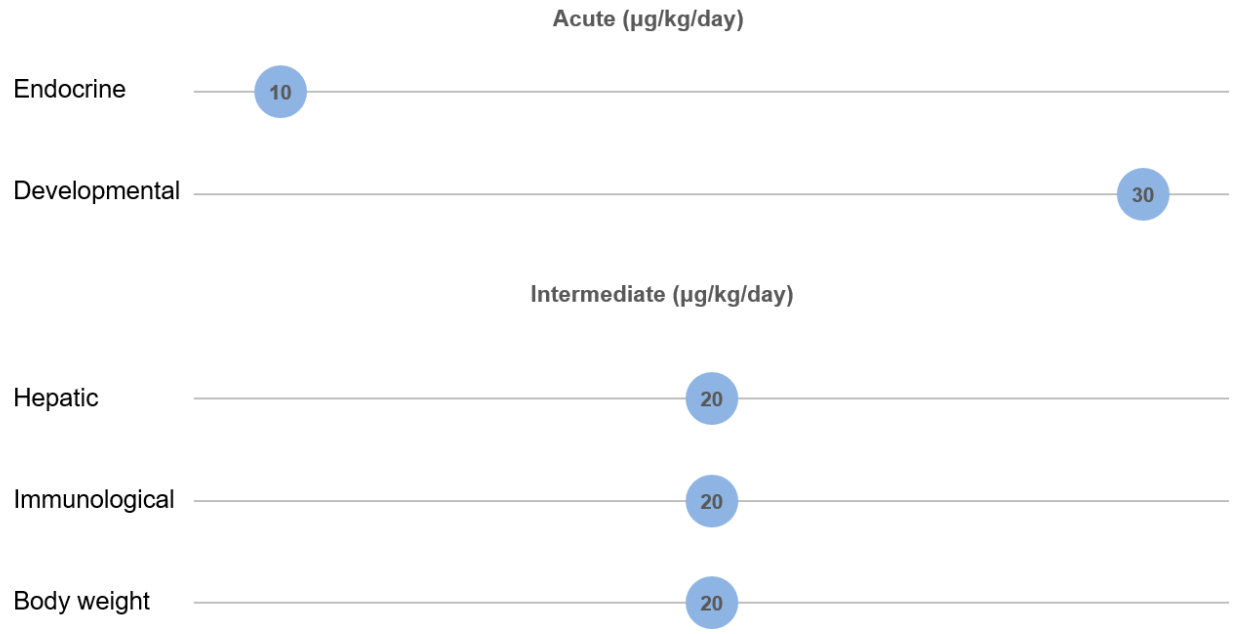


Figure 1-7. Summary of Sensitive Targets of 2,3,4,7,8-Pentachlorodibenzofuran – Oral

The liver, adrenal gland, thyroid, and thymus, and developing organisms are the most sensitive targets of 2,3,4,7,8-pentachlorodibenzofuran oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

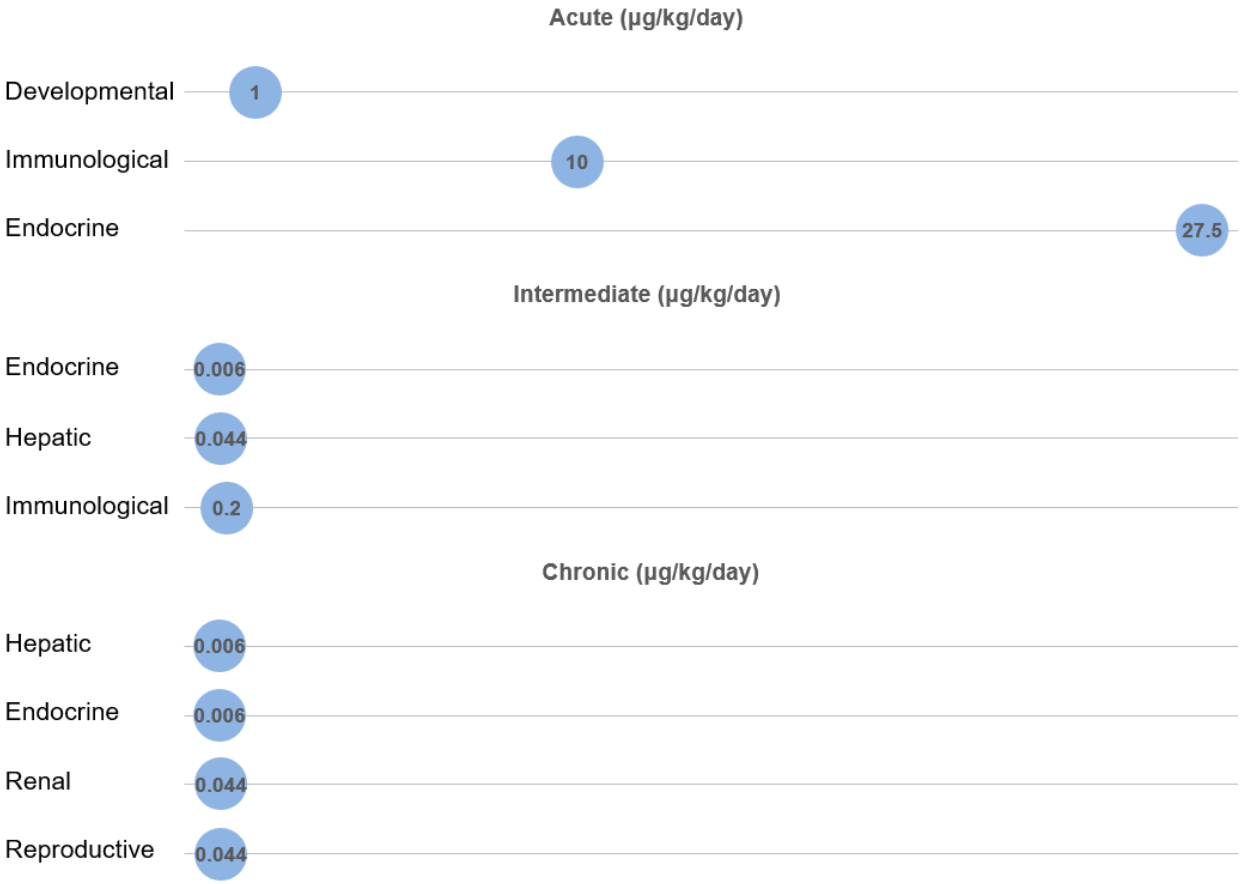


Figure 1-8. Summary of Sensitive Targets of 1,2,3,6,7,8-Hexaachlorodibenzofuran – Oral

The liver, thymus, and body weight are the most sensitive targets of 1,2,3,6,7,8-hexachlorodibenzofuran oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

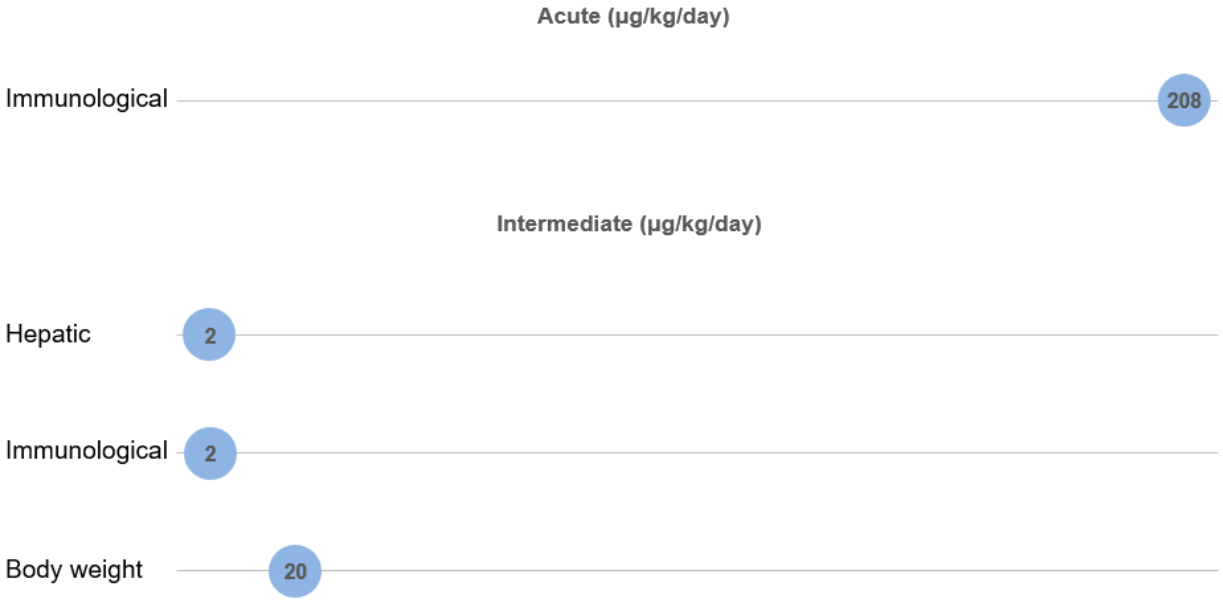


Table 1-1. Minimal Risk Levels (MRLs) for 1,2,3,7,8-Pentachlorodibenzofuran[a]

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty and modifying factors	Reference
Inhalation exposure					
Acute	Insufficient data for derivation of an MRL				
Intermediate	Insufficient data for derivation of an MRL				
Chronic	Insufficient data for derivation of an MRL				
Oral exposure (µg/kg/day)					
Acute	Insufficient data for derivation of an MRL				
Intermediate (provisional)	0.007	Increase in relative liver weight in rats	$BMDL_{1SD}$: 0.68	UF: 100	Pluess et al. 1988a
Chronic	Insufficient data for derivation of an MRL				

[a]See Appendix A for additional information.

BMDL = 95% lower confidence limit on the benchmark dose (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control); UF = uncertainty factor

Table 1-2. Minimal Risk Levels (MRLs) for 2,3,4,7,8-Pentachlorodibenzofuran[a]

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty and modifying factors	Reference
Inhalation exposure					
Acute	Insufficient data for derivation of an MRL				
Intermediate	Insufficient data for derivation of an MRL				
Chronic	Insufficient data for derivation of an MRL				
Oral exposure (µg/kg/day)					
Acute (provisional)	0.0005 (5×10^{-4})	Decreased thymus weight in pups	LOAEL: 0.5	UF: 100 MF: 10	Madsen and Larsen 1989
Intermediate (provisional)	0.000007 (7×10^{-6})	Decreases in serum total T4 levels in female rats	BMDL: 0.00095 ($BMDL_{ADJ}$: 0.00068)	UF: 100	NTP 2006
Chronic (provisional)	0.000004 (4×10^{-6})	Hepatocellular hypertrophy and cystic degeneration in adrenal cortex	LOAEL: 0.006 ($LOAEL_{ADJ}$: 0.0043)	UF: 1,000	NTP 2006

[a]See Appendix A for additional information.

ADJ = adjusted; BMDL = 95% lower confidence limit on the benchmark dose; LOAEL = lowest-observed-adverse-effect level; MF = modifying factor; T4 = thyroxine; UF = uncertainty factor

Table 1-3. Minimal Risk Levels (MRLs) for 1,2,3,6,7,8-Hexachlorodibenzofuran[a]

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty and modifying factors	Reference
Inhalation exposure					
Acute	Insufficient data for derivation of an MRL				
Intermediate	Insufficient data for derivation of an MRL				
Chronic	Insufficient data for derivation of an MRL				
Oral exposure (µg/kg/day)					
Acute	Insufficient data for derivation of an MRL				
Intermediate (provisional)	0.005	Increased relative liver weight and decreased absolute thymus weight in rats	$BMDL_{1SD}$: 0.48	UF: 100	Pluess et al. 1988a
Chronic	Insufficient data for derivation of an MRL				

[a]See Appendix A for additional information.

BMDL = 95% lower confidence limit on the benchmark dose (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure dose associated with a 1 standard deviation change from the control); UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

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

As noted in Chapter 1, this toxicological profile focuses on the tetra-, penta-, hexa-, hepta-, and octa-chlorinated CDF congeners. Although humans are exposed to mixtures of numerous CDF congeners, animal studies involving exposure to a single CDF congener are only available for eight congeners: 2,3,7,8-tetraCDF, 1,2,3,4,8-pentaCDF, 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,6,7,8-hexaCDF, 1,2,3,4,6,7,8-heptaCDF, and octaCDF.

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

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

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to CDFs, but may not be inclusive of the entire body of literature.

Animal oral studies are presented in Table 2-2 and Figure 2-2. Table 2-1 is divided by exposure duration and by congener. Animal dermal studies are presented in Table 2-3; no inhalation data were identified for CDFs.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs were classified into "less serious" or "serious" effects. "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of CDFs are indicated in Tables 2-2 and 2-3 and Figure 2-2.

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

Much of the information that pertains to human health effects of CDFs comes from large numbers of people who consumed rice oil contaminated with PCB-containing heat exchange fluid in Japan in 1968 (Yusho incident) and Taiwan in 1979 (Yu-Cheng incident) (Chen and Hsu 1986; Kuratsune 1989; Kashimoto and Miyata 1986; Okumura 1984; Rogan 1989). The PCB-containing fluid was heated in thermal heat exchangers before contamination occurred and also during cooking resulting in the production of relatively high concentrations of CDFs and polychlorinated quaterphenyl (PCQ) impurities by thermal degradation. Yusho involved at least 1,854 victims exposed over ≈10 months, and Yu-Cheng involved at least 2,061 victims exposed over ≈9 months (Chen et al. 1985a; Hsu et al. 1984; Kuratsune 1989; Rogan 1989). The concentrations of PCBs and PCQs in the rice oils were l00- to 500-fold greater than the CDFs. Because there are no data on human health effects of CDFs alone and little is known about any potential interactive effects between CDFs and other components of the contaminated rice oil mixtures, the health effects in Yusho and Yu-Cheng victims cannot be attributed solely to CDFs.

However, CDFs are generally considered to be the main causal agent based predominantly on: (1) comparisons with Japanese workers with higher PCB blood levels who had few or none of the symptoms present in the rice oil poisonings, (2) decreasing serum levels of PCBs in victims with persisting health effects, (3) induction of Yusho health effects in animals exposed to reconstituted mixtures of CDF congeners similar to those in Yusho oils, but not by exposure to PCBs or PCQs alone, and (4) comparative toxicity evaluations of PCB and CDF congeners in unheated source mixtures, contaminated rice oil, and tissues of victims (Bandiera et al. 1984a; Kunita et al. 1984; Masuda and Yoshimura 1984; Ryan et al. 1990; Safe 1990a; Takayama et al. 1991; Tanabe et al. 1989).

In general, clinical severity of signs and symptoms was closely related to the total amount of oil consumed, but not to the amount consumed per kg body weight per day (Hayabuchi et al. 1979; Kuratsune 1989). Concentrations of CDFs in the Yu-Cheng oil were much lower than in the Yusho oil, and intake of Yu-Cheng oil was believed to be much higher than for Yusho oil (Chen et al. 1985a). This resulted in very similar estimated average total intakes of PCBs, CDFs, and PCQs of 633, 3.3, and 596 mg, respectively, for Yusho (Hayabuchi et al. 1979), and 973, 3.8, and 586 mg, respectively, for Yu-Cheng (Chen et al. 1985a). Based on the Yusho intake, the average daily amount of CDFs ingested per kg body weight was 0.9 µg/kg/day (Hayabuchi et al. 1979). Of more than 40 CDF congeners present in Yusho and Yu-Cheng oils, the two major congeners that accumulated in the victims were 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF. Contributions of other 2,3,7,8-chlorine substituted CDF congeners to the toxic effects are not considered to be substantial since they were not present in significant amounts in the rice oils, were not detectably accumulated in human tissues, and/or were of lower potency (Ryan et al. 1990).

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

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

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

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

Compound	1998 TEF[a]	2005 TEF[a]
Chlorinated dibenzo-*p*-dioxins (CDDs)		
2,3,7,8-TCDD	1	1
1,2,3,7,8-PentaCDD	1	1
1,2,3,4,7,8-HexaCDD	0.1	0.1
1,2,3,6,7,8-HexaCDD	0.1	0.1
1,2,3,7,8,9-HexaCDD	0.1	0.1
1,2,3,4,6,7,8-HeptaCDD	0.01	0.01
OctaCDD	0.0001	0.0003
Chlorodibenzofurans (CDFs)		
2,3,7,8-TetraCDF	0.1	0.1
1,2,3,7,8-PentaCDF	0.05	0.03
2,3,4,7,8-PentaCDF	0.5	0.3
1,2,3,4,7,8-HexaCDF	0.1	0.1

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

Compound	1998 TEF[a]	2005 TEF[a]
1,2,3,6,7,8-HexaCDF	0.1	0.1
1,2,3,7,8,9-HexaCDF	0.1	0.1
2,3,4,6,7,8-HexaCDF	0.1	0.1
1,2,3,4,6,7,8-HeptaCDF	0.01	0.01
1,2,3,4,7,8,9-HeptaCDF	0.01	0.01
OctaCDF	0.0001	0.0003
Non-*ortho*-substituted polychlorinated biphenyls (PCBs)		
3,3′,4,4′-TetraCB (PCB 77)	0.0001	0.0001
2,3,4,4′,5-TetraCB (PCB 81)	0.0001	0.0003
3,3′,4,4′,5-PentaCB (PCB 126)	0.1	0.1
3,3′,4,4′,5,5′-HexaCB (PCB 169)	0.01	0.03
Mono-*ortho*-substituted polychlorinated biphenyls (PCBs)		
2,3,3′,4,4′-pentaCB (PCB105)	0.0001	0.00003
2,3, 4,4′,5-pentaCB (PCB114)	0.0005	0.00003
2,3′,4,4′,5-pentaCB (PCB118)	0.0001	0.00003
2′,3,4,4′,5-pentaCB (PCB123)	0.0001	0.00003
2,3,3′,4,4′,5-hexaCB (PCB156)	0.0005	0.00003
2,3,3′,4,4′,5′-hexaCB (PCB157)	0.0005	0.00003
2,3′,4,4′,5,5′-hexaCB (PCB167)	0.000001	0.00003
2,3,3′,4,4′,5,5′-heptaCB (PCB189)	0.0001	0.00003

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

Source: Van den Berg et al. 2006

The epidemiological database evaluating the toxicity of CDDs, CDFs, and/or PCBs is extensive. The database consists of occupational exposure studies, studies of communities living near point sources, communities affected by accidental releases, and the general population exposed to background levels, primarily from CDDs, CDFs, and/or PCBs in the food supply. These studies have identified a number of adverse health outcomes associated with exposure to dioxin-like compounds. The health outcomes include chloracne; evidence of liver damage including increases in serum hepatic enzyme levels, hepatomegaly, and increases in serum lipid levels; evidence of altered thyroid function; increased risk of diabetes and abnormal glucose tolerance tests; alterations in immune endpoints; endometriosis; altered

offspring sex ratio; and neurodevelopmental alterations (ATSDR 1998, 2000, 2012). The results of these studies should be interpreted cautiously particularly because some of the outcomes were still within the range found in unexposed populations. With the exception of some occupational exposure and community exposure studies, exposure levels were not measured; most studies used serum CDF, CDD, and/or PCB levels as a biomarker for exposure. Studies reported serum levels as individual congener levels; total CDD, CDF, and/or PCB levels; total CDD/CDF levels; TEFs for individual congeners; and total CDD/CDF or CDD/CDF/PCB TEQs. The discussion of epidemiological data in this profile is limited to studies of known exposure (e.g., Yusho and Yu-Cheng incidents) and studies measuring serum levels of CDF congeners, total CDF congeners, CDF congener TEQs, or total CDF TEQ.

Because humans are exposed to a mixture of dioxin-like compounds, it is difficult to ascribe an effect to a particular compound or congener; rather it is likely that many, if not all, contribute to the adverse health outcomes. None of the available CDF epidemiological studies controlled for co-exposure to other dioxin-like compounds or other chemicals. Some of the studies, but not all, controlled for confounders that may affect the outcome such as age, smoking history, etc. The epidemiological data are not adequate to establish causality. Although some studies found associations or inverse associations between serum CDF levels and health outcomes, the results were not consistent, or there were too few studies to evaluate the weight of evidence, and/or a small of number of individuals were examined.

Information regarding health effects in animals exposed to CDFs was located for the following congeners: 2,3,7,8-tetraCDF, 1,2,3,4,8-pentaCDF, 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,6,7,8-hexaCDF, 1,2,3,4,6,7,8-heptaCDF, and 1,2,3,4,6,7,8,9-octaCDF.

As illustrated in Figure 2-1, there are epidemiological and laboratory animal data available for the 18 health endpoints discussed in the toxicological profile. The most studied endpoints are developmental, immunological, and hepatic. Most of the epidemiological studies did not provide information on the route of exposure; for environmental exposures, it was assumed to be oral exposure. Over 95% of the epidemiological and toxicological studies involved oral exposure to CDFs. As noted earlier, humans are exposed to a mixture of CDF congeners. Most laboratory animal studies involved exposure to a single congener, although there are several studies examining effects associated with exposure to a mixture of CDF congeners. Of the over 50 laboratory animal toxicity studies, 45% evaluated the toxicity of 2,3,4,7,8-pentaCDF and 26% evaluated 2,3,7,8-tetraCDF. Four congeners (1,2,3,4,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,4,6,7,8-heptaCDF, and octaCDF) each had only one study.

The human and animal studies suggest several sensitive targets of CDFs toxicity:

- **Hepatic Endpoints.** Hepatic effects are observed in humans and animals orally exposed to CDFs. The effects include increases in liver weight, lipid accumulation and hypertrophy in the liver, and alterations in serum triglyceride levels.

- **Immunological Endpoints.** Clinical observations of increased susceptibility to respiratory and dermal infections and various changes in immune parameters, including decreased antibody and leukocyte levels and delayed-type skin hypersensitivity response, have been observed in Yusho and Yu-Cheng cohorts. Studies in animals indicate that the immunological system may be the most sensitive to effects caused by CDFs. Pronounced decreases in thymus weight and/or histologic thymic atrophy were consistently observed following oral exposure in all tested species. There are also limited data suggesting that CDFs impair immune responses to mitogens.

- **Thyroid Endpoints.** A small number of epidemiological studies examined potential thyroid effects; the small number of studies limits drawing conclusions. Decreases in serum T4 levels were reported in rats exposed to tetra- and pentaCDF congeners.

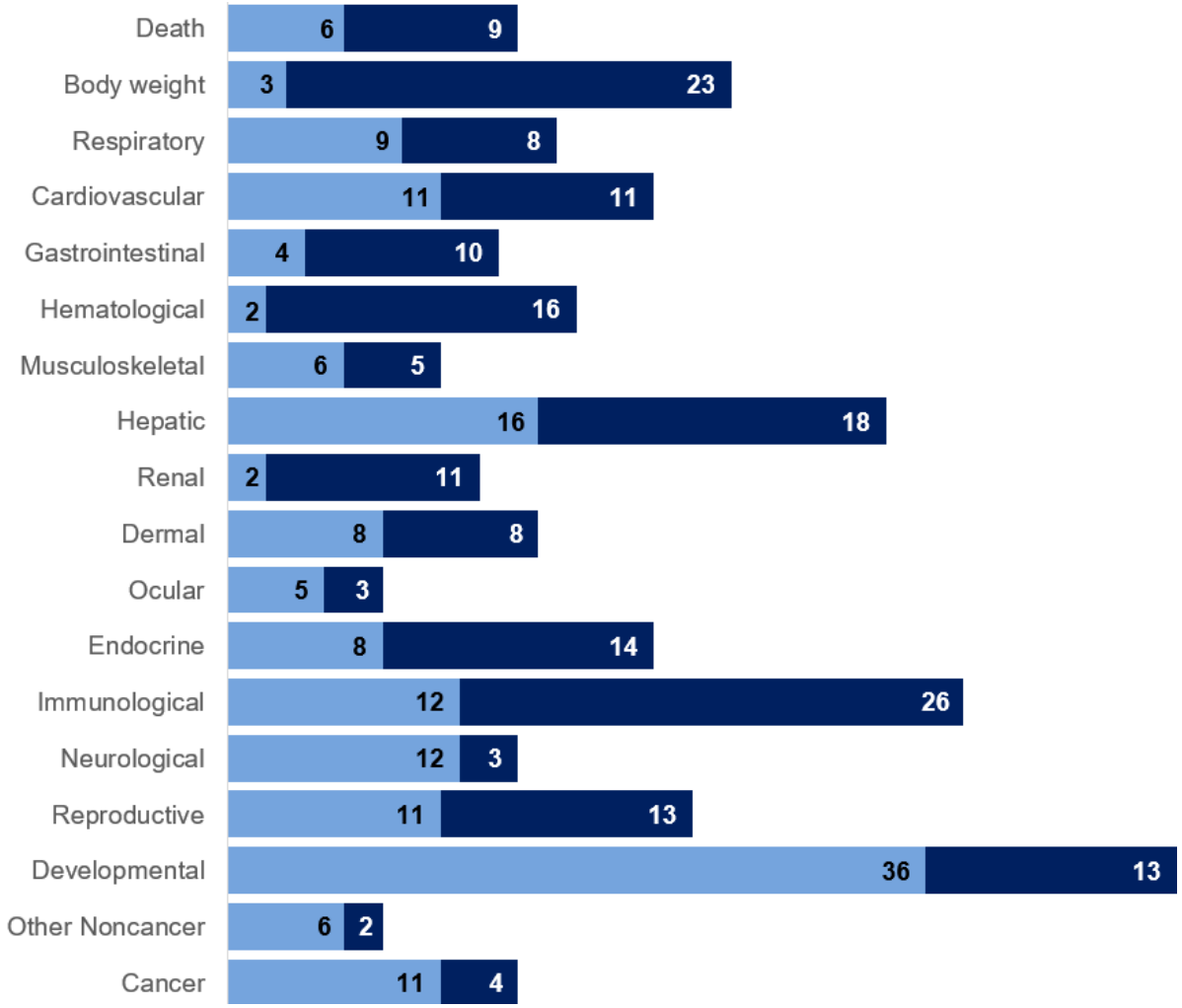
- **Developmental Endpoints.** Various signs of toxicity have been observed in children born to mothers exposed during the Yusho and Yu-Cheng incidents. Toxic effects include dermal lesions similar to those found in exposed adults, perinatal deaths in some babies with dermal lesions, decreased birth weights, and neurobehavioral deficits. Developmental effects observed in animals include hydronephrosis and cleft palate in mice, fetal mortality, decreases in fetal weights, and impaired development of the reproductive system.

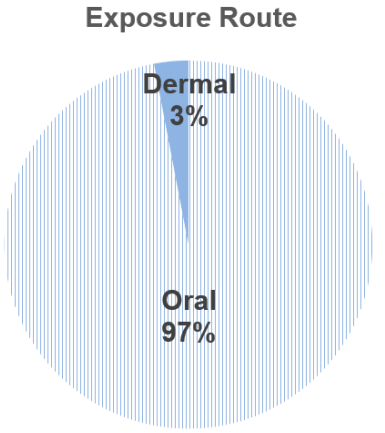
The discussions of the available data for each health effect in Sections 2.2 through 2.19 are divided into several subsections. Each health effect section begins with a discussion of epidemiological data, if available. Congener-specific discussions of laboratory animal data follow. It is noted that for most health effects, there are no data for a number of congeners.

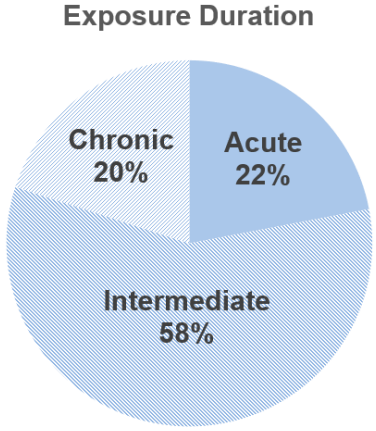
Figure 2-1. Overview of the Number of Studies Examining Chlorodibenzofurans (CDFs) Health Effects*

Most studies examined the potential immunological, hepatic, and developmental effects of CDFs

More studies evaluated health effects in **animals** than **humans** (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 147 studies (including those finding no effect) examined toxicity; most studies examined multiple endpoints and a number of animal studies examined several congeners.

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
ACUTE EXPOSURE									
2,3,7,8-TetraCDF									
1	Monkey (Rhesus) 2–4 F	1 day (GO)	0, 500, 1,000, 1,500	BW GN HP BC CS BI	Death			1,000	2/4 animals died at 1,000 µg/kg and 2/2 died at 1,500 µg/kg
					Bd wt		500	1,000	LOAEL: decreased weight gain (magnitude not reported) Serious LOAEL: weight loss in surviving monkeys at 1,000 µg/kg
					Resp	1,500			
					Cardio	1,500			
					Gastro	500	1,000		Loss of parietal cells, increase in mucous cells, and microcystic dilation of crypts in the glandular stomach
					Hemato		500		Mild anemia, lymphopenia, neutrophilia
					Hepatic	500	1,000		Gall bladder and bile duct hypertrophy
					Renal	1,500			
					Dermal		500		Facial edema, occluded or dilated ceruminous and sebaceous glands, nail loss, epidermal hyperkeratosis
					Ocular		500		Occluded or dilated meibomian glands, eyelash loss
					Endocr	1,500			
					Immuno	500	1,000		Thymus and spleen atrophy
					Neuro	1,500			
					Other noncancer		1,000		Degranulation of exocrine pancreatic cells in animals dying early
2,3,7,8-TetraCDF **Moore et al. 1979**									

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
2	Rat (Long-Evans) 4–14 F	4 days (GO)	0.3–100	BW BC	Endocr		4.65		30% decrease in serum total T4 levels
2,3,7,8-TetraCDF Crofton et al. 2005									
3	Rat (Long-Evans) NS F	4 days (G)	0.3, 1, 3, 10, 30, 100	BC	Endocr	0.3	1		Decreased serum total T4 levels (approximately 26, 17, 50, 53, and 55% at 1, 3, 10, 30, and 100 µg/kg/day, respectively)
2,3,7,8-TetraCDF Ross et al. 2000									
4	Mouse (C57BL/6fh) 8 M	1 day (GO)	0, 400, 600, 800, 1,200, 1,500, 2,500, 4,000, 6,000	HP CS	Resp Cardio Gastro Musc/skel Renal Dermal Endocr	6,000 6,000 6,000 6,000 6,000 6,000 6,000			
2,3,7,8-TetraCDF Moore et al. 1976, 1979									
5	Mouse (C57BL/6N) 6 F	GD 10 (GO)	0, 250, 500, 1,000	BW OW CS FX MX DX	Develop			250	Fetal mortality, hydronephrosis
2,3,7,8-TetraCDF Weber et al. 1984									
6	Mouse (C57BL/6N) 7–11 F	GD 10 (GO)	0, 300, 600, 900	BW OW CS FX MX DX	Develop			300	Hydronephrosis; cleft palate at ≥600 µg/kg
2,3,7,8-TetraCDF Weber et al. 1985									

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
7	MOUSE (C57BL/ 6N) 8–11 F	GDs 10–13 (GO)	0, 10, 30, 50, 100	BW OW CS FX MX DX	Develop			10	Hydronephrosis; cleft palate at ≥50 µg/kg
2,3,7,8-TetraCDF Weber et al. 1984									
8	Guinea pig (Hartley) 6 M	1 day (GO)	0, 1, 5, 10, 15	BW GN HP BC CS	Death			10	100% mortality; mean time to death was 14.6 days
					Bd wt		1	10	LOAEL: decreased body weight gain (magnitude not reported) Serious LOAEL: rapid and progressive weight loss
					Resp	15			
					Cardio	15			
					Gastro	15			
					Hemato	15			
					Musc/skel		5		Reduction in muscle mass
					Renal	5	10		Hyperplasia of epithelial cells in renal pelvis, ureter, and urinary bladder
					Dermal	15			
					Ocular	15			
					Endocr	5	10		Adrenal hemorrhage
					Immuno		5		Marked reduction in size of thymus at ≥5 µg/kg; loss of lymphoid cells in thymic cortex and hypocellularity of bone marrow and lymphoid elements in spleen and Peyers patches at ≥10 µg/kg
					Neuro	15			
					Repro	5	10		Hypocellularity of seminiferous tubules
2,3,7,8-TetraCDF Moore et al. 1979									

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
1,2,3,7,8-PentaCDF									
9	Rat (Long-Evans) 4–14 F	4 days (GO)	0.03–100	BW BI	Endocr		15.6		30% decrease in serum total T4 levels
1,2,3,7,8-PentaCDF Crofton et al. 2005									
10	Rat (Long-Evans) NS F	4 days (G)	0.3, 1, 3, 10, 30, 100	BC	Endocr	3	10		Decreased serum total T4 levels (approximately 15, 40, and 33% at 10, 30, and 100 µg/kg/day, respectively)
1,2,3,7,8-PentaCDF Ross et al. 2000									
11	Mouse (C57BL/6N) 10–13 F	GDs 10–13 (GO)	0, 1, 3, 10, 30, 100, 150, 200	BW OW CS FX MX DX	Bd wt	30	100		Decreased maternal weight gain (30%)
					Develop	10		30	Hydronephrosis; cleft palate at ≥100 µg/kg/day
1,2,3,7,8-PentaCDF Birnbaum et al. 1987a									
2,3,4,7,8-PentaCDF									
12	Rat (Wistar) 8–10 F	GD 16 (GO)	0, 0.5, 2, 10	OW BI FX	Develop	0.5[a]	2		14% decreased relative neonatal thymus weight
2,3,4,7,8-PentaCDF Madsen and Larsen 1989									
13	Rat (Sprague-Dawley) 5 M	1 day (GO)	0, 53	BW OW BI	Bd wt	53			
					Hepatic	53			
					Immuno	53			
2,3,4,7,8-PentaCDF Ahlborg et al. 1989									

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
14	Rat (Fischer-344) 8 M	1 day (GO)	0, 100, 250, 500, 1,000, 2,000	BW OW HP BC CS BI UR	Death			916	
					Bd wt	250	500		17% lower terminal body weight
					Resp	2000			
					Gastro	250	500		Epithelial hyperplasia of nonglandular stomach
					Hemato		100		Decreased hemoglobin (6%), MCH (9%), and MCV (4%) 35 days post-exposure
					Hepatic		100		Lipid accumulation, increased serum cholesterol (60%) 35 days post-exposure
					Renal	1,000	2,000		Increased BUN (64%), increased relative kidney weight (34%)
					Dermal		500		Nail hemorrhages
					Immuno		100	500	LOAEL: decreased thymus weight (30–90%) Serious LOAEL: thymic atrophy and lymphoid depletion in the thymus and spleen
					Repro	2,000			
2,3,4,7,8-PentaCDF Brewster et al. 1988									
15	Rat (F344) 9–12 F	GDs 8,10, or 12 (GO)	0, 10, 30, 100, 300	BW OW CS FX MX DX	Develop		30	100	LOAEL: decreased fetal weight Serious LOAEL: increased fetal mortality
2,3,4,7,8-PentaCDF Couture et al. 1989									

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
16	Rat (Long-Evans) 4–14	4 days (GO)	0.03–90	BW BC	Endocr		27.5		30% decrease in serum total T4 levels
2,3,4,7,8-PentaCDF Crofton et al. 2005									
17	Rat (Long-Evans) NS F	4 days (G)	0.03, 0.09, 0.3, 0.9, 3, 9, 30, 90	BC	Endocr	9	30		Decreased serum total T4 levels (approximately 26 and 47% at 30 and 90 µg/kg/day, respectively)
2,3,4,7,8-PentaCDF Ross et al. 2000									
18	Rat (Sprague-Dawley) 3–4 F	GD 15 (GO)	0, 1.0, 10.0	BW RX	Develop			1	Decreased offspring body weight on PND 140, decreased number of days spent in estrus, and decreases in ovulation rate
2,3,4,7,8-PentaCDF Salisbury and Marcinkiewicz 2002									
19	Rat (Wistar) 3–13 F	GD 15 (GO)	0, 1, 2, 5, 10, 15, 25, 50, 300, 1,000	BC BW DX	Develop		12.6		ED_{50} for reduction in growth hormone levels in female fetuses; ED_{50} in male fetuses was 27.4 µg/kg; ED_{50} values for serum LH levels were 21.5 and 25.5 µg/kg in male and female fetuses, respectively; and ED_{50} values for decreases in fetal body weights were 56.3 and 140 µg/kg in male and females, respectively
2,3,4,7,8-PentaCDF Taura et al. 2014									

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
20	Rat (Wistar) 3–13 F	GD 15 (GO)	0, 15, 50	DX	Develop	15	50		Altered sexual behavior in male offspring (increases in mount latency and latency until first intromission and decreases in mount frequency and intromission frequency)
2,3,4,7,8-PentaCDF Taura et al. 2014									
21	Rat (Wistar) NS M	1 day (GO)	0, 1, 5, 50, 150, 500, 1,000, 2,000	BW OW	Bd wt		146		ED_{50} for decrease in body weight gain in pubertal rats
					Immuno		71.9		ED_{50} for decrease in thymus weight in pubertal rats
2,3,4,7,8-PentaCDF Taura et al. 2014									
22	Mouse (C57BL/ 6N) NS F	GDs 10–13 (GO)	0, 5, 10, 30	BW OW CS FX MX DX	Develop			5	Hydronephrosis; cleft palate at 30 µg/kg/day
2,3,4,7,8-PentaCDF Birnbaum et al. 1987b									
23	Mouse (C57BL/ 6N) 11–20 F	GDs 10–13 (GO)	0, 1, 3, 10, 20, 30, 40, 60, 80	BW OW CS MX DX	Develop	3		10	Hydronephrosis; cleft palate at ≥30 µg/kg/day
2,3,4,7,8-PentaCDF Birnbaum et al. 1987a									
24	Mouse (C57BL/ 6N) 2 F	GDs 10–13 (GO)	0, 80	HP MX	Repro		80		Rupture of the placental labyrinth barrier and transplacental passage of embryonic erythrocytes into maternal blood
					Develop		80		Impaired embryonic erythropoiesis in the liver, increased number of hepatocytes, and reduction in liver sinusoids
2,3,4,7,8-PentaCDF Khera 1992									

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
25	Mouse (B6C3F1) 14 F	1 day (GO)	0, 3, 9, 15, 30, 90	BW OW IX	Bd wt	90			
					Immuno		10.119		50% reduction in immune response to SRBC
2,3,4,7,8-PentaCDF Johnson et al. 2000									
26	Guinea pig (Hartley) 6 M	1 day (GO)	0, 1, 3, 10, 30	BW GN HP CS	Death			10	
					Bd wt		1	10	LOAEL: decreased body weight gain (magnitude not reported) Serious LOAEL: rapid and progressive weight loss
					Resp	30			
					Cardio	30			
					Gastro	30			
					Hemato	30			
					Musc/skel		3		Reduction in muscle mass
					Renal	3	10		Hyperplasia of epithelial cells in renal pelvis, ureter, and urinary bladder
					Dermal	30			
					Ocular	30			
					Endocr	3	10		Adrenal hemorrhage
					Immuno		3		Marked reduction in size of thymus at ≥3 µg/kg; at ≥10 µg/kg, loss of lymphoid cells in thymic cortex and hypocellularity of bone marrow and lymphoid elements in spleen and Peyers patches
					Neuro	30			
					Repro	3	10		Hypocellularity of seminiferous tubules
2,3,4,7,8-PentaCDF Moore et al. 1979									

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
1,2,3,4,7,8-HexaCDF									
27	Mouse (C57BL/6N) 10–13 F	GD 10-13 (GO)	0, 100, 200, 300, 600, 1,000	BW OW CS FX MX DX	Develop			100	Hydronephrosis and increased fetal weight; cleft palate at ≥300 µg/kg/day
1,2,3,4,7,8-HexaCDF Birnbaum et al. 1987a									
28	Mouse (C57BL/6N) 9–13 F	GD 10-13 (GO)	0, 100, 200, 300	BW OW CS FX MX DX	Develop			100	Hydronephrosis
1,2,3,4,7,8-HexaCDF Birnbaum et al. 1987b									
1,2,3,4,6,7,8-HeptaCDF									
29	Mouse (C57BL/6N) 6 NS	1 day (GO)	0, 25, 100, 600	IX	Immuno		208		ED_{50} for decreased antibody response to SRBC
1,2,3,4,6,7,8-HeptaCDF Kerkvliet et al. 1985									
1,2,3,4,6,7,8,9-OctaCDF									
30	RAT (Long-Evans) 4–14	4 days (GO)	0.03–90	BW BC	Endocr	300			
1,2,3,4,6,7,8,9-OctaCDF Crofton et al. 2005									

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
INTERMEDIATE EXPOSURE									
2,3,7,8-TetraCDF									
31	Monkey (Rhesus) 3 M	2 months (F)	2.1	BW GN HP BC CS	Death			2.1	1/3 monkeys died
					Gastro		2.1		Intramucosal cysts
					Hemato	2.1			
					Hepatic		2.1		Altered bile duct epithelium
					Dermal			2.1	Facial and body hair and nail loss, absent sebaceous glands
					Ocular		2.1		Periorbital edema
					Immuno			2.1	Thymic atrophy
2,3,7,8-TetraCDF McNulty et al. 1981									
32	Monkey (Rhesus) 3 M	6 months (F)	0.21	BW GN HP BC CS	Death			0.21	1/3 monkeys died
					Gastro		0.21		Metaplasia of gastric mucosa
					Hemato	0.21			
					Dermal		0.21		Partial sebaceous gland atrophy, hyperkeratotic nail beds
					Ocular		0.21		Periorbital edema, meibomian gland enlargement
					Immuno			0.21	Thymic atrophy
2,3,7,8-TetraCDF McNulty et al. 1981									
33	Mouse (C57BL/ 6N) 8 M	30 days 5 days/week (GO)	0, 30, 100, 300	BW GN HP BC CS	Bd wt	300			
					Hemato	100	300		37% decreased total leukocytes
					Immuno		300		Marked decrease in thymus weight
2,3,7,8-TetraCDF Moore et al. 1979									

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
34	Guinea pig (Hartley) 3–8 F	6 weeks 1 day/week (GO)	0, 0.05, 0.17, 0.5, 1.0	BW OW GP	Death			1	30% mortality
					Bd wt	1			
					Hemato	1			
					Immuno	0.17	0.5		Thymic atrophy, macrophage inhibition
2,3,7,8-TetraCDF									
Luster et al. 1979a, 1979b									
1,2,3,4,8-PentaCDF									
35	Rat (Sprague-Dawley) 6 M, 6 F	13 weeks (F)	0, 60, 600	BW OW GN HP BC CS	Bd wt	600			
					Cardio	600			
					Hemato	600			
					Hepatic	600			
					Renal	600			
					Endocr	600			
					Immuno	600			
					Repro	600			
1,2,3,4,8-PentaCDF									
Pluess et al. 1988a (results also reported in Poiger et al. 1989)									
1,2,3,7,8-PentaCDF									
36	Rat (Sprague-Dawley) 6 M, 6 F	13 weeks (F)	0, 0.2, 2, 20	BW OW GN HP BC	Bd wt	2 F	20 F		11% decreased terminal body weight
					Cardio	20			
					Hemato	20			
					Hepatic	2 M	20 M		Increased liver weight, vacuolization with lipid accumulation, single cell necrosis
					Renal	20			
					Endocr	20			

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
					Immuno	2[b]	20		Decreased thymus weight ($BMDL_{1SD}$ of 0.68 µg/kg/day)
					Repro	20			
1,2,3,7,8-PentaCDF Pluess et al. 1988a (results also reported in Poiger et al. 1989)									
2,3,4,7,8-PentaCDF									
37	Rat (Sprague-Dawley) 10 F	14 weeks 5 days/week (GO)	0, 0.006, 0.020, 0.044, 0.092, 0.200	CS BW OW BC HP	Bd wt	0.2			
					Resp	0.2			
					Gastro	0.2			
					Hepatic	0.044	0.092		Hepatocellular hypertrophy
					Endocr	0.02	0.044		Thyroid gland follicular cell hypertrophy; decreased total T4 levels (25%) at 0.092 µg/kg
					Immuno	0.2			
					Repro	0.2			
2,3,4,7,8-PentaCDF NTP 2006									
38	Rat (Sprague-Dawley) 10 F	31 weeks 5 days/week (GO)	0, 0.006, 0.020, 0.044, 0.092, 0.200	CS BW OW BC HP	Bd wt	0.2			
					Resp	0.2			
					Gastro	0.2			
					Hepatic	0.02	0.044		Hepatocellular hypertrophy
					Endocr		0.006[c]		Decreased (16%) total T4 levels; increased total T3 levels at ≥0.092 µg/kg ($BDML_{ADJ}$ of 0.00068 µg/kg/day)
					Immuno	0.092	0.2		Thymic cortical atrophy
					Repro	0.2			
2,3,4,7,8-PentaCDF NTP 2006									

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
39	Rat (Sprague-Dawley) 6 M, 6 F	13 weeks (F)	0, 0.2, 2, 20	BW OW GN HP BC CS	Death			20	92% mortality
					Bd wt	0.2	2	20	LOAEL: 11% decreased body weight gain Serious LOAEL: 47–54% body weight loss
					Cardio	20			
					Hemato	20			
					Hepatic		0.2		Increased serum bilirubin (32–52%), decreased serum triglycerides (males, 18%), slight fatty degeneration in liver
					Renal	20			
					Endocr	20			
					Immuno		0.2 F		LOAEL: decreased thymus weight (24% at 0.2 µg/kg/day and 90% at 2 µg/kg/day)
					Repro	20			
2,3,4,7,8-PentaCDF **Pluess et al. 1988b (results also reported in Poiger et al. 1989)**									
40	MOUSE (B6C3F1) 10–12 F	5 times in a 16-week period (GO)	0, 10, 30, 100	OW HP	Immuno	10	30		Decreased thymus weight (13%)
					Repro	30	100		Enhanced promotion of surgically-induced endometriosis
2,3,4,7,8-PentaCDF **Johnson et al. 1997**									
1,2,3,6,7,8-HexaCDF									
41	Rat (Sprague-Dawley) 6 M, 6 F	13 weeks (F)	0, 0.2, 2, 20	BW OW GN HP BC	Bd wt	2	20		14–20% decreased body weight gain
					Cardio	20			
					Hemato	20			
					Hepatic	0.2	2		Increased liver weight, vacuolization with lipid accumulation, single cell necrosis
					Renal	20			

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
					Endocr	20			
					Immuno	0.2[d]	2		LOAEL: decreased thymus weight (40–42% at 2 µg/kg/day and 75–79% at 20 µg/kg/day) ($BMDL_{1SD}$ of 0.48 µg/kg/day)
					Repro	20			
1,2,3,6,7,8-HexaCDF Pluess et al. 1988a (results also reported in Poiger et al. 1989)									
Mixed CDFs									
42	Rat (Sprague-Dawley) 6 M	4 weeks (F)	0, 50, 500	BI	Hemato			50	Hemolytic anemia
					Hepatic		50		Porphyria
Mixed CDFs Oishi and Hiraga 1978									
43	Rat (Sprague-Dawley) 10 M	4 weeks (F)	0, 97, 960	OW GN BC CS	Bd wt		97		15% decreased body weight gain
					Cardio	960			
					Hemato		97		Decreased hemoglobin, hematocrit and MCV, increased MCHC
					Hepatic		97		Increased liver weight and lipid content
					Renal	960			
					Dermal	97		960	Chloracne
					Immuno		97		Decreased thymus weight
					Repro	97	960		Decreased relative seminal vesicle weight and testosterone concentration in testes
Mixed CDFs Oishi et al. 1978									

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
44	Mouse (ICR) 10 M	4 weeks 1 day/week (GO)	0, 10, 100	OW CS	Immuno	10	100		Decreased thymus weight
Mixed CDFs Oishi and Hiraga 1980									
CHRONIC EXPOSURE									
2,3,4,7,8-PentaCDF									
45	Rat (Sprague-Dawley) 80 F	105 weeks 5 days/week (GO)	0, 0.006, 0.020, 0.044, 0.092, 0.200	CS BW OW BC HP	Bd wt	0.2			
					Resp	0.044	0.092		Bronchiolar metaplasia of alveolar epithelium
					Cardio	0.092	0.2		Cardiomyopathy
					Gastro	0.092	0.2		Squamous hyperplasia of the forestomach
					Musc/skel	0.2			
					Hepatic		0.006[e]		Minimal hepatocellular hypertrophy; diffuse fatty changes at ≥0.02 µg/kg; minimal to mild necrosis, bile duct hyperplasia, bile duct fibrosis, and cholangiofibrosis at 0.2 µg/kg
					Renal	0.02	0.044		Nephropathy
					Dermal	0.2			
					Ocular	0.2			
					Endocr		0.006		Cystic degeneration in adrenal cortex at ≥0.006 µg/kg; follicular cell hypertrophy in thyroid gland at ≥0.020 µg/kg; decreased (22%) serum total T4 levels at ≥0.044 µg/kg (measured at 53 weeks), increased (23%) serum total T3 levels at ≥0.092 (measured at 53 weeks); and arterial chronic active inflammation in pancreas at 0.200 µg/kg
					Immuno	0.092	0.2		Increased severity of thymic atrophy

Table 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
					Neuro	0.2			
					Repro	0.02	0.044		Squamous metaplasia in uterus
					Other noncancer	0.02	0.044		Gingival squamous hyperplasia
					Cancer			0.2	Hepatocellular adenoma and cholangiocarcinoma of the liver and gingival squamous cell carcinoma of the oral mucosa
2,3,4,7,8-PentaCDF NTP 2006									

[a]Used to derive a provisional acute-duration oral MRL of 0.0005 µg/kg/day for 2,3,4,7,8-pentaCDF. The NOAEL of 0.5 µg/kg was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability) and modifying factor of 10. See Appendix A for details.
[b]Used to derive a provisional intermediate-duration oral MRL of 0.007 µg/kg/day for 1,2,3,7,8-pentaCDF. The $BMDL_{1SD}$ of 0.68 µg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). See Appendix A for details.
[c]Used to derive a provisional intermediate-duration oral MRL of 0.000007 µg/kg/day for 2,3,4,7,8-pentaCDF. The $BMDL_{1SD}$ of 0.00095 µg/kg/day was adjusted to continuous exposure to a $BMDL_{ADJ}$ of 0.00068 µg/kg/day and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). See Appendix A for details.
[d]Used to derive a provisional intermediate-duration oral MRL of 0.005 µg/kg/day for 1,2,3,6,7,8-hexaCDF. The $BMDL_{1SD}$ of 0.48 µg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). See Appendix A for details.
[e]Used to derive a provisional chronic-duration oral MRL of 0.000004 µg/kg/day for 2,3,4,7,8-pentaCDF. The LOAEL of 0.006 µg/kg/day adjusted to continuous exposure to a $LOAEL_{ADJ}$ of 0.0042 µg/kg/day and divided by an uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans and 10 for human variability). See Appendix A for details.

ADJ = adjusted; BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; BMDL = 95% lower confidence limit on the benchmark dose; BUN = blood urea nitrogen; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; ED_{50} = 50% effective dose; Endocr = endocrine; (F) = feed; F = female(s); FX = fetal toxicity; (G) = gavage; (GO) = gavage in oil; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; Hemato = hemato-logical; HP = histopathology; Immuno = immunological; IX = immune function; LOAEL = lowest-observed-adverse-effect level; M = male(s); MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MRL = Minimal Risk Level; Musc/skel = muscular/skeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity; SD = standard deviation; SRBC = sheep red blood cell; T4 = thyroxine; UR = urinalysis

Principal study for an MRL.

Figure 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral
Acute (≤14 days)

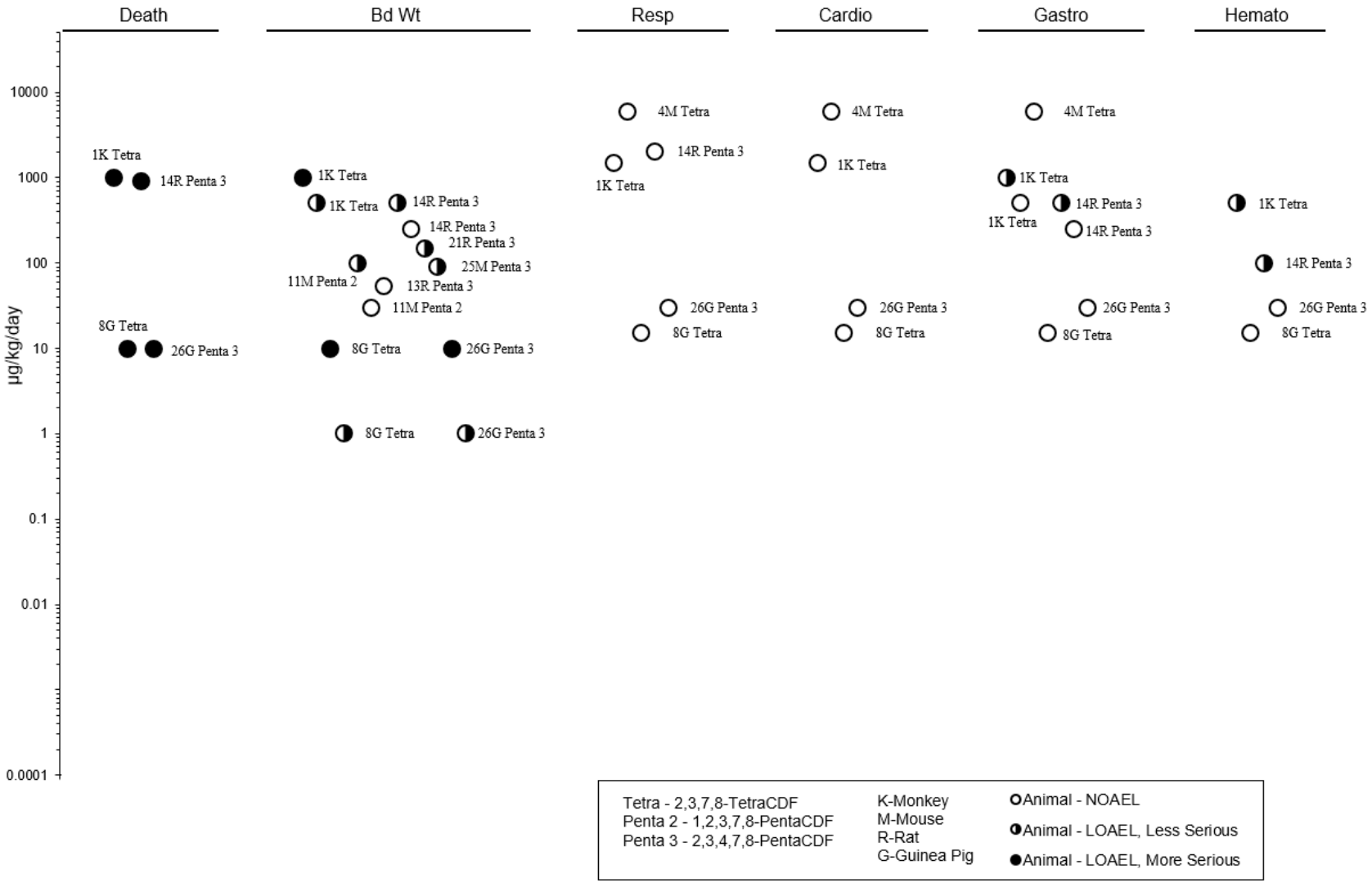


Figure 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral
Acute (≤14 days)

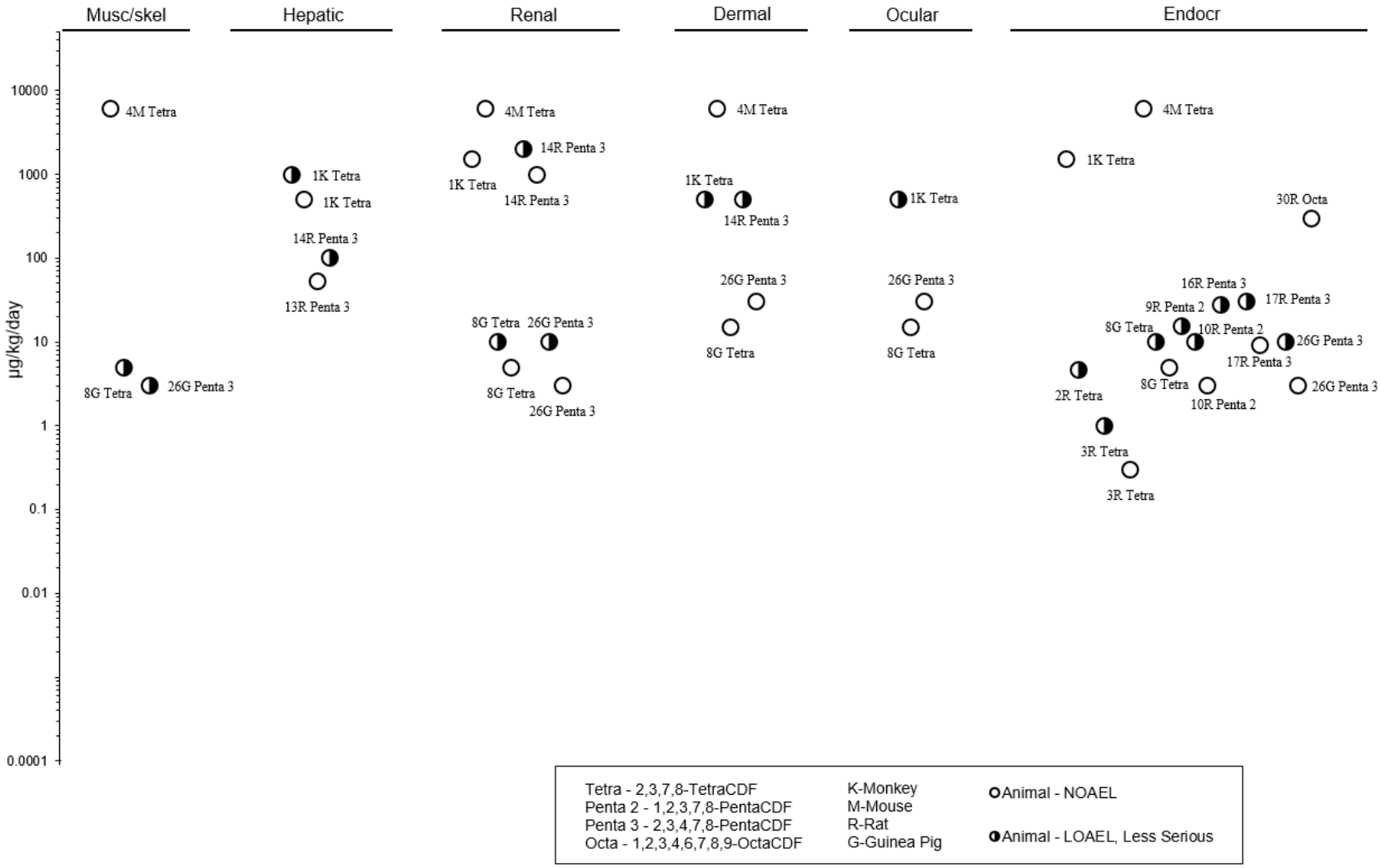


Figure 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral
Acute (≤14 days)

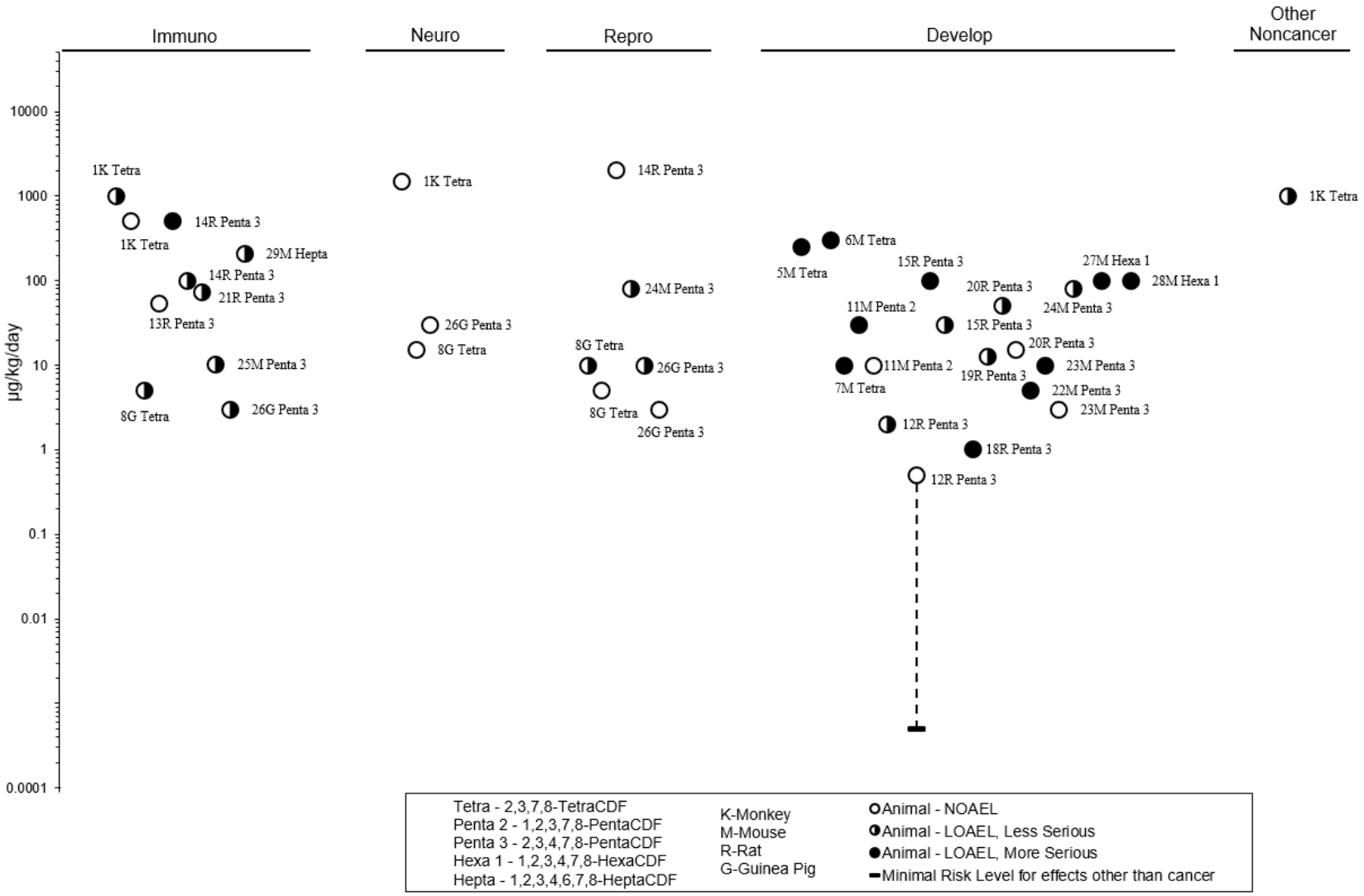


Figure 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral
Intermediate (15-364 days)

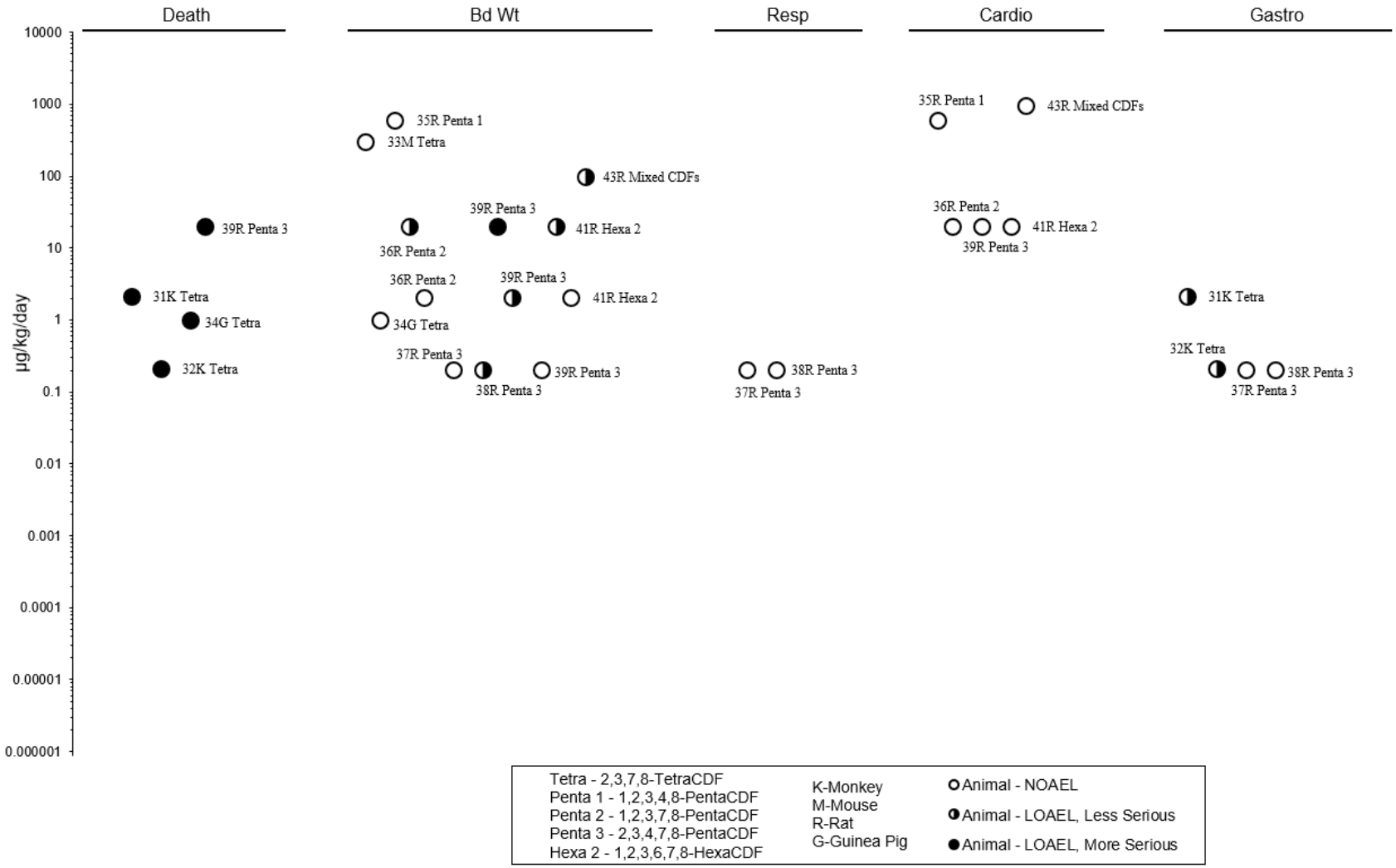


Figure 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral
Intermediate (15-364 days)

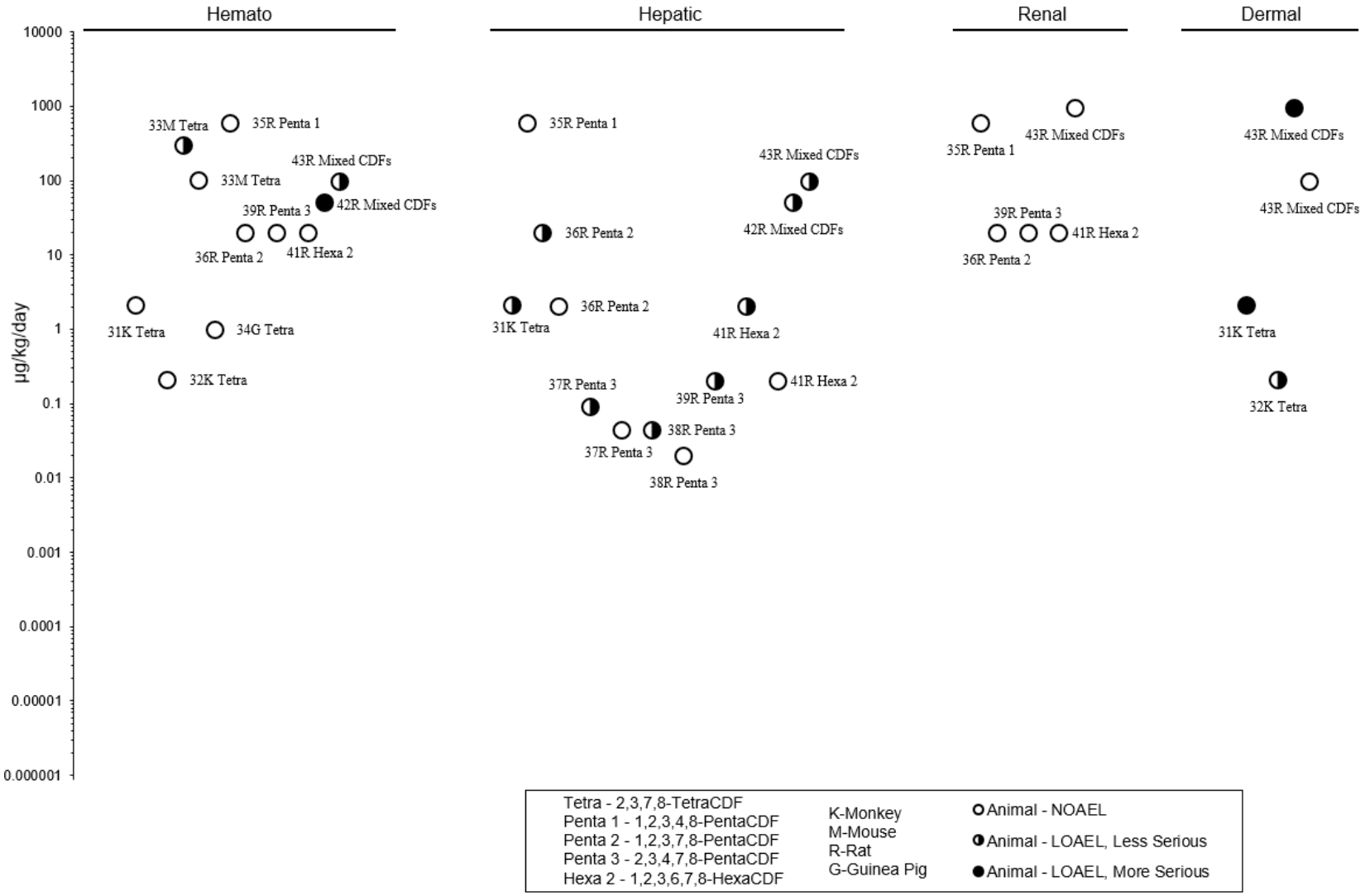


Figure 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral
Intermediate (15-364 days)

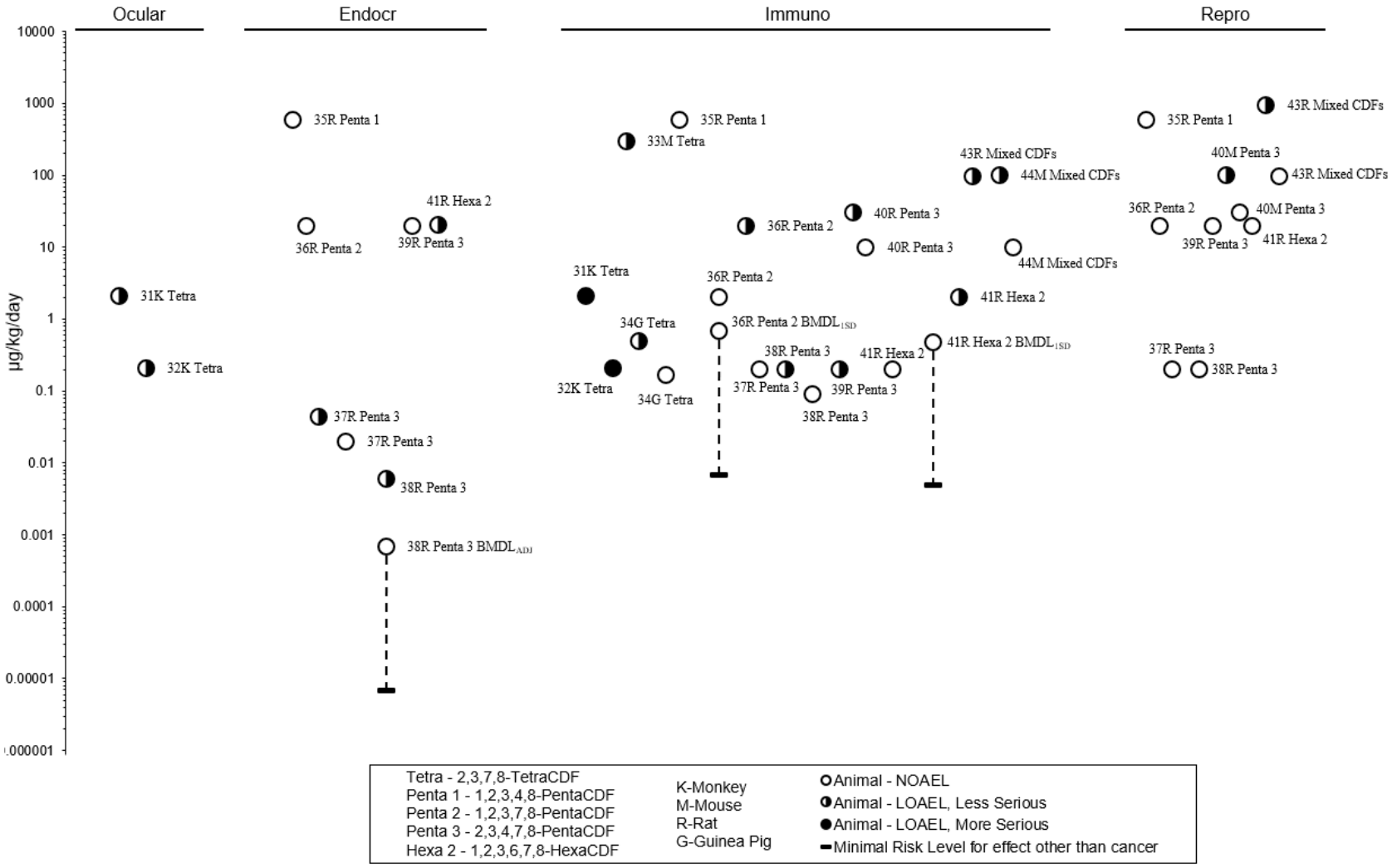


Figure 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral
Chronic (≥365 days)

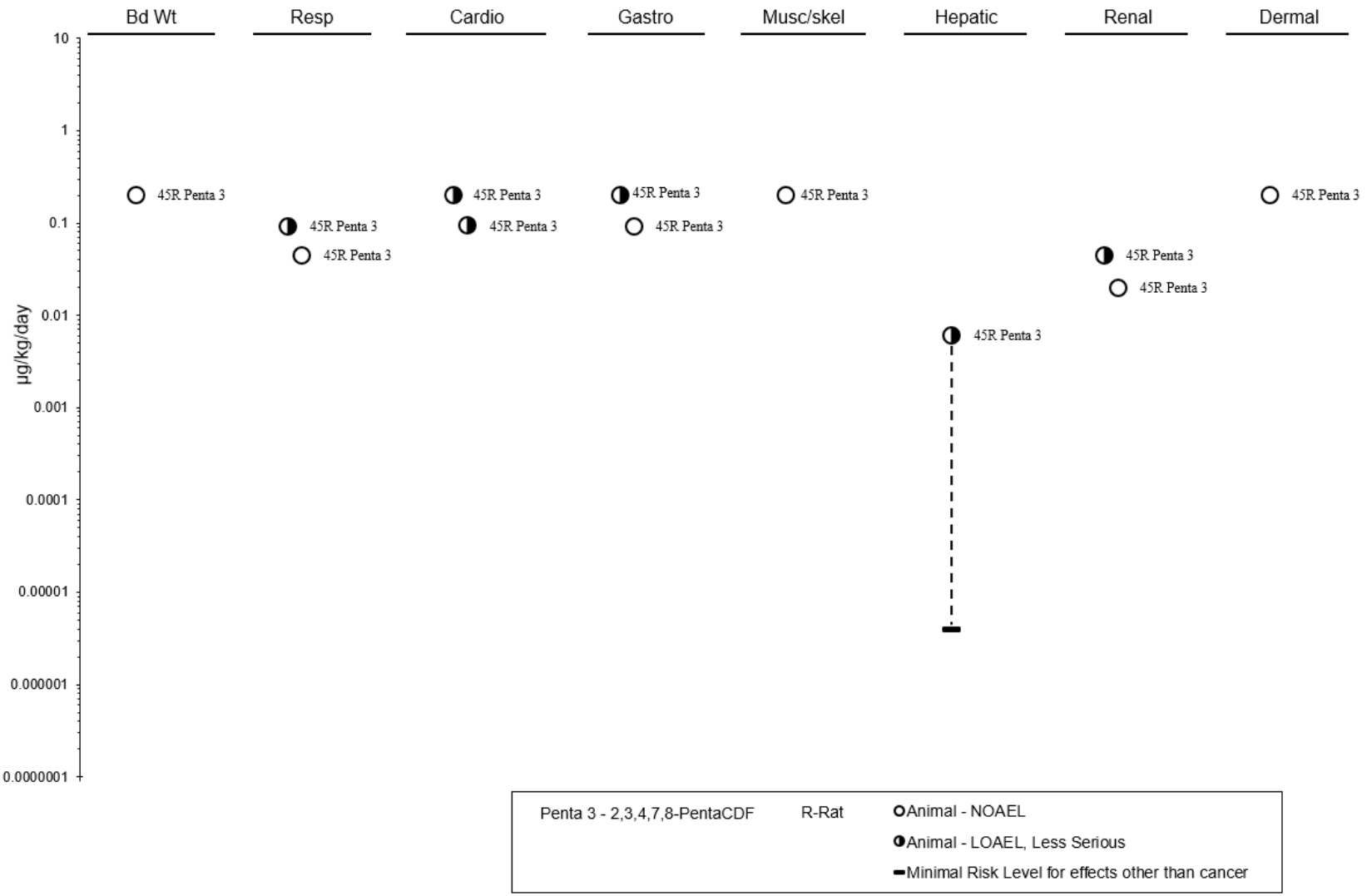


Figure 2-2. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Oral
Chronic (≥365 days)

Table 2-3. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Dermal

Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
INTERMEDIATE EXPOSURE								
Mouse (HRS/J) 20 F	20 weeks 2 days/week	0, 33.3	GN	Cancer			33.3 F	CEL: skin papillomas following initiation
Comment: Mice were treated with a single 5 µmol dermal dose of MNNG in acetone prior to exposure to 2,3,7,8-tetraCDF.								
2,3,7,8-TetraCDF **Poland et al. 1982**								
Mouse (HRS/J) 20 F	20 weeks 2 days/week	0, 3.3	BW OW HP CS	Bd wt		3.3 F		12% decreased body weight gain
				Gastro	3.3 F			
				Hepatic		3.3 F		Increased liver weight and hypertrophy
				Immuno			3.3 F	Thymic and splenic lymphoid atrophy
Comment: Mice were treated with a single dermal dose of acetone prior to exposure to 2,3,4,7,8-pentaCDF.								
2,3,4,7,8-PentaCDF **Hebert et al. 1990**								
Mouse (HRS/J) 20 F	20 weeks 2 days/week	0, 0.08, 1.7 or 3.3	BW OW HP CS	Cancer			0.08 F	CEL: skin proliferative lesions following initiation
Comment: Mice were treated with a single 5 µmol dermal dose of MNNG in acetone prior to exposure to 2,3,4,7,8-pentaCDF.								
2,3,4,7,8-PentaCDF **Hebert et al. 1990**								
Mouse (HRS/J) 20 F	20 weeks 2 days/week	0, 3.3	HP	Death			3.3 F	35% mortality
				Bd wt		3.3 F		8% body weight loss
				Gastro		3.3 F		Mucous cell hyperplasia of glandular stomach
				Hepatic		3.3 F		Increased liver weight and hypertrophy
				Immuno			3.3 F	Thymic and splenic lymphoid atrophy
Comment: Mice were treated with a single dermal dose of acetone prior to exposure to 1,2,3,4,7,8-hexaCDF.								
1,2,3,4,7,8-HexaCDF **Hebert et al. 1990**								

Table 2-3. Levels of Significant Exposure to Chlorodibenzofurans (CDFs) – Dermal

Species (strain) No./group	Exposure parameters	Doses (µg/kg/day)	Parameters monitored	Endpoint	NOAEL (µg/kg/day)	Less serious LOAEL (µg/kg/day)	Serious LOAEL (µg/kg/day)	Effects
Mouse (HRS/J) 20 F	20 weeks 2 days/week	0, 8.3, 16.7, 33.3	BW OW HP CS	Death			33.3 F	Increased mortality
				Cancer			8.3 F	CEL: skin proliferative lesions following initiation

Comment: Mice were treated with a single 5 µmol dermal dose of MNNG in acetone prior to exposure to 1,2,3,4,7,8-hexaCDF.

1,2,3,4,7,8-HexaCDF
Hebert et al. 1990

Bd wt or BW = body weight; CEL = Cancer Effect Level; CS = clinical signs; F = female(s); Gastro = gastrointestinal; HP = histopathology; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; MNNG = methylnitronitrosoguanidine; NOAEL = no-observed-adverse-effect level; OW = organ weight

2.2 DEATH

Several studies evaluated mortality among Yusho and Yu-Cheng victims. No increases in deaths from all causes were observed when Yusho victims were followed through 1983 (Kuratsune et al. 1987) or 2007 (Onozuka et al. 2009). Similarly, studies of the Yu-Cheng victims did not demonstrate increases in deaths from all causes when victims were followed through 1991 (Yu et al. 1997) or 2003 (Tsai et al. 2007). However, in a study that used neighborhood referents rather than national referents, an increase in the prevalence of deaths from all causes was found among Yu-Cheng victims followed through 2008 (Li et al. 2013). A meta-analysis of the results of the Onozuka et al. (2009) and Li et al. (2013) studies of Yusho and Yu-Cheng victims reported an increase in deaths from all causes (standardized mortality ratio [SMR] 1.1, 95% confidence interval (CI) 1.1–1.2) (Li et al. 2015a). Studies also reported cause-specific deaths, which are discussed in subsequent sections of this chapter.

Information on lethality of CDFs in animals following acute oral exposure is available for several congeners. Due to a long latent period for the onset of toxicity, reliable determination of toxic dose following acute exposure requires a sufficient observation period (typically 30 days in rodents).

2,3,7,8-TetraCDF. Single 2,3,7,8-tetraCDF doses ≥1,000 µg/kg, but not 500 µg/kg, were lethal in rhesus monkeys observed for 60 days post-exposure, but small numbers of animals (two to four) were tested (Moore et al. 1979). A CDF mixture containing 88% 2,3,7,8-tetraCDF (remainder primarily an unidentified pentaCDF) did not cause death in mice when tested at doses ≤6,000 µg/kg (Moore et al. 1976, 1979). The Hartley guinea pig was the most sensitive of the species tested as indicated by lethality following single doses of 10 µg/kg 2,3,7,8-tetraCDF (Moore et al. 1979).

Although limited by small numbers of animals (three to eight per dosage), gavage studies with 2,3,7,8-tetraCDF indicate that Hartley guinea pigs are much more sensitive than C57B1/6Fh mice following repeated exposure (Ioannou et al. 1983; Moore et al. 1979). Weekly doses of 1 µg/kg for 6–14 weeks produced 30–70% mortality in guinea pigs, whereas 22 doses of 300 µg/kg in 30 days caused no deaths in mice observed for an additional 30 days (Luster et al. 1979a, 1979b). One of three monkeys died following dietary administration of 2,3,7,8-tetraCDF in estimated dosages of 2.1 µg/kg/day for 2 months or 0.21 µg/kg/day for 6 months (McNulty et al. 1981).

1,2,3,4,8-PentaCDF. No deaths were observed in Sprague-Dawley rats exposed to ≤600 µg/kg/day in the diet for 13 weeks (Pluess et al. 1988a).

1,2,3,7,8-PentaCDF. Dietary exposure to doses as high as 20 µg/kg/day did not results in deaths in Sprague-Dawley rats exposed for 13 weeks (Pluess et al. 1988a).

2,3,4,7,8-PentaCDF. An LD_{50} of 916 µg/kg was estimated for 2,3,4,7,8-pentaCDF in male rats (Brewster et al. 1988). Lethality was observed in Hartley guinea pigs administered a single gavage dose of 10 µg/kg 2,3,4,7,8-pentaCDF as low as 10 µg/kg (Moore et al. 1979).

Dietary administration of 20 µg/kg/day 2,3,4,7,8-pentaCDF for 13 weeks caused >90% mortality in rats (Pluess et al. 1988b). No deaths were observed in female rats administered via gavage ≤0.2 µg/kg 2,3,4,7,8-pentaCDF 5 days/week for 2 years (NTP 2006).

1,2,3,6,7,8-HexaCDF. No deaths were observed in a 13-week study of rats exposed to ≤20 µg/kg/day 1,2,3,6,7,8-hexaCDF in the diet (Pluess et al. 1988a).

Summary. The existing lethality data indicate that congeners substituted in the 2,3,7,8-positions, particularly 2,3,4,7,8-pentaCDF and 2,3,7,8-tetraCDF, are the most toxic congeners tested. There is a marked species variation in sensitivity, with the guinea pig and monkey being particularly sensitive, although this may differ for other endpoints. Single and repeated doses were extremely toxic, causing death at levels as low as 20 µg/kg and 0.2 µg/kg/day, respectively. A wasting syndrome was the major toxic effect at lethal doses in most species (see Section 2.3), but this may not be the only cause of death.

2.3 BODY WEIGHT

Several epidemiological studies evaluated body weight endpoints (see Table 2-4). A study of Yusho victims reported an association between serum 2,3,4,7,8-pentaCDF levels and body weight loss (Imamura et al. 2007). In a study of residents living near a highly dioxin-contaminated site in Taiwan, abdominal obesity, defined as a waist to hip ratio of greater than 0.8 in women and 0.9 in men, was associated with serum concentrations of several tetra-, penta-, and hexaCDF congeners in men and with some heptaCDF congeners in females (Chang et al. 2016). In a third study of the general population, no association between total CDF TEQ levels and the risk of having a body mass index (BMI) of ≥25 kg/m^2 was found (Uemura et al. 2009).

Table 2-4. Results of Epidemiological Studies Evaluating Exposure to CDFs and Body Weight Effects

Reference, study type, and population	Biomarker[a]	Outcome evaluated	Result
Chang et al. 2016 Cross-sectional; 2,876 adults living near a highly dioxin-contaminated site (Taiwan)	Serum 2,3,7,8-tetraCDF TEQ (levels not reported)	Abdominal obesity	↑ 3Q (males) ↔ (females)
	Serum 1,2,3,7,8-pentaCDF TEQ (levels not reported)	Abdominal obesity	↑ 2Q (males) ↔ (females)
	Serum 2,3,4,7,8-pentaCDF TEQ (levels not reported)	Abdominal obesity	↑ 3Q (males) ↔ (females)
	Serum 1,2,3,4,7,8-hexaCDF TEQ (levels not reported)	Abdominal obesity	↑ 2Q (males) ↔ (females)
	Serum 1,2,3,6,7,8-hexaCDF TEQ (levels not reported)	Abdominal obesity	↑ 3Q (males) ↔ (females)
	Serum 2,3,4,6,7,8-hexaCDF TEQ (levels not reported)	Abdominal obesity	↑ 3Q (males) ↑ 3Q (females)
	Serum 1,2,3,7,8,9-hexaCDF TEQ (levels not reported)	Abdominal obesity	↔ (males) ↔ (females)
	Serum 1,2,3,4,6,7,8-heptaCDF TEQ (levels not reported)	Abdominal obesity	↔ (males) ↑ 4Q (females)
	Serum 1,2,3,4,7,8,9-heptaCDF TEQ (levels not reported)	Abdominal obesity	↔ (males) ↑ 3Q (females)
	Serum octaCDF TEQ (levels not reported)	Abdominal obesity	↔ (males) ↔ (females)
	Serum total CDF TEQ (levels not reported)	Abdominal obesity	↑ 2Q (males) ↔ (females)
Imamura et al. 2007 Retrospective, 241 adults in Yusho cohort	Serum total CDF mean of 264.26 pg/g lipid	Body weight	↑
Uemura et al. 2009 Cross sectional, 1,374 adults (Japan)	Serum total CDF TEQ 4th quartile ≥6.60 pg/g lipid	BMI ≥25 kg/m^2	↔

[a]TEQs were calculated using the WHO 1998 TEF values.

↑ = association between biomarker level and outcome; ↓ = inverse association between biomarker level and outcome; ↔ = no association between biomarker level and outcome; BMI = body mass index; CDF = chlorodibenzofuran; Q = quartile; TEF = toxic equivalency factor; TEQ = toxic equivalent; WHO = World Health Organization

2,3,7,8-TetraCDF. A single gavage doses caused wasting effects in guinea pigs at ≥10 µg/kg 2,3,7,8-tetraCDF (Moore et al. 1979) and monkeys at 1,000 µg/kg 2,3,7,8-tetraCDF (Moore et al. 1979), as evidenced by rapid and progressive weight loss. Decreases in weight gain were also observed in monkeys administered 500 µg/kg and guinea pigs administered 1 µg/kg 2,3,7,8-tetraCDF (Moore et al. 1979). No alterations in body weight gain were observed in intermediate-duration studies in which mice

were administered 300 µg/kg 5 days/week for 30 days (Moore et al. 1979) or in guinea pigs administered 1 µg/kg 1 day/week for 6 weeks (Luster et al. 1979a, 1979b).

1,2,3,4,8-PentaCDF. No alterations in body weight gain were observed in rats exposed to 600 µg/kg/day in the diet for 13 weeks (Pluess et al. 1988a).

1,2,3,7,8-PentaCDF. A 6.5–11% decrease in body weight gain was observed in rats exposed to 20 µg/kg/day 1,2,3,7,8-pentaCDF in the diet for 13 weeks (Pluess et al. 1988a); no alterations were observed at 2 µg/kg/day.

2,3,4,7,8-PentaCDF. Wasting effects were observed in guinea pigs administered a lethal gavage dose of 10 µg/kg (Moore et al. 1979). At lower concentrations (≥1 µg/kg), decreases in body weight gain were observed. Rats appear to be less sensitive to the body weight effects of 2,3,4,7,8-pentaCDF. A decrease in body weight gain was observed in rats administered a single dose of 500 µg/kg (Brewster et al. 1988). An ED_{50} (50% decrease in body weight gain) of 146 µg/kg was estimated in pubertal rats administered a single dose of 2,3,4,7,8-pentaCDF (Taura et al. 2014). Single dose studies of 2,3,4,7,8-pentaCDF did not result in alterations in body weight in rats administered 53 µg/kg (Ahlborg et al. 1989) or in mice administered 90 µg/kg (Johnson et al. 2000).

In intermediate-duration studies, body weight gain was decreased (11%) in rats fed 2 µg/kg/day dosages of 2,3,4,7,8-pentaCDF and weight loss (47–50%) was observed at 20 µg/kg/day dosage (Pluess et al. 1988b). No alterations in body weight gain were observed in rats administered 0.2 µg/kg 5 days/week (NTP 2006). In the only available chronic study, no alterations in body weight gain were observed in female rats administered ≤0.2 µg/kg 2,3,4,7,8-pentaCDF 5 days/week for 2 years (NTP 2006).

Mixed Chlorodibenzofurans. Body weight gain was decreased in rats exposed to ≥97 µg/kg/day of an uncharacterized mixture of two tetra-, four penta-, and four hexaCDFs in the diet for 4 weeks (Oishi et al. 1978).

Summary. Studies in laboratory animals reported decreases in body weight gain at lower doses and a wasting syndrome in animals exposed to high, often lethal, doses. The wasting syndrome is characterized by progressive decreased weight gain, with immediate moderate to severe body weight loss generally occurring at near-lethal doses.

2.4 RESPIRATORY

Clinical observations strongly suggest that Yusho and Yu-Cheng cohort members experienced frequent or more severe respiratory infections (Akahane et al. 2018; Kuratsune 1989; Rogan 1989). Chronic bronchitis accompanied by persistent cough and sputum production was observed in 40–50% of some examined patients, with symptoms gradually improving during 5–10 years following onset (Nakanishi et al. 1985; Shigematsu et al. 1971, 1977). Physical findings differed from those in usual bronchitis in that many nonsmokers showed no crackles and some showed wheezes without radiologic, physiologic, or immunologic evidence of bronchial asthma or pulmonary emphysema (Nakanishi et al. 1985; Shigematsu et al. 1971). Kanagawa et al. (2008) found an association between serum levels of 2,3,4,7,8-pentaCDF and abnormal respiratory sounds in a retrospective study of 501 Yusho victims. A mortality study of the Yu-Cheng cohort did not find increases in the risk of death from respiratory disease (examination period was 1980–2003) (Tsai et al. 2007).

2,3,7,8-TetraCDF. A single dose exposure did not result in histological alterations in the trachea or lungs of monkeys administered ≤1,500 μg/kg, mice administered ≤6,000 μg/kg, or guinea pigs administered ≤15 μg/kg 2,3,7,8-tetraCDF (Moore et al. 1976, 1979); these dose levels resulted in deaths of monkeys and guinea pigs.

2,3,4,7,8-PentaCDF. No histological alterations were observed in the respiratory tract of rats receiving a single dose of 2,000 μg/kg 2,3,4,7,8-pentaCDF (Brewster et al. 1988) or guinea pigs administered a single dose of 30 μg/kg (Moore et al. 1979). Intermediate-duration studies conducted by the National Toxicology Program (NTP 2006) did not report respiratory lesions in rats administered ≤0.2 μg/kg 2,3,4,7,8-pentaCDF 5 days/week for 14 or 31 weeks. In a chronic-duration study by this group, bronchiolar metaplasia of the alveolar epithelium was observed in rats administered ≥0.092 μg/kg for 2 years (NTP 2006).

Summary. The Yusho and Yu-Cheng data provide evidence that CDFs-induced bronchitis and related respiratory effects in humans. There is no evidence of pulmonary histological changes in animals exposed to single doses of CDFs or following intermediate-duration exposure; lung damage was evident after chronic exposure to 2,3,4,7,8-pentaCDF.

2.5 CARDIOVASCULAR

Cardiovascular endpoints were examined in the Yusho and Yu-Cheng cohorts and a general population study; studies evaluating the possible association between CDF levels and health outcomes (Imamura et al. 2007; Kondo et al. 2018; Uemura et al. 2009) are summarized in Table 2-5. Mixed results were found in lethality studies. No increases in death from circulatory disease were found in two studies of the Yu-Cheng cohort examining 1979–1991 (Yu et al. 1997) and 1980–2003 (Tsai et al. 2007) periods; no increases in deaths from heart disease, hypertension, or cerebrovascular disease were found in the Yusho cohort examined through 2007 (Onozuka et al. 2009). In contrast, Li et al. (2013) reported an increase in the prevalence of deaths from circulatory system diseases, other forms of heart disease, cardiac dysrhythmias, and late effects of cerebrovascular disease among Yu-Cheng females and myocardial infarctions among Yu-Cheng males. A meta-analysis of the results from the Li et al. (2013) Yu-Cheng study and the Onozuka et al. (2009) Yusho study found an increased risk of deaths from heart disease (SMR 1.3, 95%CI 1.0–1.7) (Li et al. 2015a).

Table 2-5. Results of Epidemiological Studies Evaluating Exposure to CDFs and Cardiovascular Effects

Reference, study type, and population	Biomarker[a]	Outcome evaluated	Result
Imamura et al. 2007 Retrospective, 241 adults in Yusho cohort (Japan)	Serum total CDF mean of 264.26 pg/g lipid	Blood pressure	↔
		Heart rate	↔
		EKG	↔
Kondo et al. 2018 Retrospective, 140 adults in Yusho cohort (Japan)	Serum 2,3,4,7,8-pentaCDF 4th quartile ≥72.27 pg/g lipid	Hypertension	↑
Uemura et al. 2009 Cross sectional, 1,374 adults (Japan)	Serum total CDF TEQ 4th quartile ≥6.60 pg/g lipid	High blood pressure[b]	↑

[a]TEQs were calculated using the WHO 1998 TEF values.
[b]High blood pressure defined as ≥130/85 or physician-diagnosed hypertension.

↑ = association between biomarker level and outcome; ↓ = inverse association between biomarker level and outcome; ↔ = no association between biomarker level and outcome; CDF = chlorodibenzofuran; EKG = electrocardiogram; TEF = toxic equivalency factor; TEQ = toxic equivalent; WHO = World Health Organization

Among living members of the Yusho cohort, Akahane et al. (2018) found an increased prevalence of enlarged heart, abnormal cardiac rhythm, fast pulse, palpitations, low blood pressure, and arterial sclerosis. Two other studies found suggestive evidence of cardiovascular effects among cohort members with higher CDF exposures. Kondo et al. (2018) reported an association between high serum 2,3,4,7,8-pentaCDF levels (≥72.27 pg/g lipid) and hypertension in the Yusho cohort, and Wang et al. (2008) found an increased risk of hypertension and cardiovascular disease among Yu-Cheng women who had chloracne. Imamura et al. (2007) did not find an association between serum 2,3,4,7,8-pentaCDF and blood pressure, heart rate, or abnormal electrocardiogram (EKG) findings in the Yusho cohort. A general population study of adults in Japan found an association between serum total CDF TEQ levels and high blood pressure.

2,3,7,8-TetraCDF. Administration of a single dose of 2,3,7,8-tetraCDF did not result in histological alterations in the heart of monkeys (≤1,500 µg/kg), mice (≤6,000 µg/kg), or guinea pigs (≤15 µg/kg) (Moore et al. 1976, 1979); the animals were examined at death or following a 30-day (mice and guinea pigs) or 60-day (monkey) observation period.

1,2,3,7,8-PentaCDF. Dietary exposure of rats to 600 µg/kg/day 1,2,3,7,8-pentaCDF for 13 weeks did not result in histological alterations in the heart (Pluess et al. 1988a).

2,3,4,7,8-PentaCDF. No histological alterations were observed in the heart of guinea pigs that were administered a single gavage dose of ≤30 µg/kg 2,3,4,7,8-pentaCDF (Moore et al. 1979). In intermediate-duration studies, no heart histological alterations were observed in rats exposed to 20 µg/kg/day in the diet for 13 weeks (Pluess et al. 1988a) or in rats administered ≤0.2 µg/kg 2,3,4,7,8-pentaCDF 5 days/week for 14 or 31 weeks (NTP 2006). Cardiomyopathy was observed in rats administered 0.2 µg/kg 2,3,4,7,8-pentaCDF 5 days/week for 2 years (NTP 2006).

1,2,3,6,7,8-HexaCDF. Dietary exposure to 20 µg/kg/day 1,2,3,6,7,8-hexaCDF for 13 weeks did not result in histological alterations in rats (Pluess et al. 1988a).

Mixed CDF Congeners. Dietary exposure to an uncharacterized mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks caused increased relative heart weight at ≥97 µg/kg/day and decreased absolute heart weight at 960 µg/kg/day in rats, but histology was not evaluated (Oishi et al. 1978). The increased relative heart weight is likely due to concurrent lower body weight (see Section 2.3).

Summary. Studies of the Yusho and Yu-Cheng cohorts provide suggestive evidence of an increased risk of heart disease, but the results are not consistent across studies. The results of animal studies with 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, and 1,2,3,6,7,8-hexaCDF suggest that less-than-lifetime exposure does not result in histological alterations in the heart; however, a 2-year study in rats administered 2,3,4,7,8-pentaCDF found altered cardiac histology. The effects of CDFs on the cardiovascular system have not been fully evaluated.

2.6 GASTROINTESTINAL

Early symptoms in Yusho cohort members included vomiting (23.6 and 28% frequencies) and diarrhea (19.1 and 17%) (Kuratsune 1989). Decades after the Yusho incident, Akahane et al. (2018) found an increased prevalence of colon polyps, gastric ulcer, intestinal obstruction, and constipation; Imamura et al. (2007) found an association between serum 2,3,4,7,8-pentaCDF and the frequency of constipation.

2,3,7,8-TetraCDF. Available studies in laboratory animals suggest that the gastrointestinal tract may be a target of 2,3,7,8-tetraCDF toxicity, although there were differences across species. A single gavage dose of 1,000 µg/kg resulted in gastric lesions in rhesus monkeys that were administered a lethal dose of 1,000 µg/kg 2,3,7,8-tetraCDF and observed for 60 days, but not at a nonlethal dose of 500 µg/kg (Moore et al. 1979). Effects including hyperemia, scattered petechial hemorrhage, focal ulceration, and mucosal cysts in the fundic and duodenal areas of the stomach and the small intestine occurred in three of six monkeys. Intermediate-duration exposure also resulted in gastric mucosal changes in rhesus monkeys treated with dietary 2,3,7,8-tetraCDF for 2 or 6 months (McNulty et al. 1981). Mucous metaplasia of the gastric mucosa was found in a monkey that died from ingestion of 0.21 µg/kg/day for 6 months. Intramucosal cysts and cystic growth of mucous glands in the submucosa occurred in the stomach of another monkey that died from ingestion of 2.1 µg/kg/day for 2 months. Although only one animal per dosage was evaluated, these findings are consistent with those observed in the acute study with monkeys and considered to be compound-related.

Unlike the monkeys, no histological alterations were observed in the esophagus, stomach, or intestine of mice or guinea pigs administered a single gavage doses of ≤6,000 or 15 µg/kg 2,3,7,8-tetraCDF, respectively, and examined 30 days post-exposure (Moore et al. 1976, 1979).

2,3,4,7,8-PentaCDF. Epithelial hyperplasia of the nonglandular stomach, characterized by acanthosis and hyperkeratosis, was observed in 344 rats that were administered a single, near-lethal, gavage dose of

500 µg/kg 2,3,4,7,8-pentaCDF and observed for 35 days, but not at doses ≤250 µg/kg (Brewster et al. 1988). In contrast, single gavage dose administration of ≤30 µg/kg 2,3,4,7,8-pentaCDF did not result in histological alterations in the esophagus, stomach, or intestine of guinea pigs examined at the time of death or 30 days post-exposure (Moore et al. 1979). No gastrointestinal lesions were observed in rats administered ≤0.2 µg/kg 5 days/week for 14 or 31 weeks (NTP 2006). However, squamous hyperplasia of the forestomach was observed in female Sprague-Dawley rats administered 0.2 µg/kg 2,3,4,7,8-pentaCDF for 2 years (NTP 2006).

Summary. Studies of the Yusho cohort reported some gastrointestinal alterations. The animal studies indicate that the gastric mucosa is a target of CDFs in monkeys and rats and suggest that guinea pigs and mice are less sensitive rodent species. Only a few studies were performed, however, and congeners other than 2,3,7,8-tetraCDF and 2,3,4,7,8- pentaCDF were not tested.

2.7 HEMATOLOGICAL

Mild normocytic anemia and leukocytosis are fairly consistent findings in Yu-Cheng cohort members (Rogan 1989). In a subsequent study of the Yu-Cheng cohort, an increased prevalence of anemia was observed in women, but not men (Guo et al. 1999).

2,3,7,8-TetraCDF. Mild anemia, mild lymphopenia, and marked neutrophilia developed in rhesus monkeys following single ≥500 µg/kg dose of 2,3,7,8-tetraCDF (Moore et al. 1979). No hematological alterations were observed in rhesus monkeys exposed to 2.1 or 0.21 µg/kg/day 2,3,7,8-tetraCDF in the diet for 2 or 6 months, respectively (McNulty et al. 1981). In mice administered 300 µg/kg 5 days/week for 30 days, a decrease in total leukocytes was observed; no alterations in total erythrocyte, hemoglobin, or platelet counts were observed (Moore et al. 1979).

No hematological alterations were observed 30 days after guinea pigs were administered a single gavage dose of ≤15 µg/kg 2,3,7,8-tetraCDF (Moore et al. 1979). No alterations in leukocyte counts were observed in guinea pigs administered 1 µg/kg 2,3,7,8-tetraCDF 1 day/week for 6 weeks (Luster et al. 1979a, 1979b).

1,2,3,4,8-PentaCDF. No hematological alterations were observed in rats exposed to 60 or 600 µg/kg/day 1,2,3,4,8-pentaCDF in the diet for 13 weeks (Pluess et al. 1988a).

1,2,3,7,8-PentaCDF. Dietary exposure to ≤20 µg/kg/day for 13 weeks did not result in hematological alterations in rats (Pluess et al. 1988a).

2,3,4,7,8-PentaCDF. In acute-duration studies, rats that were administered single gavage doses of ≥100 µg/kg 2,3,4,78-pentaCDF and evaluated 7–35 days following treatment showed dose-related decreased hemoglobin concentration, mean corpuscular hemoglobin (MCH), and mean corpuscular volume (MCV) (Brewster et al. 1988). The largest decreases were observed at day 35; the hemoglobin, MCH, and MCV were approximately 6, 9, and 4%, respectively, lower than controls. The toxicological significance of these small alterations is not known. There were no changes in mean corpuscular hemoglobin concentration (MCHC), red blood cell count, or platelet number, and measurements of white blood cell count were inconclusive. No hematological alterations were observed in rats exposed to ≤20 µg/kg/day for 13 weeks (Pleuss et al. 1988b). Single gavage doses of ≤30 µg/kg 2,3,4,7,8-pentaCDF produced no treatment-related hematological changes in Hartley guinea pigs observed for 30 days (Moore et al. 1979).

1,2,3,6,7,8-HexaCDF. No consistent alterations in hematological parameters were observed in rats exposed to 1,2,3,6,7,8-hexaCDF in the diet for 13 weeks (Pluess et al. 1988a).

Mixed Congeners. Dietary exposure to uncharacterized mixtures of two tetra-, four penta-, and four hexaCDFs for 4 weeks caused hemolytic anemia in blood smears, reduced hemoglobin, hematocrit and MCV, and/or increased MCHC in rats at ≥50 µg/kg/day (Oishi and Hiraga 1978; Oishi et al. 1978).

Summary. The results of epidemiological and laboratory animal studies suggest that the hematological system may be a target of toxicity following exposure to high levels of CDFs. No consistent findings were found in studies testing lower dose levels.

2.8 MUSCULOSKELETAL

Several studies have evaluated musculoskeletal endpoints in the Yusho and Yu-Cheng cohorts. A mortality study found an increased prevalence of deaths from diseases of the musculoskeletal system and connective tissue among the Yu-Cheng cohort (Li et al. 2013). Another study of the Yu-Cheng cohort found an increased prevalence of arthritis and herniated discs in men, but not women (Guo et al. 1999). Akahane et al. (2018) observed an increased prevalence of slipped disc, osteoporosis, bony deformity, joint pain, stiff shoulders, and back pain among the Yusho cohort. Studies that measured serum

2,3,4,7,8-pentaCDF levels found an association between serum 2,3,4,7,8-pentaCDF and the prevalence of arthralgia (Kanagawa et al. 2008) and an increased prevalence of osteoporosis among subjects with high serum 2,3,4,7,8-pentaCDF levels (≥72.27 pg/g lipid) (Kondo et al. 2018).

2,3,7,8-TetraCDF. Reduced muscle mass, but no histological alterations in muscle, was observed in guinea pigs administered a single gavage dose of ≥5 μg/kg 2,3,7,8-tetraCDF (Moore et al. 1979). The reduced muscle mass appears to be a manifestation of a generalized wasting syndrome (see Section 2.3). No histological alterations were observed in muscles or bones of rats administered gavage doses of ≤0.2 μg/kg for 2 years (NTP 2006); this dose level was not associated with alterations in body weight.

2,3,4,7,8-PentaCDF. A single gavage exposure to ≥3 μg/kg 2,3,4,7,8-pentaCDF resulted in a reduction in muscle mass in guinea pigs; no histological alterations were found in muscle (Moore et al. 1979). The reduced muscle mass appears to be a manifestation of a generalized wasting syndrome (see Section 2.3).

Summary. A small number of studies evaluated potential musculoskeletal effects associated with CDF exposure. Studies in the Yusho and Yu-Cheng cohorts provide suggestive evidence, particularly for 2,3,4,7,8-pentaCDF and skeletal effects. No evidence of muscular or skeletal effects were observed in laboratory animals exposed to 2,3,7,8-tetraCDF or 2,3,4,7,8-pentaCDF.

2.9 HEPATIC

Increases in the risk of death from chronic liver disease and cirrhosis were observed in several studies of the Yu-Cheng cohort (Li et al. 2013; Tsai et al. 2007; Yu et al. 1997), but were not found in a study of the Yusho cohort (Onozuka et al. 2009). A meta-analysis of the Li et al. (2013) and Onozuka et al. (2009) studies found an increase in deaths from hepatic disease among females (SMR 2.0, 95%CI 1.1–3.6) (Li et al. 2015a).

Mild hepatic alterations were described in the Yusho and Yu-Cheng cohorts (Kuratsune 1989; Rogan 1989). Markedly increased serum triglycerides with unchanged serum cholesterol was an abnormal laboratory finding peculiar to both Yusho and Yu-Cheng cohorts (Okumura et al. 1979; Uzawa et al. 1969). The elevated triglycerides generally persisted for several years following exposure and subsequently declined to normal. Kanagawa et al. (2008) found an association between serum 2,3,4,7,8-pentaCDF levels ≥50 pg/g lipid and increases in total cholesterol levels in the Yusho cohort. In a general population study of 1,374 adults in Japan, an association between serum total CDF TEQ levels

in the third quartile (≥4.40–6.60 pg/g lipid) and high triglycerides (≥150 mg/dL) was found; there was no association with low high-density lipoprotein (HDL) levels (<40 mg/dL) for participants with serum total CDF TEQ levels in the fourth quartile (≥6.60 pg/g lipid). A small number of abnormalities in serum levels of liver enzymes or in liver function tests were found in the Yusho cohort (Kuratsune 1989), but elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are fairly consistent findings in the Yu-Cheng cohort (Rogan 1989). Increased urinary excretion of uroporphyrin, but not coproporphyrin or porphobilinogen, is another consistent finding in the Yu-Cheng cohort, including children born to exposed mothers (Chang et al. 1980; Gladen et al. 1988; Lu et al. 1980). An association between serum total bilirubin levels and serum 2,3,4,7,8-pentaCDF levels ≥50 pg/g lipid has also been found in the Yusho cohort (Kanagawa eta l. 2008).

Ultrastructural changes, particularly alterations in the endoplasmic reticulum, and pleomorphic and enlarged mitochondria, appear to be the predominant morphological finding in Yusho cohort members (Kuratsune 1989). Approximately half of 24 deaths observed in 2,061 Yu-Cheng victims by the end of 1983 were attributed to cirrhosis, unspecified liver diseases with hepatomegaly, or hepatoma (Hsu et al. 1985). Diagnoses were made from clinical symptoms and unspecified laboratory examinations. These findings are inconclusive due to unreported background incidences and high prevalences of hepatitis B, cirrhosis, and liver cancer in Taiwan (Rogan et al. 1989). A follow-up study found an increased prevalence of liver dysfunction among the Yusho cohort (Akahane et al. 2018).

2,3,7,8-TetraCDF. Information on the hepatotoxicity of 2,4,7,8-tetraCDF is limited to three studies in rhesus monkeys. A single dose administration of 1,000 μg/kg resulted in gall bladder and bile duct hypertrophy in monkeys (Moore et al. 1979). Decreases in serum cholesterol were also observed in monkeys administered ≥500 μg/kg; the magnitude of the decrease was not reported. In monkeys exposed to 2.1 μg/kg/day 2,3,7,8-tetraCDF in the diet for 2 months, histological alterations consisting of an increase in the height and number of goblet cells in intrahepatic bile duct epithelium were observed (McNulty et al. 1981). Similar lesions appear to have occurred in monkeys exposed to 0.21 μg/kg/day for 6 months, based on the investigator's statement that the postmortem findings were similar to those reported in a monkey exposed to 2.1 μg/kg/day, although liver lesions were not specifically noted. The liver effects observed in monkeys occurred at lethal doses; interpretation of the results of these studies is limited by the poor quality of the study results reporting.

1,2,3,4,8-PentaCDF. No histological alterations were observed in the liver of rats exposed to 60 or 600 μg/kg/day 1,2,3,4,8-pentaCDF in the diet for 13 weeks (Pluess et al. 1988a).

1,2,3,7,8-PentaCDF. Exposure to 20 μg/kg/day 1,2,3,7,8-pentaCDF in the diet for 13 weeks resulted in increases in liver weight and vacuolization with lipid accumulation and single cell necrosis; no liver lesions were reported at 2 μg/kg/day (Pluess et al. 1988a).

2,3,4,7,8-PentaCDF. Several studies have evaluated the hepatotoxicity of 2,3,4,7,8-pentaCDF following acute, intermediate, or chronic oral exposure. Lipid accumulation in the liver and increases in serum cholesterol were observed in rats administered a single dose of 100 μg/kg 2,3,4,7,8-pentaCDF (Brewster et al. 1988). No alterations in liver weight (histological examination of the liver not conducted) were observed in rats administered a single dose of 53 μg/kg (Ahlborg et al. 1989). Rats exposed to 0.2 μg/kg/day 2,3,4,7,8-pentaCDF in the diet for 13 weeks exhibited increases in relative liver weight, vacuolization, single cell necrosis, and fatty changes in the liver (Pluess et al. 1988b).

Minimal hepatocellular hypertrophy was observed in rats administered 0.092 μg/kg 5 days/week for 14 weeks (NTP 2006); increases in relative liver weight (10–23%) were also observed at ≥0.006 μg/kg. When the exposure period was extended to 31 weeks, increased incidences of minimal hepatocellular hypertrophy and pigmentation were observed at ≥0.044 μg/kg (NTP 2006); increases in liver weight (14–21%) were observed at ≥0.02 μg/kg. After 2 years of exposure, hepatocellular hypertrophy was observed at ≥0.006 μg/kg (NTP 2006). Other effects observed in the 2-year study include multinucleated hepatocytes, diffuse fatty changes, and pigmentation at ≥0.02 μg/kg; oval cell hyperplasia at ≥0.044 μg/kg; nodular hyperplasia at 0.092 μg/kg; and mild hepatocellular necrosis, minimal to mild bile duct hyperplasia and fibrosis, and mild cholangiofibrosis at 0.2 μg/kg. The effects observed in rats administered 0.2 μg/kg for 2 years were similar to those in rats exposed to 0.2 μg/kg for 30 weeks and allowed to recover for 75 weeks with the exception of the bile duct effects (NTP 2006); the incidences of liver lesions were significantly lower in the stop-exposure group.

1,2,3,6,7,8-HexaCDF. One study evaluated the hepatotoxicity of 1,2,3,6,7,8-hexaCDF. In this study, an increase in relative liver weight and vacuolization with lipid accumulation and single cell necrosis were observed in rats exposed to 2 μg/kg/day in the diet for 13 weeks (Pluess et al. 1988a).

Mixed Congeners. Hepatic effects in rats exposed to an uncharacterized dietary mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks included increased hepatic uroporphyrin concentrations at 250 μg/kg/day and increased liver weight, lipid content, and serum cholesterol at ≥97 μg/kg/day (Oishi and Hiraga 1978; Oishi et al. 1978).

Mechanisms. CDFs generally induce similar spectra of mild to moderate hepatic effects in animals following single-dose or intermediate-duration oral exposures. Typical changes observed primarily in rats and monkeys included hepatic microsomal enzyme induction, increased serum enzyme levels and liver weight, altered serum cholesterol and triglycerides, fatty and/or necrotic changes in the liver, and bile duct epithelial hyperplasia (Ahlborg et al. 1989; Brewster et al. 1988; Doyle and Fries 1986; Moore et al. 1979; McNulty et al, 1981; Oishi and Hiraga 1978; Oishi et al. 1978; Pluess et al. 1988a, 1988b). Tetra-, penta-, and hexaCDF congeners substituted in the 2,3,7,8 positions were more hepatotoxic than congeners substituted in other positions. This pattern of toxicity was demonstrated in both acute intraperitoneal studies in rats and guinea pigs and *in vitro* structure-activity relationship studies in rat hepatomas that evaluated induction of hepatic microsomal mixed function oxygenase (MFO) enzymes (e.g., aryl hydrocarbon hydroxylase [AHH], 7-ethoxyresorufin 0-deethylase [EROD]) in rats (Bandiera et al. 1984b; Holcomb et al. 1988; Mason et al. 1985; Safe et al. 1986). Assays for activity of the MFO (AHH) were performed in Sprague-Dawley rats 3 days following a single 40 µg/kg gavage dose of 25 di-, tetra-, penta-, hexa-, hepta-, and octaCDF congeners. Hepatic AHH activity was significantly increased (2.1–4.7-fold) by three congeners with chlorine in all four lateral positions (2,3,7,8-tetraCDF, 2,3,4,7,8-pentaCDF, and octaCDF), and the 2,7- and 2,8-diCDFs, but other doses and endpoints were not evaluated (Doyle and Fries 1986). A single gavage dose of 53 µg/kg 2,3,4,7,8-pentaCDF produced hepatic biochemical changes (increased microsomal EROD activity, decreased vitamin A content) in Sprague-Dawley rats, but there was no change in relative liver weight, and histology was not evaluated (Ahlborg et al. 1989).

As discussed in greater detail in Section 2.20, structure-activity relationships for the induction response are comparable to structure-Ah receptor binding relationships, and the inductive potency *in vitro* correlates well with that observed *in vivo*. These and other findings strongly indicate that induction of certain cytochrome P450IA-dependent microsomal MFO enzymes by CDFs, including AHH and EROD, is mediated by the Ah receptor. Although induction of these enzymes is a characteristic effect of CDFs and related compounds and indicates that interaction with the Ah receptor has occurred, it does not necessarily indicate that hepatotoxic effects will also occur (Poland and Knutson 1982). Based on studies with 2,3,7,8-TCDD and PCBs, there is some evidence that effects of CDFs on lipids (increased serum triglycerides and cholesterol, fatty infiltration of liver) may be Ah receptor-mediated and related to alterations in synthesis of apoproteins involved in lipid formation and utilization (Goldstein and Safe 1989). The extrahepatic biliary epithelial effects may be related to elimination of CDFs and metabolites in the bile (McConnell 1989).

Summary. Epidemiological and laboratory animal studies provide strong evidence that the liver is a target of CDF toxicity. The effects include alterations in serum triglycerides and cholesterol levels, increases in liver weight, lipid accumulation in the liver, and hepatocellular hypertrophy. Bile duct effects have also been reported in laboratory animals. The different congeners appear to have similar liver effects, although there are differences in toxicity and no liver effects were observed in the only non 2,3,7,8-substituted congener that was tested (1,2,3,4,8-pentaCDF). A series of studies conducted by Pluess et al. (1988a, 1988b) tested the toxicity of several congeners. The LOAELs for lipid accumulation in the liver were 0.2 µg/kg/day for 2,3,4,7,8-pentaCDF, 2 µg/kg/day for 1,2,3,6,7,8-hexaCDF, and 20 µg/kg/day for 1,2,3,4,8-pentaCDF.

2.10 RENAL

Two epidemiological studies evaluated potential renal outcomes. Akahane et al. (2018) reported an increased prevalence of kidney inflammation, hematuria, and proteinuria in the Yusho cohort. In a study of teens (ages 12–19 years) participating in the National Health and Nutrition Examination Survey (NHANES), no association was found between the incidence of nephropathy and blood 2,3,4,7,8-pentaCDF levels ≥54.02 fg/g whole blood (Everett and Thompson 2016).

2,3,7,8-TetraCDF. Acute-duration studies found mild renal effects in animals exposed to lethal doses of CDFs. Hyperplasia of the epithelium in the renal pelvis, ureter, and urinary bladder was observed in guinea pigs up to 30 days after single gavage doses of ≥10 µg/kg 2,3,7,8-tetraCDF (Moore et al. 1979). No histological alterations were observed in the kidneys of mice 30 days after a single, nonlethal gavage dose of 6,000 µg/kg/day 2,3,7,8-tetraCDF (Moore et al. 1979). Blood urea nitrogen (BUN) was increased in rhesus monkeys administered a single gavage dose of ≥1,000 µg/kg 2,3,7,8-tetraCDF only during the period that immediately preceded death, but this was not accompanied by altered kidney weight or histology, and only small numbers were evaluated (Moore et al. 1979).

1,2,3,4,8-PentaCDF. There were no treatment-related kidney histological alterations in rats that ingested ≤600 µg/kg 1,2,3,4,8-pentaCDF via diet for 13 weeks (Pluess et al. 1988a).

1,2,3,7,8-PentaCDF. No histological alterations were observed in the kidneys of rats exposed to ≤20 µg/kg 1,2,3,7,8-pentaCDF in the diet for 13 weeks (Pluess et al. 1988a).

2,3,4,7,8-PentaCDF. Increased relative kidney weight, decreased absolute kidney weight, and 64% increased BUN was found in rats observed for 35 days following single gavage doses of ≥500, ≥1,000, and 2,000 µg/kg 2,3,4,7,8-pentaCDF, respectively (Brewster et al. 1988). Reduced body weight contributed to the increased relative kidney weights. There were no histological alterations in the kidneys or bladder in any of the treated rats. Because both organ weight and functional (BUN) changes occurred at 2,000 mg/kg, this dose is a LOAEL.

In an intermediate-duration study, no histological alterations were observed in rats exposed to ≥20 µg/kg/day 2,3,4,7,8-pentaCDF in the diet for 13 weeks (Pluess et al. 1988b). Chronic gavage exposure to 2,3,4,7,8-pentaCDF resulted in an increased incidence of nephropathy in female rats administered ≥0.044 µg/kg 5 days/week for 2 years (NTP 2006).

1,2,3,6,7,8-HexaCDF. Dietary exposure to ≤20 µg/kg/day 1,2,3,6,7,8-hexaCDF did not result in alterations in kidney histology in rats exposed for 13 weeks (Pluess et al. 1988a).

Mixed Congeners. In intermediate-duration studies, kidney histology was not evaluated in Sprague-Dawley rats exposed to ≤960 µg/kg/day of an uncharacterized dietary mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks (Oishi et al. 1978). However, based on unchanged relative kidney weight, no adverse effects were observed.

Summary. The kidney does not appear to be a sensitive target of CDF toxicity following acute or intermediate exposure. Mild to moderate renal effects have been observed in guinea pigs, rats, and monkeys exposed to lethal doses of 2,3,7,8-tetraCDF or 2,3,4,7,8-pentaCDF. Chronic nonlethal doses of 2,3,4,7,8-pentaCDF did result in nephropathy in rats.

2.11 DERMAL

Effects in the skin and eyes are the most obvious manifestations of exposure in the Yusho and Yu-Cheng cohorts; they were evaluated in a number of studies and were observed in the majority of cases (Hsu et al. 1993; Kuratsune 1989; Lu and Wu 1985; Rogan 1989). Characteristic skin changes included marked enlargement, elevation and keratotic plugging of follicular orifices, comedones (blackhead) formation, acneiform eruptions, hyperpigmentation, hyperkeratosis, and deformed nails. The acne most commonly developed in the face and other parts of the head, axillae, trunk, and external genitalia, with follicular plugging occurring in the axillae, groin, glenoid regions such as elbow and knee flexures, trunk, thigh,

and outer aspect of the forearm. Dark-colored pigmentation frequently occurred in the gingival and buccal mucosa, lips, and nails and improved only gradually in most patients. Decades after the Yusho and Yu-Cheng incidents, increases in the prevalence of acne, black comedones, and abnormal nails are still reported (Akahane et al. 2018; Guo et al. 1999; Mitoma et al. 2015). Associations between serum 2,3,4,7,8-pentaCDF and the prevalence of the dermal effects have also been reported (Imamura et al. 2007; Kanagawa et al. 2008; Mitoma et al. 2015); the results of these three studies are summarized in Table 2-6.

Table 2-6. Results of Epidemiological Studies Evaluating Exposure to CDFs and Dermal Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Imamura et al. 2007 Retrospective, 241 adults in Yusho cohort (Japan)	Serum total CDF mean of 264.26 pg/g lipid	Recent purulent skin eruptions	↑
		Recurrence of cystic lesions	↑
		History of acneiform eruptions	↑
		History of pigmentation	↑
		Black comedones	↑
		Acneiform eruptions	↑
		Scar formation	↑
		Nail deformity	↑
Kanagawa et al. 2008 Retrospective, 501 adults in Yusho cohort (Japan)	Serum 2,3,4,7,8-pentaCDF ≥50 pg/g lipid	Acneiform eruptions	↑
Mitoma et al. 2015 Retrospective, 352 adults in Yusho cohort (Japan)	Serum 2,3,4,7,8-pentaCDF mean 130.8 pg/g lipid	Severity of black comedones and scar formation	↑
		Scar formation	↑

↑ = association between biomarker level and outcome; ↓ = inverse association between biomarker level and outcome; ↔ = no association between biomarker level and outcome; CDF = chlorodibenzofuran

2,3,7,8-TetraCDF. Rhesus monkeys that were treated with single, nonlethal (500 µg/kg) or lethal (≥1,000 µg/kg) doses of 2,3,7,8-tetraCDF and observed for 60 days developed progressive and dose-related skin lesions (Moore et al. 1979). These included dry leathery skin, facial edema, loss of fingernails, exudate with occlusion and squamous metaplasia of ear canal (ceruminous) glands, and epidermal hyperkeratosis; dilation of sebaceous gland ducts and follicular hyperkeratosis were also observed at 1,500 µg/kg. No skin histological alterations were observed in guinea pigs 30 days after

single gavage doses of ≤15 µg/kg 2,3,7,8-tetraCDF or in C57BU6Fh mice administered a single dose of 6,000 µg/kg 2,3,7,8-tetraCDF (Moore et al. 1979).

Dermal lesions also developed in rhesus monkeys treated with 2,3,7,8-tetraCDF in intermediate-duration studies (McNulty et al. 1981). Dietary dosages of 0.21 µg/kg/day for ≤6 months caused partial atrophy of sebaceous glands and hyperkeratotic nail beds. Similar exposure to a higher dosage of 2.1 µg/kg/day caused more severe skin changes, including thickening and partial facial hair loss after 1 month, body hair and nail loss, and absent sebaceous glands. Surviving monkeys were completely recovered 2–3 months after either exposure.

2,3,4,7,8-PentaCDF. Nail hemorrhages were observed in rats administered a single dose of 500 µg/kg 2,3,4,7,8-pentaCDF (Brewster et al. 1988). No dermal alterations were observed in guinea pigs receiving a single dose of 30 µg/kg (Moore et al. 1979) or in rats administered via gavage ≤0.2 µg/kg 2,3,4,7,8-pentaCDF 5 days/week for 2 years (NTP 2006).

Mixed Congeners. Chloracne-like lesions developed on the ears of rats exposed to 960 µg/kg/day dietary dosages of an uncharacterized mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks (Oishi et al. 1978).

Summary. Effects in the skin are the most obvious manifestations of CDF toxicity in humans and animals. The studies in animals, although limited by number of congeners and species tested, indicate that high doses of 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF cause dermal alterations and that monkeys are more sensitive than rodents.

2.12 OCULAR

Most subjects showed eye discharge and other severe ocular effects during the acute phase of the Yusho and Yu-Cheng syndrome (Fu 1984; Kuratsune 1989; Lu and Wu 1985; Rogan 1989). These effects include meibomian gland changes (enlargement, inflammation, hypersecretion of cheese-like material) and dark-colored pigmentation of the conjunctivae and eyelids. Post-exposure, improvement of the ocular changes was gradual and occurred with improvement of dermal effects. Increased prevalences of excessive eye discharge, cataracts, near sightedness, and “lazy eye” were observed in the Yusho cohort several decades after the rice oil exposure incident (Akahane et al. 2018).

2,3,7,8-TetraCDF. Ocular effects observed in monkeys administered a single dose of ≥500 µg/kg 2,3,4,7,8-pentaCDF included loss of eyelashes, exudate with occlusion, and squamous metaplasia of eyelid (meibomian) glands (Moore et al. 1979). No eye histological alterations were observed in guinea pigs 30 days after single gavage doses of ≤15 µg/kg 2,3,7,8-tetraCDF (Moore et al. 1979).

Ocular lesions also developed in rhesus monkeys treated with 2,3,7,8-tetraCDF in intermediate-duration studies (McNulty et al. 1981). Periorbital edema and meibomian gland enlargement were observed at 0.21 µg/kg/day. Similar exposure to a higher dosage of 2.1 µg/kg/day resulted in eyelid reddening after 1 month. Surviving monkeys completely recovered 2–3 months after exposure termination.

2,3,4,7,8-PentaCDF. No ocular effects were observed in guinea pigs administered a single dose of ≤30 µg/kg 2,3,4,7,8-pentaCDF (Moore et al. 1979) or in rats administered gavage doses of ≤0.2 µg/kg 2,3,4,7,8-pentaCDF 5 days/week for 2 years (NTP 2006).

Summary. Ocular effects have been observed in humans and monkeys exposed to high doses of CDFs, but have not been observed at lower doses in rodent studies.

2.13 ENDOCRINE

Endocrinological evaluations of the Yu-Cheng cohort found a tendency for increased urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids (Nagai et al. 1971). Effects on reproductive endocrinology in the Yu-Cheng and Yusho cohorts have also been reported (see Section 2.16). Three studies evaluated potential thyroid effects. Increased prevalences of hypothyroidism in the Yusho cohort (Akahane et al. 2018) and goiter in the Yu-Cheng cohort (Guo et al. 1999) have been reported. Another study reported that serum triiodothyronine (T3), T4, free T4, and thyroid stimulating hormone (TSH) levels were within the normal range in the Yusho cohort (Nagayama et al. 2001).

Several epidemiological studies have evaluated possible associations between diabetes and CDF exposure and found conflicting results. An increase in the prevalence of diabetes was reported in the Yusho cohort (Akahane et al. 2018) and among women in the Yu-Cheng cohort, particularly in women with a history of chloracne (Wang et al. 2008). However, another study did not find an increase in the risk of deaths from diabetes mellitus among the Yu-Cheng cohort (Tsai et al. 2007). Uemura et al. (2009) reported an association between serum total CDF TEQ levels in the third quartile (≥4.40–<6.60 pg/g lipid) and HbA1c levels of >5.6% or physician-diagnosed diabetes among Yusho cohort participants. A study of

NHANES participants with blood 2,3,4,7,8-pentaCDF levels ≥51.74 fg/g whole blood found an increased risk of diabetes with or without nephropathy (Everett and Thompson 2014).

2,3,7,8-TetraCDF. Several studies have evaluated potential endocrine effects in laboratory animals orally exposed to 2,3,7,8-tetraCDF and reported thyroid and adrenal effects. Decreases in serum total T4 levels were reported in rats following exposure to 2,3,7,8-tetraCDF for 4 days. The magnitude of the decrease was approximately 26% in rats exposed to 1 μg/kg/day (Ross et al. 2000), 30% at 4.65 μg/kg/day (Crofton et al. 2005), and 50% at 10 μg/kg/day (Ross et al. 2000). Administration of a single dose of 2,3,7,8-tetraCDF did not result in histological alterations in the thyroid of monkeys administered ≤1,500 μg/kg, mice administered 6,000 μg/kg, or guinea pigs administered 15 μg/kg (Moore et al. 1976, 1979); it is noted that the animals were allowed to recover for 30 days (mice and guinea pigs) or 60 days (monkeys) prior to sacrifice.

Adrenal hemorrhage was found in Hartley guinea pigs that received single, lethal, gavage doses of ≥10 μg/kg 2,3,7,8-tetraCDF (Moore et al. 1979). No adrenal effects were observed in monkeys (≤1,500 μg/kg) or mice (≤6,000 μg/kg) (Moore et al. 1976, 1979). No consistent effects on serum hydrocortisone levels occurred in Hartley guinea pigs treated by gavage with weekly ≤1 μg/kg/day doses of 2,3,7,8-tetraCDF for 6 weeks (Luster et al. 1979a, 1979b). The Moore et al. (1976, 1979) study did not find histological alterations in the pancreases of the three tested species.

1,2,3,4,8-PentaCDF. One study evaluated the potential endocrine toxicity of oral exposure to 1,2,3,4,8-pentaCDF. No histological alterations were observed in the adrenal or thyroid/parathyroid glands of rats exposed to 600 μg/kg/day in the diet for 13 weeks (Pluess et al. 1988a).

1,2,3,7,8-PentaCDF. Information on the toxicity of 1,2,3,7,8-pentaCDF to the endocrine system is limited to two 4-day studies that measured serum total T4 levels. The magnitude of the decrease was 15% at 10 μg/kg/day (Ross et al. 2000), 30% at 15.6 μg/kg/day (Crofton et al. 2005), and 40% at 30 μg/kg/day (Ross et al. 2000).

In an intermediate-duration study, no histological alterations were observed in the adrenal or thyroid glands of rats exposed to ≤20 μg/kg/day 1,2,3,7,8-pentaCDF in the diet for 13 weeks (Pluess et al. 1988a).

2,3,4,7,8-PentaCDF. Similar to 2,3,7,8-tetraCDF and 1,2,3,7,8-pentaCDF, a 4-day exposure to 2,3,4,7,8-pentaCDF resulted in decreases in serum total T4 levels. A 27–30% decrease was observed at

27.5–30 μg/kg/day (Crofton et al. 2005; Ross et al. 2000) and a 47% decrease was observed at 90 μg/kg/day (Ross et al. 2000). Administration of 2,3,4,7,8-pentaCDF to female rats 5 days/week for 14 weeks resulted in thyroid gland follicular cell hypertrophy at ≥0.044 μg/kg and a decrease in serum total T4 levels (25%) at ≥0.092 μg/kg (NTP 2006). Decreases in serum total T4 levels (16%) were observed in rats following gavage administration of ≥0.006 μg/kg 2,3,4,7,8-pentaCDF 5 days/week for 31 weeks; increased total T3 levels were observed at ≥0.092 μg/kg (NTP 2006). No histological alterations were observed in the thyroid gland after 31 weeks of exposure to ≤0.2 μg/kg (NTP 2006). Chronic administration of 2,3,4,7,8-pentaCDF resulted in follicular cell hypertrophy in the thyroid gland at ≥0.02 μg/kg (NTP 2006). After 53 weeks of exposure, alterations in thyroid hormone levels included decreases (22%) in serum total T4 levels at ≥0.044 μg/kg and increases (23%) in serum total T3 levels at ≥0.092 μg/kg; there were no alterations in TSH levels (NTP 2006).

Administration of a single dose of 10 μg/kg 2,3,4,7,8-pentaCDF resulted in adrenal hemorrhage in guinea pigs (Moore et al. 1979). No alterations in adrenal histology were observed in rats administered dietary dosages ≤20 μg/kg/day 2,3,4,7,8-pentaCDF for 13 weeks (Pluess et al. 1988b). NTP (2006) also reported cystic degeneration in the adrenal cortex at ≥0.006 μg/kg and arterial chronic inflammation in the pancreas at 0.2 μg/kg in the chronic-duration study.

1,2,3,6,7,8-HexaCDF. Adrenal and thyroid/parathyroid histology was normal in rats administered dietary dosages of ≤20 μg/kg/day 1,2,3,6,7,8-hexaCDFfor 13 weeks (Pluess et al. 1988a, 1988b). These dosages were sublethal except for 10 μg/kg/day 2,3,4,7,8-pentaCDF.

OctaCDF. In the only study evaluating potential thyroid effects, Crofton et al. (2005) did not find any significant alterations in the serum total T4 levels in rats administered octaCDF for 4 days. The investigators suggested that the lack of an effect may be due to the poor absorption of octaCDFs.

Mechanisms. The mechanisms by which CDFs decrease serum T4 levels have not been fully elucidated. A likely mechanism involves the catabolism of T4 via T4 glucuronidation. CDFs induce hepatic uridine 5′-diphospho-glucuronosyltransferase (UDPGT) likely through an Ah receptor-mediated pathway (Ross et al. 2000). Exposure of rats to 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, or 2,3,4,7,8-pentaCDF resulted in decreases in serum T4 levels and increases in UDPGT activity (Ross et al. 2000). However, the magnitude of the decrease in T4 was not directly related to the increase in UDPGT activity. For example, there was a 50% decrease in serum T4 levels in rats exposed to 100 μg/kg/day and an 11 % increase in UDGPT activity at this dose level.

Microsomal enzyme inducers can induce UDPGT and increase the biliary excretion of T4, resulting in a reduction of serum T4 levels. Compensatory increases in serum TSH levels have been observed for some chemicals such as phenobarbital and pregnenolone-16α-carbonitrile (PCN). However, other chemicals such as PCB (Aroclor 1254) and 3-methylcholanthrene do not increase serum TSH levels (Hood and Klaassen 2000; Hood et al. 2003; Richardson and Klaassen 2010). Although most of the research was conducted in rats, decreases in serum T4 have also been observed in mice exposed to 3-methlycholanthrene and PCB (Hood et al. 2003). However, slight increases in TSH levels were also observed in mice. CDFs appear to work by a similar mechanism as methylcholanthrene and PCB. Decreases in serum T4 levels were reported in rats exposed to 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, and 1,2,3,6,7,8-hexaCDF (Crofton et al. 2005; NTP 2006; Ross et al. 2000); no changes in TSH levels were observed in rats exposed to 2,3,4,7,8-pentaCDF (NTP 2006). Epidemiological studies on the potential thyroid toxicity of CDFs are inconclusive. Occupational exposure studies involving CDDs (ATSDR 1998, 2012) and PCBs (ATSDR 2000) have found alterations in thyroid hormone levels.

Summary. The data from the available epidemiological studies on the association between CDF exposure and thyroid effects are inconclusive. Animal studies provide strong evidence that oral exposure to 2,3,7,8-substituted congeners result in decreases in serum T4 levels. The results of studies evaluating 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, and 2,3,4,7,8-pentaCDF found greater decreases in serum T4 levels in rats exposed to 2,3,7,8-tetraCDF compared to the two pentaCDF congeners (Crofton et al. 2005; Ross et al. 2000). In addition to the thyroid effects, a chronic oral study in rats found histological alterations in the adrenals (NTP 2006).

2.14 IMMUNOLOGICAL

Clinical observations strongly suggest that the Yusho and Yu-Cheng cohorts experienced frequent or more severe skin and respiratory infections and lowered resistance to illness (Kuratsune 1989; Rogan 1989). Various changes in immune status were reported among the Yusho and Yu-Cheng cohorts, including decreased serum IgA and IgM levels and lymphocyte subpopulations, diminished phagocyte complement and IgG receptors, and diminished delayed-type skin hypersensitivity response (Chang et al. 1981, 1982a, 1982b; Lu and Wu 1985; Nakanishi et al. 1985; Shigematsu et al. 1971). Higher levels of certain interleukins suggestive of dysregulated T_H17 cell-mediated immune responses were also observed (Kuwatsuka et al. 2014). Follow-up studies of the Yusho and Yu-Cheng cohorts have found alterations in

the prevalence of immune-related diseases such as asthma, rheumatoid arthritis, and drug and skin allergies (Akahane et al. 2018; Guo et al. 1999). Tsai et al. (2007) found an increase in deaths from systemic lupus erythematosus in women in the Yu-Cheng cohort; most of the deaths occurred in the 1988–1995 time period rather than the 1996–2003 time period.

Decreased thymus weight and thymic atrophy, characterized by lymphoid cell loss, involutions, and/or lack of corticomedullary differentiation, have been consistently observed in animals exposed to CDFs. Thymus weight decreases were often pronounced, particularly at lethal doses where reductions as high as 80–90% were observed.

2,3,7,8-TetraCDF. Acute- and intermediate-duration studies of 2,3,7,8-tetraCDF provide strong evidence that the immune system, particularly the thymus, is a target of CDF toxicity. In monkeys, thymic atrophy was reported following administration of a lethal dose of 1,000 μg/kg 2,3,7,8-tetraCDF (Moore et al. 1979) and dietary exposure to 2.1 or 0.21 μg/kg/day for 2 or 6 months (McNulty et al. 1981). A marked reduction of thymus size was also observed in guinea pigs administered a single dose of 5 μg/kg (Moore et al. 1979) and in mice administered 300 μg/kg 5 days/week for 30 days (Moore et al. 1979). Other histological alterations in the immune system include loss of lymphoid cells in the thymic cortex, hypocellularity of bone marrow, lymphoid elements in the spleen, and Peyer's patches were observed in guinea pigs administered a single dose of 10 μg/kg (Moore et al. 1979).

One study evaluated immune function in guinea pigs administered 2,3,7,8-tetraCDF 1 day/week for 6 weeks (Luster et al. 1979a, 1979b). No alterations in humoral immunity were found as evaluated by measuring serum proteins (albumin, α-globulins, β-globulins, γ-globulins, and IgG levels) or the response to immunization with bovine gamma globulin; however, a decreased lymphoproliferative response to lipopolysaccharide provides an indication that humoral immunity was compromised. Cell-mediated immunity was impaired in the guinea pigs administered 0.5 μg/kg as evidenced by the impaired lymphoproliferative response to phytohemagglutinin in the 0.5 μg/kg group; there was no effect on the response to concanavalin A.

1,2,3,4,8-PentaCDF. No alterations in thymus or spleen weight or histology were observed in rats exposed to 600 μg/kg/day 1,2,3,4,8-pentaCDF in the diet for 13 weeks (Pluess et al. 1988a).

1,2,3,7,8-PentaCDF. A 13-week exposure of rats to 20 μg/kg/day 1,2,3,7,8-pentaCDF resulted in decreases in thymus weight and minimal thymic atrophy (Pluess et al. 1988a). No alterations were observed in the spleen.

2,3,4,7,8-PentaCDF. Decreases in thymus weight have been observed in rats and guinea pigs administered single doses of 2,3,4,7,8-pentaCDF. Taura et al. (2014) estimated an ED_{50} (50% decrease in thymus weight) of 71.9 μg/kg in pubertal rats (5 weeks of age) receiving a single gavage dose of 2,3,4,7,8-pentaCDF. A 100 μg/kg dose resulted in 30–90% decreases in thymic weight in rats (Brewster et al. 1988). At 500 μg/kg, thymic atrophy was observed. No alterations in thymus weight were observed in rats administered 53 μg/kg (Ahlborg et al. 1989). Guinea pigs appear to be more sensitive than rats; a reduction in thymus size was observed at 3 μg/kg and a loss of lymphoid cells were observed in the thymic cortex at 10 μg/kg.

Intermediate-duration exposure resulted in decreases in thymus weight at 0.2 μg/kg and thymic atrophy at 2 μg/kg in rats exposed for 13 weeks (Pluess et al. 1988b) and thymic atrophy in rats administered 0.2 μg/kg 5 days/week for 31 weeks (NTP 2006). No alterations in thymus weight or pathology were observed in rats administered 0.2 μg/kg 5 days/week for 14 weeks (NTP 2006). In a chronic study, an increase in the severity of thymic atrophy was observed in rats administered 0.2 μg/kg 5 days/week for 2 years (NTP 2006).

Laboratory animal studies have also reported histological alterations in other tissues. Lymphoid depletion was observed in the spleen of rats administered a single dose 500 μg/kg (Brewster et al. 1988). In guinea pigs administered a 10 μg/kg dose, loss of lymphoid cells in the thymic cortex, hypocellularity of bone marrow, and lymphoid elements in the spleen and Peyer's patches were observed (Moore et al. 1979).

One study evaluated immune function following a single dose exposure to 2,3,4,7,8-pentaCDF (Johnson et al. 2000). An ED_{50} of 10.119 was calculated for a 50% reduction in the response to sheep red blood cells (SRBCs).

1,2,3,6,7,8-HexaCDF. Severe thymic atrophy was observed in rats exposed to 20 μg/kg/day 1,2,3,6,7,8-hexaCDF in the diet for 13 weeks; no alterations were observed at 2 μg/kg/day (Pluess et al. 1988a).

1,2,3,4,6,7,8-HeptaCDF. An ED_{50} of 208 µg/kg for decreased antibody response to SRBCs was estimated in mice receiving a single dose of 1,2,3,4,6,7,8-heptaCDF (Kerkvliet et al. 1985).

Mixed Congeners. A decrease in thymus weight was observed in rats fed ≈44 µg/kg/day of a CDF mixture similar to that in Yusho oil for 10 days (Kunita et al. 1984). Dietary exposure to an uncharacterized mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks caused decreased thymus weight at ≥97 µg/kg/day in Sprague-Dawley rats (Oishi et al. 1978). Thymus weights were decreased in ICR/JCL mice treated with four weekly 100 µg/kg gavage doses of a mixture containing 88% pentaCDFs and 12% tetraCDFs (congeners not identified) (Oishi and Hiraga 1980); spleen weights were unaffected.

Studies of mortality from injected Escherichia coli lipopolysaccharide endotoxin in mice treated with four weekly 100 µg/kg doses of a pentaCDFs/tetraCDFs mixture were inconclusive (Oishi and Hiraga 1980).

Mechanisms. The immunotoxicity of CDFs, chlorinated dibenzo-*p*-dioxins (CDDs), and PCBs appears to be associated with binding to the Ah receptor (Section 2.3.5) (Harper et al. 1993; Vos and Luster 1989). This receptor has been identified in various tissues, including human and murine lymphocytes, thymic epithelial cells, and bone marrow cells. Thymic atrophy and suppressed antibody responses, induced by CDF, 2,3,7,8-TCDD, and/or PCB congeners, have been shown to be Ah receptor-mediated. Although there is evidence that the immunotoxicity of CDFs and related chlorinated aromatic compounds is associated with the Ah receptor, the mechanisms responsible for toxicity following interaction of the receptor-ligand complex with the Ah locus are unknown (Vos and Luster 1989). There is some evidence that additional loci may be involved and that these compounds can directly affect the thymic epithelium, leading to thymic atrophy and suppression of cell-mediated immunity.

Studies with 2,3,7,8-TCDD, as reviewed by Marshall and Kerkvliet (2010), provide information on mechanisms of immunotoxicity that are likely relevant to CDFs. The major cells of the immune system express Ah receptor; the effects associated with 2,3,7,8-TCDD Ah receptor activation is dependent on the cell type, the cell's activation status, and the type of antigenic stimulation. The innate and adaptive immune systems are affected. In the innate system, 2,3,7,8-TCDD alters the function of the dendritic cells. Initially, the dendritic cells expressed increased levels of major histocompatibility complex (MHC) class II molecules, intercellular adhesion molecule type 1 (ICAM-1) and CD24 adhesion molecules, costimulatory molecule CD40, and IL-2; an increase in T-cell stimulating ability was also observed. However, 4–7 days after mice were exposed to 2,3,7,8-TCDD, there were decreases in the number of

dendritic cells in the spleen and increased Fas-mediated apoptosis of bone marrow derived dendritic cells. The decrease in the number of dendritic cells likely results in a decrease in the strength and duration of a T-cell-mediated response. Other Ah receptor-mediated effects on dendritic cells included altered signaling of the canonical and noncanonical NF-κB pathways. In the adaptive immune system, 2,3,7,8-TCDD has a number of targets including B cells, $CD4^+$ T cells, and $CD8^+$ T cells. 2,3,7,8-TCDD exposure can result in the premature cessation of T-cell proliferation and inhibition of cytotoxic T lymphocyte activation. 2,3,7,8-TCDD inhibits $CD4^+$ T cell differentiation into T helper 1, 2, and 17 cells (Th1, Th2, and Th17) and suppresses Th1-, Th2-, and Th17-mediated responses. 2,3,7,8-TCDD also appears to induce the development of adaptive T regulatory cells (Tregs) that do not express Foxp3 and increase the number of Foxp3 positive Tregs.

A study with 2,3,7,8-TCDD in mice found alterations in the gut microbiome, which resulted in increased production of myeloid derived-suppressor cells (MDSCs) via Ah receptor activation (Neamah et al. 2020). The MDSCs have been shown to be immunosuppressive.

Summary. In conclusion, available studies suggest that CDFs have the potential to impair immunocompetence and that thymic effects are part of the spectrum of adverse effects on the immune system. Immunologic effects were observed in all animal species tested, but mice appear to be less sensitive than other rodents and monkeys. Based on the animal data, the most potent congeners are those substituted in the 2,3,7,8- positions, particularly, 2,3,4,7,8-pentaCDF.

2.15 NEUROLOGICAL

Various neurological symptoms, including numbness, weakness and neuralgia of limbs, hypesthesia, and headaches, were common in Yusho and Yu-Cheng victims (Chia and Chu 1984, 1985; Kuratsune 1989; Rogan 1989). Conduction velocities were reduced in sensory nerves (radial and/or sural) in 9 of 23 Yusho cohort members examined soon after poisoning (Kuroiwa et al. 1969). Sensory fibers appear to be preferentially affected, as conduction velocities in motor nerves (ulnar and tibial) were reduced in only two cases and motor functions were normal. Follow-up studies were not performed on the Yusho cohort, but disappearance of related symptoms and signs indicated that the effects on nerve conduction did not persist. Reduced sensory and motor nerve conduction velocities also occurred in Yu-Cheng cohort members (Chen et al. 1985b; Chia and Chu 1984, 1985). Evaluation of 110 members in the Yu-Cheng cohort within 1 year of exposure showed abnormally slow sensory nerve (median and ulnar) and motor nerve (tibial and peroneal) conduction velocities in ≈44 and 22% of the patients, respectively (Chen et al.

1985b). All of the subjects had developed eye and skin manifestations of toxicity, but there were no significant correlations between nerve conduction values and blood levels of PCBs, CDFs or PCQs. Electroencephalographic examination of Yu-Cheng cohort members did not show any abnormalities potentially indicative of central nervous system damage (Chia and Chu 1984, 1985).

Several studies have followed up on the Yusho and Yu-Cheng cohorts. Yu et al. (1997) did not find increases in deaths from mental or psychoneurotic disorders among the Yu-Cheng cohort during the 1979–1991 time period. Members of the Yusho cohort reported a number of neurological effects including increased prevalence of headaches, nerve pain, forgetfulness, prone to losing temper and irritability, insomnia, anxiety, vertigo, impaired hearing, numbness in extremities, body cramping, and muscle pain (Akahane et al. 2018). An increased prevalence of headaches was also reported in the Yu-Cheng cohort (Guo et al. 1999). Associations between serum total CDF levels (mean of 264.26 pg/g lipid) and the prevalence of numbness (Imamura et al. 2007) was found in the Yusho cohort. In another study of the Yusho cohort, depression and severe insomnia were reported in participants with serum 2,3,4,7,8-pentaCDF levels of ≥72.27 pg/g lipid (Kondo et al. 2018). A study of elderly cohort Yu-Cheng cohort members reported a reduced learning ability among females, with no effects in males (Lin et al. 2008, 2010). Neurobehavioral deficits have also been observed in children born to mothers in the Yu-Cheng cohort (see Section 2.17).

2,3,7,8-TetraCDF. Single gavage doses of ≤15 µg/kg to guinea pigs or ≤6,000 µg/kg to mice produced no histological alterations in the brain in the animals examined 30 days after exposure (Moore et al. 1976, 1979).

2,3,4,7,8-PentaCDF. Signs of toxicity in rats given single, lethal doses of 2,3,4,7,8-pentaCDF included piloerection, splayed and hunched posture, and hypoactivity at ≥1,000 µg/kg, and tremors and lacrimation in one animal at 2,000 µg/kg (Brewster et al. 1988). No histological alterations were observed in the brain of guinea pigs administered a single dose of ≤30 µg/kg 2,3,4,7,8-pentaCDF and examined 30 days later (Moore et al. 1979) or in rats administered via gavage ≤0.2 µg/kg 5 days/week for 2 years (NTP 2006).

Mixed Congeners. Dietary exposure to an uncharacterized mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks caused grossly observable cerebral edema and “flabby” brain appearance in Sprague-Dawley rats at ≥97 µg/kg/day, but slight fluid accumulation also occurred in the thorax and abdomen (Oishi et al. 1978).

Summary. Studies of the Yusho and Yu-Cheng cohorts have consistently reported neurological effects. Studies in laboratory animal have not reported direct effects on the central nervous system; observed effects were probably secondary to other changes (e.g., wasting syndrome, stress) occurring in intoxicated or dying animals. However, there were no studies evaluating potential effects on neurobehavioral function.

2.16 REPRODUCTIVE

The potential reproductive toxicity of CDFs in humans was evaluated in studies of the Yusho and Yu-Cheng cohorts, in populations living in areas of Vietnam that were highly contaminated with Agent Orange, and in the general population. Studies that evaluated possible associations between serum levels of CDFs and a health outcome are summarized in Table 2-7 (Cai et al. 2011; Martinez-Zamora et al. 2015; Sun et al. 2016, 2017; Tsukimori et al. 2008; Van Luong et al. 2018).

Table 2-7. Results of Epidemiological Studies Evaluating Exposure to CDFs and Reproductive Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Cai et al. 2011 Case control, 10 cases with endometriosis, 7 controls (Japan)	Serum total CDF 7.5 pg/g lipid (cases) and 6.9 pg/g lipid (controls)	Endometriosis	↔
Van Luong et al. 2018 Cross sectional, 42 men living in areas highly exposed to Agent Orange (Vietnam)	Serum 2,3,7,8-tetraCDF geometric mean 7.0 pg/g lipid	FSH	↔
		LH	↔
		Progesterone	↔
		Prolactin	↔
		Estradiol	↔
		Testosterone	↓
	Serum 1,2,3,7,8-pentaCDF geometric mean 4.8 pg/g lipid	FSH	↔
		LH	↔
		Progesterone	↔
		Prolactin	↔
		Estradiol	↔
		Testosterone	↓

Table 2-7. Results of Epidemiological Studies Evaluating Exposure to CDFs and Reproductive Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Serum 2,3,4,7,8-pentaCDF geometric mean13.2 pg/g lipid	FSH	↔
		LH	↔
		Progesterone	↔
		Prolactin	↔
		Estradiol	↔
		Testosterone	↔
	Serum 1,2,3,4,7,8-hexaCDF geometric mean 17.3 pg/g lipid	FSH	↔
		LH	↔
		Progesterone	↔
		Prolactin	↔
		Estradiol	↔
		Testosterone	↔
	Serum 1,2,3,6,7,8-hexaCDF geometric mean 12.8 pg/g lipid	FSH	↔
		LH	↔
		Progesterone	↔
		Prolactin	↑
		Estradiol	↓
		Testosterone	↔
	Serum 1,2,3,7,8,9-hexaCDF geometric mean 4.9 pg/g lipid	FSH	↔
		LH	↔
		Progesterone	↔
		Prolactin	↔
		Estradiol	↔
		Testosterone	↔
	Serum 2,3,4,6,7,8-hexaCDF geometric mean 5.5 pg/g lipid	FSH	↔
		LH	↔
		Progesterone	↔
		Prolactin	↔
		Estradiol	↔
		Testosterone	↓
	Serum 1,2,3,4,6,7,8-heptaCDF geometric mean 17.6 pg/g lipid	FSH	↔
		LH	↔
		Progesterone	↔
		Prolactin	↔
		Estradiol	↓
		Testosterone	↓

Table 2-7. Results of Epidemiological Studies Evaluating Exposure to CDFs and Reproductive Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Serum 1,2,3,4,7,8,9-heptaCDF geometric mean 6.1 pg/g lipid	FSH	↔
		LH	↔
		Progesterone	↔
		Prolactin	↔
		Estradiol	↔
		Testosterone	↓
	Serum octaCDF geometric mean 16.7 pg/g lipid	FSH	↔
		LH	↔
		Progesterone	↔
		Prolactin	↔
		Estradiol	↔
		Testosterone	↓
Martinez-Zamora et al. 2015 Case control, 30 cases with deep infiltrating endometriosis and 30 controls (Spain)	Serum mean 2,3,4,7,8-pentaCDF 4.98 pg/g lipid (cases) and 3.95 pg/g lipid (controls)	Deep infiltrating endometriosis	↑
Sun et al. 2016 Cross sectional, 97 men living in areas highly exposed to Agent Orange and 85 controls (Vietnam)	Serum geometric mean 2,3,7,8-tetraCDF 0.16 pg/g lipid (exposed) and 0.15 pg/g lipid (controls)	Prostate specific antigen	↔
	Serum geometric mean 1,2,3,7,8-pentaCDF 0.06 pg/g lipid (exposed) and 0.04 pg/g lipid (controls)	Prostate specific antigen	↔
	Serum geometric mean 2,3,4,7,8-pentaCDF 3.98 pg/g lipid (exposed) and 2.14 pg/g lipid (controls)	Prostate specific antigen	↔
	Serum geometric mean 1,2,3,4,7,8-hexaCDF 2.75 pg/g lipid (exposed) and 0.44 pg/g lipid (controls)	Prostate specific antigen	↔
	Serum geometric mean 1,2,3,6,7,8-hexaCDF 2.09 pg/g lipid (exposed) and 0.49 pg/g lipid (controls)	Prostate specific antigen	↔
	Serum geometric mean 1,2,3,7,8,9-hexaCDF 0.31 pg/g lipid (exposed) and 0.26 pg/g lipid (controls)	Prostate specific antigen	↔

Table 2-7. Results of Epidemiological Studies Evaluating Exposure to CDFs and Reproductive Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Serum geometric mean 2,3,4,6,7,8-hexaCDF 0.38 pg/g lipid (exposed) and 0.26 pg/g lipid (controls)	Prostate specific antigen	↔
	Serum geometric mean 1,2,3,4,6,7,8-heptaCDF 0.41 pg/g lipid (exposed) and 0.04 pg/g lipid (controls)	Prostate specific antigen	↔
	Serum geometric mean 1,2,3,4,7,8,9-heptaCDF 0.04 pg/g lipid (exposed) and 0.03 pg/g lipid (controls)	Prostate specific antigen	↔
	Serum geometric mean octaCDF 0.0023 pg/g lipid (exposed) and 0.0020 pg/g lipid (controls)	Prostate specific antigen	↔
Sun et al. 2017 Cross-sectional, 50 men living in areas highly exposed to Agent Orange and 48 controls (Vietnam)	Serum geometric mean 1,2,3,4,7,8-hexaCDF 32.8 pg/g lipid (exposed) and 3.9 pg/g lipid (controls)	Testosterone	↔
		DHT	↔
		DHEA	↔
		Estradiol	↔
		3β-HSD	↔
	Serum geometric mean 1,2,3,6,7,8-hexaCDF 24.9 pg/g lipid (exposed) and 4.4 pg/g lipid (controls)	Testosterone	↔
		DHT	↔
		DHEA	↔
		Estradiol	↔
		3β-HSD	↔
	Serum geometric mean 1,2,3,4,6,7,8-heptaCDF 47.4 pg/g lipid (exposed) and 4.2 pg/g lipid (controls)	Testosterone	↔
		DHT	↔
		DHEA	↔
		Estradiol	↔
		3β-HSD	↔

Table 2-7. Results of Epidemiological Studies Evaluating Exposure to CDFs and Reproductive Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Tsukimori et al. 2008 Retrospective, 214 women in the Yusho cohort who gave birth prior to exposure (152 women, 204 births), during 1968–1977 (69 women, 122 births), 1978–1987 (21 women, 88 births), and 1988–2003 (15 women, 98 births) (Japan)	Serum estimated geometric mean 2,3,4,7,8-pentaCDF • Prior to exposure 7.25 pg/g lipid (general population levels) • 1968–1977 2899.3 pg/g lipid • 1978–1987 697.7 pg/g lipid • 1988–2003 39.5 pg/g lipid	Induced abortion	↑
		Spontaneous abortion	↑
		Preterm delivery (1968–1977)	↑
		Pregnancy loss	↑

↑ = association between biomarker level and outcome; ↓ = inverse association between biomarker level and outcome; ↔ = no association between biomarker level and outcome; CDF = chlorodibenzofuran; DHEA = dehydroepiandrosterone; DHT = dihydrotestosterone; FSH = follicle stimulating hormone; 3β-HSD = 3β-hydroxysteroid dehydrogenase; LH = luteinizing hormone

Irregular menstrual cycles and abnormal basal body temperature patterns were observed in ≈60 and 85% of female Yusho cohort members, respectively (Kusuda 1971). These alterations were accompanied by decreased urinary excretion of estrogens, pregnanediol, and pregnanetriol, and possibly suggest corpus luteum insufficiency and retarded follicular maturation. In a follow-up study, Yusho cohort members reported an increased prevalence of abnormal uterine bleeding, menorrhagia, and hypomenorrhea (Akahane et al. 2018). A study of the Yu-Cheng cohort found slightly shorter menstrual cycle lengths, with a greater reduction among women with skin lesions (Yang et al. 2011). No effects on menstrual cycle irregularity or dysmenorrhea were observed. However, among women exposed prior to menarche, a reduction in cycle length and longer days of menstrual flow were observed. Two general population studies examined the possible relationship between CDF exposure and risk of endometriosis (Table 2-7). Martínez-Zamora et al. (2015) found higher serum 2,3,4,7,8-pentaCDF levels among women with deep infiltrating endometriosis; the study also found associations for two CDD congeners (2,3,7,8-TCDD and 1,2,3,7,8-pentaCDD). The second study found no differences in total serum CDF levels between women with endometriosis and those without endometriosis (Cai et al. 2011).

An increase in self-reported male impotency was found among men in the Yusho cohort (Akahane et al. 2018). Hsu et al. (2016) reported an increase in abnormal sperm morphology in the Yu-Cheng cohort; there were no alterations in semen volume, sperm count, or percentage of motile sperm. The study also reported a nonsignificant increase in the ratio of normal X to normal Y sperm. Three studies of

Vietnamese men living in areas sprayed with Agent Orange examined potential male reproductive effects associated with elevated levels of CDF congeners (Table 2-7); it is noted that Agent Orange was contaminated with 2,3,7,8-TCDD and the observed effects may be due to dioxin exposure. Van Luong et al. (2018) reported inverse associations between serum testosterone levels and serum 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, 2,3,4,6,7,8-hexaCDF, 1,2,3,4,6,7,8-heptaCDF, 1,2,3,4,7,8,9-heptaCDF, and octaCDF levels; inverse associations between serum estradiol levels and serum 1,2,3,6,7,8-hexaCDF, and 1,2,3,4,6,7,8-heptaCDF levels; and an association between serum prolactin levels and 1,2,3,6,7,8-hexaCDF and 1,2,3,4,6,7,8-heptaCDF. In contrast, Sun et al. (2017) found no associations between CDF congener levels and steroid hormone levels (testosterone, dihydrotestosterone, dehydroepiandrosterone, estradiol, and 3β-hydroxysteroid dehydrogenase). The third study found no associations between prostate specific antigen (PSA) levels and individual CDF congener levels (Sun et al. 2016).

There is limited epidemiological information on the potential effect of CDFs on fertility. Tsukimori et al. (2008) found an increased risk of induced abortions and preterm deliveries in the 10-year period after the Yusho incident but did not find alterations in the next two 10-year periods. The study also found associations between serum pentaCDF levels and induced abortion, spontaneous abortion, preterm delivery, and pregnancy loss (Table 2-7). A study of Yu-Cheng women found a prolonged time to pregnancy and reduced fertility (Yang et al. 2008).

There is limited information on the potential reproductive toxicity of CDFs in laboratory animals.

2,3,7,8-TetraCDF. Hypocellularity of the seminiferous tubules was observed in guinea pigs given single lethal gavage doses of ≥10 µg/kg/day 2,3,7,8-tetraCDF (Moore et al. 1979).

1,2,3,4,8-PentaCDF. Histology of the testis, ovary, and uterus was normal in rats administered dietary dosages of ≤600 µg/kg/day 1,2,3,4,8-pentaCDF for 13 weeks (Pluess et al. 1988a).

1,2,3,7,8-PentaCDF. A 13-week dietary exposure to ≤20 µg/kg/day did not result in histological alterations in the testis, ovary, or uterus of rats (Pluess et al. 1988a).

2,3,4,7,8-PentaCDF. A single lethal gavage dose of ≥10 µg/kg 2,3,4,7,8-pentaCDF resulted in hypocellularity of the seminiferous tubules in guinea pigs (Moore et al. 1979). There were no testicular histological changes in rats treated with a single gavage dose of ≤2,000 µg/kg 2,3,4,7,8-pentaCDF

(Brewster et al. 1988). No histological alterations were observed in the testis, ovary, or uterus of rats exposed to ≤20 µg/kg/day 2,3,4,7,8-pentaCDF in the diet for 13 weeks (Pluess et al. 1988b), and no uterine alterations were observed in rats administered 0.2 µg/kg 2,3,4,7,8-pentaCDF 5 days/week for 14 or 31 weeks (NTP 2006). However, in a chronic gavage study, squamous metaplasia was observed in the uterus of rats administered ≥0.044 µg/kg 2,3,4,7,8-pentaCDF for 2 years (NTP 2006).

Mixed Congeners. Dietary exposure to an uncharacterized mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks caused increased testes weight at ≥97 µg/kg/day and decreased seminal vesicle and ventral prostate weights and decreased testicular testosterone concentration at 960 µg/kg/day in Sprague-Dawley rats (Oishi et al. 1978). The apparent increase in testes weight may be due to concurrent depression of total body weight.

Summary. Irregular menstrual cycles have been reported among the Yusho and Yu-Cheng cohorts. Histological alterations have not been reported in the reproductive tissues of animals exposed to nonlethal doses for acute or intermediate durations. Uterine lesions were observed in rats chronically exposed to 2,3,4,7,8-pentaCDF. No animal studies evaluated reproductive function.

2.17 DEVELOPMENTAL

A number of developmental effects were reported in children born to mothers in the Yusho or Yu-Cheng cohorts, and associations between CDF levels and developmental outcomes were observed in children living in areas of Vietnam that were sprayed with Agent Orange and in general population studies. It is noted that communities living in Agent Orange contaminated areas were likely exposed to high levels of CDDs, particularly 2,3,7,8-TCDD. Studies that evaluated possible associations between maternal serum or breast milk CDF levels and health outcomes are summarized in Table 2-8; effects examined include birth outcome and growth (Konishi et al. 2009; Tawara et al. 2009; Van Tung et al. 2016; Vartiainen et al. 1998; Wang et al. 2019), endocrine (Nagayama et al. 2007; Oanh et al. 2018), neurodevelopmental (Huisman et al. 1995; Li et al. 2015a; Nakajima et al. 2006, 2017; Nguyen et al. 2018; Nishijo et al. 2012; Tai et al. 2013), and other effects (Pluim et al. 1994). Observed developmental effects included skin lesions, alterations in birth outcome, neurodevelopmental delays, altered reproductive system development, and altered immune system development. Skin lesions were commonly observed in children born to mothers in the Yusho or Yu-Cheng cohorts. The dermal changes were consistent with those observed in exposed adults (see Section 2.11) and include hyperpigmentation of the skin, nails, and gingivae; deformed nails; conjunctivitis; and acne (Funatsu et al. 1971; Gladen et al. 1990; Hsu et al.

1985, 1993; Rogan et al. 1988; Taki et al. 1969; Yamaguchi et al. 1971; Yoshimura 1974). These effects generally diminished as the babies grew older.

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Huisman et al. 1995 Prospective, 418 mother-infant pairs (Netherlands)	Breast milk median 2,3,7,8-tetraCDF 0.73 mg/kg lipid	Neurological optimality score	↑
	Breast milk median 1,2,3,7,8-pentaCDF 0.09 mg/kg lipid	Neurological optimality score	↔
	Breast milk median 2,3,4,7,8-pentaCDF 6.48 mg/kg lipid	Neurological optimality score	↑
	Breast milk median 1,2,3,4,7,8-hexaCDF 5.59 mg/kg lipid	Neurological optimality score	↔
	Breast milk median 1,2,3,6,7,8-hexaCDF 0.08 mg/kg lipid	Neurological optimality score	↔
	Breast milk median 1,2,3,7,8,9-hexaCDF mg/kg lipid	Neurological optimality score	↔
	Breast milk median 2,3,4,6,7,8-hexaCDF 3.00 mg/kg lipid	Neurological optimality score	↔
	Breast milk median 1,2,3,4,6,7,8-heptaCDF 6.32 mg/kg lipid	Neurological optimality score	↔
	Breast milk median 1,2,3,4,7,8,9-heptaCDF 0.19 mg/kg lipid	Neurological optimality score	↔
	Breast milk median octaCDF 0.38 mg/kg lipid	Neurological optimality score	↔
Konishi et al. 2009 Prospective, 514 mother-infant pairs (Japan)	Maternal serum mean total CDFs 20.5 pg/g lipid	Birth weight	↓
	Maternal serum mean 2,3,7,8-tetraCDF not reported	Birth weight	↔
	Maternal serum mean 2,3,4,7,8-pentaCDF not reported	Birth weight	↓
	Maternal serum mean 1,2,3,4,7,8-hexaCDF not reported	Birth weight	↔
	Maternal serum mean 1,2,3,6,7,8-hexaCDF not reported	Birth weight	↔
	Maternal serum mean 1,2,3,4,6,7,8-heptaCDF not reported	Birth weight	↔

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Li et al. 2015b Retrospective, 53 prenatally exposed adults (21 years of age) (Yu-Cheng) and 87 referents (Taiwan)	Estimated serum median 2,3,4,7,8-pentaCDF 1298.72 pg/g lipid	Hearing threshold at 250, 500, and 1,000 Hz in right ear and 500 and 4,000 Hz in left ear	↑
		Average hearing threshold in right and left ears	↑
		DPOAE at 1.5 and 2 Hz in right ear	↓
		Average DPOAE in right and left ears	↓
Nagayama et al. 2007 Case-control, 34 case (22 neonates diagnosed with cretinism, 4 with hyper-TSH-emia, and 4 negative in re-evaluation) and 102 controls (Japan)	Breast milk mean total CDF TEQ[a] 0.16 pg/g lipid (infants with cretinism), 0.09 pg/g lipid (hyper-TSH-emia), 0.09 pg/g lipid (negative), and 0.06 pg/g lipid (control)	Induction of cretinism	↑
Nakajima et al. 2006 Prospective, 134 mother-infant (6 months of age) pairs (Japan)	Maternal serum mean 2,3,7,8-tetraCDF 0.7 pg/g lipid	MDI	↔
		PDI	↓
	Maternal serum mean 1,2,3,7,8-pentaCDF 0.6 pg/g lipid	MDI	↔
		PDI	↓
	Maternal serum mean 2,3,4,7,8-pentaCDF 6.5 pg/g lipid	MDI	↔
		PDI	↔
	Maternal serum mean 1,2,3,4,7,8-hexaCDF 2.6 pg/g lipid	MDI	↔
		PDI	↔
	Maternal serum mean 1,2,3,6,7,8-hexaCDF 3.0 pg/g lipid	MDI	↔
		PDI	↓
	Maternal serum mean 2,3,4,6,7,8-hexaCDF 1.1 pg/g lipid	MDI	↔
		PDI	↔
	Maternal serum mean 1,2,3,4,6,7,8-heptaCDF 3.1 pg/g lipid	MDI	↔
		PDI	↔
	Maternal serum mean octaCDF 2.1 pg/g lipid	MDI	↔
		PDI	↔
	Maternal serum mean total CDF TEQ[a] 4.2 pg/g lipid	MDI	↔
		PDI	↔

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Nakajima et al. 2017 Prospective, mother-infant pairs (190 pairs at 6 months of age and 121 pairs at 18 months of age) (Japan)	Maternal serum 75th percentile 2,3,7,8-tetraCDF 1.1 pg/g lipid	MDI at 6 months	↔
		PDI at 6 months	↓ (males only)
		MDI at 18 months	↔
		PDI at 18 months	↔
	Maternal serum 1,2,3,7,8-pentaCDF not detected below 75th percentile	MDI at 6 months	↔
		PDI at 6 months	↓ (males only)
		MDI at 18 months	↔
		PDI at 18 months	↔
	Maternal serum median 2,3,4,7,8-pentaCDF 5.8 pg/g lipid	MDI at 6 months	↔
		PDI at 6 months	↔
		MDI at 18 months	↔
		PDI at 18 months	↔
	Maternal serum median 1,2,3,4,7,8-hexaCDF 2.5 pg/g lipid	MDI at 6 months	↔
		PDI at 6 months	↔
		MDI at 18 months	↔
		PDI at 18 months	↔
	Maternal serum median 1,2,3,6,7,8-hexaCDF 2.7 pg/g lipid	MDI at 6 months	↔
		PDI at 6 months	↔
		MDI at 18 months	↔
		PDI at 18 months	↔
	Maternal serum 2,3,4,6,7,8-hexaCDF not detected below 75th percentile	MDI at 6 months	↔
		PDI at 6 months	↔
		MDI at 18 months	↔
		PDI at 18 months	↔
	Maternal serum 1,2,3,7,8,9-hexaCDF not detected below 75th percentile	MDI at 6 months	↔
		PDI at 6 months	↔
		MDI at 18 months	↔
		PDI at 18 months	↔
	Maternal serum median 1,2,3,4,6,7,8-heptaCDF 2.4 pg/g lipid	MDI at 6 months	↔
		PDI at 6 months	↔
		MDI at 18 months	↓ (females only)
		PDI at 18 months	↔
	Maternal serum octaCDF not detected below 75th percentile	MDI at 6 months	↔
		PDI at 6 months	↔
		MDI at 18 months	↔
		PDI at 18 months	↔

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Maternal serum median total CDF 19.7 pg/g lipid	MDI at 6 months	↔
		PDI at 6 months	↔
		MDI at 18 months	↔
		PDI at 18 months	↔
Nguyen et al. 2018 Prospective, 185 mother-infant (3 years old) pairs (106 males and 79 females) living in areas highly exposed to Agent Orange (Vietnam)	Breast milk median 2,3,7,8-tetraCDF 0.5 pg/g lipid males and 0.6 pg/g lipid females	Tests of eating behavior	↔
	Breast milk median 1,2,3,7,8-pentaCDF 1.2 pg/g lipid males and 1.3 pg/g lipid females	Tests of eating behavior	↔
	Breast milk median 2,3,4,7,8-pentaCDF 7.2 pg/g lipid males and 8.1 pg/g lipid females	Tests of eating behavior	↔
	Breast milk median 1,2,3,4,7,8-pentaCDF 16.5 pg/g lipid males and 19.9 pg/g lipid females	Tests of eating behavior	↔
	Breast milk median 1,2,3,6,7,8-hexaCDF 10.8 pg/g lipid males and 12.0 pg/g lipid females	Tests of eating behavior	↔
	Breast milk median 1,2,3,7,8,9-hexaCDF 0.2 pg/g lipid males and 0.3 pg/g lipid females	Tests of eating behavior	↓ enjoyment of food test ↔ for 4 other tests
	Breast milk median 1,2,3,7,8,9-hexaCDF 0.2 pg/g lipid males and 0.3 pg/g lipid females	Tests of eating behavior	↔
	Breast milk median 2,3,4,6,7,8-hexaCDF 1.3 pg/g lipid males and 1.5 pg/g lipid females	Tests of eating behavior	↔
	Breast milk median 1,2,3,4,6,7,8-heptaCDF 10.8 pg/g lipid males and 13.5 pg/g lipid females	Tests of eating behavior	↔
	Breast milk median 1,2,3,4,7,8,9-heptaCDF 1.2 pg/g lipid males and 1.6 pg/g lipid females	Tests of eating behavior	↓ enjoyment of food test ↔ for 4 other tests

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Breast milk median octaCDF 0.5 pg/g lipid males and 0.5 pg/g lipid females	Tests of eating behavior	↓ enjoyment of food, food responsiveness, and food approach tests ↔ for 2 other tests
	Breast milk median total CDF TEQ[b] 5.2 pg/g lipid males and 5.7 pg/g lipid females	Tests of eating behavior	↔
Nishijo et al. 2012 Prospective, 122 mother-infant (3 years old) pairs living in areas highly exposed to Agent Orange (Vietnam)	Breast milk 2,3,7,8-tetraCDF levels not reported	Autism spectrum tests	↓ Atypical language score ↔ other autism tests
	Breast milk 1,2,3,7,8-pentaCDF levels not reported	Autism spectrum tests	↑ Social communication and social/ emotional reciprocity scores ↔ other autism tests
	Breast milk 2,3,4,7,8-pentaCDF levels not reported	Autism spectrum tests	↔
	Breast milk 1,2,3,4,7,8-hexaCDF levels not reported	Autism spectrum tests	↔
	Breast milk 1,2,3,6,7,8-hexaCDF levels not reported	Autism spectrum tests	↔
	Breast milk 1,2,3,7,8,9-hexaCDF levels not reported	Autism spectrum tests	↔
	Breast milk 2,3,4,6,7,8-hexaCDF levels not reported	Autism spectrum tests	↓ Attention/self-regulation score ↔ other autism tests
	Breast milk 1,2,3,4,6,7,8-heptaCDF levels not reported	Autism spectrum tests	↔
	Breast milk 1,2,3,4,7,8,9-heptaCDF levels not reported	Autism spectrum tests	↓ Attention/self-regulation score ↔ other autism tests
	Breast milk octaCDF levels not reported	Autism spectrum tests	↔

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Oanh et al. 2018 Prospective, 35 mother-infant (5 years old) pairs living in areas highly exposed to Agent Orange and 50 mother-infant controls (Vietnam)	Breast milk geometric mean 2,3,7,8-tetraCDF 0.6 pg/g lipid in hot spot and 0.6 pg/g lipid in control area	Androstenedione	↑
		DHEA	↔
		Testosterone	↔
	Breast milk geometric mean 1,2,3,7,8-pentaCDF 1.8 pg/g lipid in hot spot and 0.4 pg/g lipid in control area	Androstenedione	↔
		DHEA	↓
		Testosterone	↓
	Breast milk geometric mean 2,3,4,7,8-pentaCDF 5.6 pg/g lipid in hot spot and 3.0 pg/g lipid in control area	Androstenedione	↑
		DHEA	↓
		Testosterone	↓
	Breast milk geometric mean 1,2,3,4,7,8-hexaCDF 13.2 pg/g lipid in hot spot and 1.9 pg/g lipid in control area	Androstenedione	↑
		DHEA	↓
		Testosterone	↓
	Breast milk geometric mean 1,2,3,6,7,8-hexaCDF 7.7 pg/g lipid in hot spot and 1.6 pg/g lipid in control area	Androstenedione	↑
		DHEA	↓
		Testosterone	↓
	Breast milk geometric mean 1,2,3,7,8,9-hexaCDF 0.3 pg/g lipid in hot spot and 0.1 pg/g lipid in control area	Androstenedione	↑
		DHEA	↓
		Testosterone	↔
	Breast milk geometric mean 2,3,4,6,7,8-hexaCDF 1.3 pg/g lipid in hot spot and 0.5 pg/g lipid in control area	Androstenedione	↑
		DHEA	↓
		Testosterone	↓
	Breast milk geometric mean 1,2,3,4,6,7,8-heptaCDF 14.0 pg/g lipid in hot spot and 1.4 pg/g lipid in control area	Androstenedione	↑
		DHEA	↓
		Testosterone	↓
	Breast milk geometric mean 1,2,3,4,7,8,9-heptaCDF 1.4 pg/g lipid in hot spot and 0.2 pg/g lipid in control area	Androstenedione	↑
		DHEA	↓
		Testosterone	↓
	Breast milk geometric mean octaCDF 1.0 pg/g lipid in hot spot and 0.3 pg/g lipid in control area	Androstenedione	↑
		DHEA	↔
		Testosterone	↔
	Breast milk geometric mean total CDF TEQ[b] 4.3 pg/g lipid in hot spot and 1.4 pg/g lipid in control area	Androstenedione	↑
		DHEA	↓
		Testosterone	↓

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Pluim et al. 1994 Prospective, 6–8 mother-infant (11 weeks old) pairs (Netherlands)	Breast milk 2,3,7,8-tetraCDF levels not reported	Vitamin K levels	↓
		PIVKA-II levels	↔
	Breast milk 2,3,4,7,8-pentaCDF levels not reported	Vitamin K levels	↔
		PIVKA-II levels	↔
	Breast milk 1,2,3,4,7,8-hexaCDF levels not reported	Vitamin K levels	↔
		PIVKA-II levels	↔
	Breast milk 1,2,3,6,7,8-hexaCDF levels not reported	Vitamin K levels	↔
		PIVKA-II levels	↑
	Breast milk 1,2,3,7,8,9-hexaCDF levels not reported	Vitamin K levels	↔
		PIVKA-II levels	↔
	Breast milk 1,2,3,4,6,7,8-heptaCDF levels not reported	Vitamin K levels	↓
		PIVKA-II levels	↔
	Breast milk octaCDF levels not reported	Vitamin K levels	↔
		PIVKA-II levels	↔
Tai et al. 2013 Prospective, 158 mother-infant (3 years old) pairs living in areas highly exposed to Agent Orange (Vietnam)	Breast milk 2,3,7,8-tetraCDF levels not reported	Cognitive composite score	↔
		Receptive score	↔
		Expressive communication	↔
		Language composite score	↔
		Fine motor	↔
		Gross motor	↔
		Motor composite score	↔
	Breast milk 1,2,3,7,8-pentaCDF levels not reported	Cognitive composite score	↔
		Receptive score	↓
		Expressive communication	↓
		Language composite score	↓
		Fine motor	↓
		Gross motor	↔
		Motor composite score	↓

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Breast milk 2,3,4,7,8-pentaCDF levels not reported	Cognitive composite score	↔
		Receptive score	↔
		Expressive communication	↔
		Language composite score	↔
		Fine motor	↔
		Gross motor	↔
		Motor composite score	↔
	Breast milk 1,2,3,4,7,8-hexaCDF levels not reported	Cognitive composite score	↔
		Receptive score	↓
		Expressive communication	↔
		Language composite score	↓
		Fine motor	↔
		Gross motor	↔
		Motor composite score	↔
	Breast milk 1,2,3,6,7,8-hexaCDF levels not reported	Cognitive composite score	↔
		Receptive score	↓
		Expressive communication	↔
		Language composite score	↓
		Fine motor	↔
		Gross motor	↔
		Motor composite score	↔
	Breast milk 1,2,3,7,8,9-hexaCDF levels not reported	Cognitive composite score	↔
		Receptive score	↓
		Expressive communication	↓
		Language composite score	↓
		Fine motor	↔
		Gross motor	↔
		Motor composite score	↔

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Breast milk 2,3,4,6,7,8-hexaCDF levels not reported	Cognitive composite score	↔
		Receptive score	↓
		Expressive communication	↔
		Language composite score	↓
		Fine motor	↔
		Gross motor	↔
		Motor composite score	↔
	Breast milk 1,2,3,4,6,7,8-heptaCDF levels not reported	Cognitive composite score	↔
		Receptive score	↓
		Expressive communication	↔
		Language composite score	↓
		Fine motor	↔
		Gross motor	↔
		Motor composite score	↔
	Breast milk 1,2,3,4,7,8,9-heptaCDF levels not reported	Cognitive composite score	↔
		Receptive score	↔
		Expressive communication	↔
		Language composite score	↔
		Fine motor	↔
		Gross motor	↔
		Motor composite score	↔
	Breast milk octaCDF levels not reported	Cognitive composite score	↔
		Receptive score	↔
		Expressive communication	↔
		Language composite score	↔
		Fine motor	↔
		Gross motor	↔
		Motor composite score	↔

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Breast milk total CDF TEQ[b], levels not reported	Cognitive composite score	↔
		Receptive score	↔
		Expressive communication	↔
		Language composite score	↔
		Fine motor	↔
		Gross motor	↔
		Motor composite score	↔
Tawara et al. 2009 Cross sectional, 75 mother-infant pairs	Breast milk mean 2,3,7,8-tetraCDF 1.02 pg/g lipid	Birth length	↔
		Birth weight	↔
		Chest circumference	↔
		Head circumference	↔
		Gestational weeks	↔
	Breast milk mean 1,2,3,7,8-pentaCDF 0.29 pg/g lipid	Birth length	↔
		Birth weight	↔
		Chest circumference	↔
		Head circumference	↔
		Gestational weeks	↔
	Breast milk mean 2,3,4,7,8-pentaCDF 8.14 pg/g lipid	Birth length	↓
		Birth weight	↔
		Chest circumference	↔
		Head circumference	↔
		Gestational weeks	↔
	Breast milk mean 1,2,3,4,7,8-hexaCDF 2.25 pg/g lipid	Birth length	↔
		Birth weight	↔
		Chest circumference	↔
		Head circumference	↔
		Gestational weeks	↔
	Breast milk mean 1,2,3,6,7,8-hexaCDF 2.27 pg/g lipid	Birth length	↓
		Birth weight	↔
		Chest circumference	↔
		Head circumference	↔
		Gestational weeks	↔

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Breast milk mean 2,3,4,6,7,8-hexaCDF 1.46 pg/g lipid	Birth length	↓
		Birth weight	↔
		Chest circumference	↔
		Head circumference	↔
		Gestational weeks	↔
	Breast milk mean 1,2,3,7,8,9-hexaCDF 0.03 pg/g lipid	Birth length	↔
		Birth weight	↔
		Chest circumference	↔
		Head circumference	↔
		Gestational weeks	↔
	Breast milk mean 1,2,3,4,6,7,8-heptaCDF 1.19 pg/g lipid	Birth length	↔
		Birth weight	↔
		Chest circumference	↔
		Head circumference	↔
		Gestational weeks	↔
	Breast milk mean 1,2,3,4,7,8,9-heptaCDF 0.04 pg/g lipid	Birth length	↔
		Birth weight	↔
		Chest circumference	↔
		Head circumference	↔
		Gestational weeks	↔
	Breast milk mean octaCDF 0.55 pg/g lipid	Birth length	↔
		Birth weight	↔
		Chest circumference	↔
		Head circumference	↔
		Gestational weeks	↔
	Breast milk mean total CDF TEQ[a] 4.89 pg/g lipid	Birth length	↓
		Birth weight	↔
		Chest circumference	↔
		Head circumference	↔
		Gestational weeks	↔

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Van Tung et al. 2016 Prospective, 58 mother-infant pairs living in areas highly exposed to Agent Orange and 62 control pairs (Vietnam)	Breast milk mean 2,3,7,8-tetraCDF TEQ[b] 0.07 pg/g lipid in hot spot and 0.067 pg/g lipid in control area	Weight	
		• Birth	↔
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Height	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Head circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Chest circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
	Breast milk mean 1,2,3,7,8-pentaCDF TEQ[b] 0.065 pg/g lipid in hot spot and 0.014 pg/g lipid in control area	Weight	
		• Birth	↔
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Height	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Head circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Chest circumference	
		• 8-9 weeks	↔
		• 12-14 weeks	↔
	Breast milk mean 2,3,4,7,8-pentaCDF TEQ[b] 1.909 pg/g lipid in hot spot and 0.914 pg/g lipid in control area	Weight	
		• Birth	↓
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Height	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Head circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Chest circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Breast milk mean 1,2,3,4,7,8-hexaCDF TEQ[b] 1.592 pg/g lipid in hot spot and 0.196 pg/g lipid in control area	Weight	
		• Birth	↔
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Height	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Head circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Chest circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
	Breast milk mean 1,2,3,6,7,8-hexaCDF TEQ[b] 0.926 pg/g lipid in hot spot and 0.166 pg/g lipid in control area	Weight	
		• Birth	↔
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Height	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Head circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Chest circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
	Breast milk mean 1,2,3,7,8,9-hexaCDF TEQ[b] 0.041 pg/g lipid in hot spot and 0.014 pg/g lipid in control area	Weight	
		• Birth	↔
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Height	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Head circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Chest circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Breast milk mean 2,3,4,6,7,8-hexaCDF TEQ[b] 0.159 pg/g lipid in hot spot and 0.055 pg/g lipid in control area	Weight	
		• Birth	↔
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Height	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Head circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Chest circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
	Breast milk mean 1,2,3,4,6,7,8-heptaCDF TEQ[b] 0.183 pg/g lipid in hot spot and 0.015 pg/g lipid in control area	Weight	
		• Birth	↔
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Height	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Head circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Chest circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
	Breast milk mean 1,2,3,4,7,8,9-heptaCDF TEQ[b] 0.018 pg/g lipid in hot spot and 0.002 pg/g lipid in control area	Weight	
		• Birth	↔
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Height	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Head circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Chest circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Breast milk mean octaCDF TEQ[b] 0.001 pg/g lipid in hot spot and 0.000 pg/g lipid in control area	Weight	
		• Birth	↔
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Height	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Head circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Chest circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
	Breast milk mean total CDF TEQ[b] 4.965 pg/g lipid in hot spot and 1.442 pg/g lipid in control area	Weight	
		• Birth	↔
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Height	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Head circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
		Chest circumference	
		• 8–9 weeks	↔
		• 12–14 weeks	↔
Vartiainen et al. 1998 Cross sectional, 167 mother-infant pairs (Finland)	Breast milk 2,3,7,8-tetraCDF, levels not reported	Birth weight	↓
	Breast milk 1,2,3,7,8-pentaCDF, levels not reported	Birth weight	↓
	Breast milk 2,3,4,7,8-pentaCDF, levels not reported	Birth weight	↓
Wang et al. 2019 Prospective, 27 mother-infant pairs living near electronic waste dismantling region and 35 controls (China)	Breast milk total CDF TEQ[b] 6.6 pg/g lipid in exposed and 2.1 pg/g lipid in controls	Height	
		• 6 months	↔
		• 3 years	↔
		Weight	
		• 6 months	↔
		• 3 years	↔
		BMI	
		• 6 months	↔
		• 3 years	↔

Table 2-8. Results of Epidemiological Studies Evaluating Exposure to CDFs and Developmental Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
		Head circumference	
		• 6 months	↔
		• 3 years	↔
		Chest circumference	
		• 6 months	↔
		• 3 years	↔

[a]TEQs were calculated using the WHO 1998 TEF values.
[b]TEQs were calculated using the WHO 2005 TEF values.

↑ = association between biomarker level and outcome; ↓ = inverse association between biomarker level and outcome; ↔ = no association between biomarker level and outcome; BMI = body mass index; CDF = chlorodibenzofuran; DHEA = dehydroepiandrosterone; DPOAE = distortion product otoacoustic emissions; MDI = mental developmental index score; PDI = psychomotor developmental index score; TEF = toxic equivalency factor; TEQ = toxic equivalency; TSH = thyroid stimulating hormone; WHO = World Health Organization

Decreased birth weight was another commonly reported effect in the Yusho and Yu-Cheng cohorts (Funatsu et al. 1971; Lan et al. 1987; Rogan 1989; Taki et al. 1969; Yamaguchi et al. 1971). A health survey of children of mothers in the Yu-Cheng cohort known to have been *in utero* during or after exposure found that mean birth weight was decreased ≈15% (Gladen et al. 1990; Rogan et al. 1988; Yen et al. 1994). The greatest decreases in birth weight were found in children born in the first year after the incident (Yen et al. 1994). Decreases in height and muscular development (as indicated by lower total lean tissue mass) were also observed in the children of the Yu-Cheng cohort; when grouped by birth order, these effects were only observed in the first child born after the incident (Guo et al. 1994a). The Guo et al. (1994b) study did not find alterations in weight or bone mineral density. An inverse association between birth weight and maternal serum total CDF levels and 2,3,4,7,8-pentaCDF was found in a general population study (Konishi et al. 2009); no associations were found for 2,3,7,8-tetraCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,6,7,8-hexaCDF, or 1,2,3,4,6,7,8-heptaCDF. Similarly, Vartianien et al. (1998) found inverse associations between birth weight and breast milk levels of 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, and 2,3,4,7,8-pentaCDF. In contrast, Tawara et al. (2009) found no association between breast milk levels of CDF congeners and birth weight, head circumference, or chest circumference in a general population study, but did find inverse associations between birth length and breast milk 2,3,4,7,8-pentaCDF, 1,2,3,6,7,8-hexaCDF, 2,3,4,6,7,8-hexaCDF, and total CDF TEQ levels. Two studies examined birth outcomes in populations living in highly contaminated areas. Van Tung et al. (2016) found an inverse association between breast milk 2,3,4,7,8-pentaCDF TEQ and birth weight among a population living in an area of Vietnam that was sprayed with Agent Orange; no associations

with birth weight were found for 2,3,7,8-tetraCDF TEQ, 1,2,3,7,8-pentaCDF TEQ, several hexaCDF and heptaCDF congener TEQs, octaCDF TEQ, or total CDF TEQ. The study also found no associations with weight, height, head circumference, or chest circumference at 8–9 or 12–14 weeks of age. Similarly, Wang et al. (2019) found no association between breast milk total CDF TEQ and height, weight, BMI, head circumference, or chest circumference at 6 months or 3 years of age among the children of women living near an electronic waste dismantling region in China. The results of the Konishi et al. (2009); Tawara et al. (2009), Van Tung et al. (2016), Vartiainen et al. (1998), and Wang et al. (2019) are presented in Table 2-8. No alterations in sex ratio were found in infants born in the Yusho affected area between 1968 and 1977 (Yoshimura et al. 2001). There is limited information on the occurrence of birth defects in the Yusho and Yu-Cheng cohorts. Wang et al. (2003) reported increases in the prevalence of dental defects (congenitally missing germ, neonatal teeth, and tooth rotation) in children of Yu-Cheng mothers. A study of Vietnamese children in an Agent Orange affected area reported higher levels of serum 1,2,3,4,8,9-hexaCDF in fathers of children with birth defects (Tawara et al. 2008). An association between breast milk levels of CDFs and the risk of cretinism was reported in a general population study (Nagayama et al. 2007). Inverse associations between vitamin K levels in 11-month-old infants and serum 1,2,3,7,8-pentaCDF and 1,2,3,4,6,7,8-heptaCDF levels were found in a general population study (Pluim et al. 1994). See Table 2-8 for a summary of the Nagayama et al. (2007) and Pluim et al. (1994) studies.

Neurobehavioral assessment based on parental reports showed that 49% of the children in the Yu-Cheng cohort were delayed in achieving developmental milestones compared to 22% of unexposed children, but this was not clearly corroborated by neurological examiners (Rogan et al. 1988; Yu et al. 1991). Cognitive testing (Bayley mental and psychomotor developmental indices, Stanford-Binet test, Wechsler Intelligence Scale for Children) showed significantly lower overall age-adjusted developmental scores in the exposed children. Delays were seen at all ages and were greater in children who were smaller in size, had neonatal signs of intoxication, and/or had a history of nail deformities. Results of follow-up testing (Stanford-Binet test and Wechsler Intelligence Scale) when the children were 4–7 years old indicate that effects on cognitive development persisted for several years following exposure (Chen et al. 1992). Delays in cognitive development were found in boys at ages 6, 7, 8, or 9 years, with no alterations in girls (Guo et al. 1995). Delays in child development were also observed in children of Yu-Cheng mothers born 7–12 years after the incident; no effects were found in children of Yu-Cheng fathers (Guo et al. 1994b). Li et al. (2015b) found an increased incidence of asymmetrical hearing threshold increases in Yu-Cheng children tested in early adulthood (see Table 2-8 for additional information). Maternal serum 2,3,4,7,8-pentaCDF levels were associated with increased hearing thresholds (>20 dB) at 250, 500, and

1,000 Hz in the right ear, at 500 and 4,000 Hz in the left ear, and at average hearing thresholds in the right and left ears. An inverse association between hearing function and maternal serum levels of 2,3,4,7,8-pentaCDF was also found. Decreased measures of distortion product otoacoustic emissions (DPOAE) at 1.5 and 2 Hz in the right ear and at the average threshold levels in both ears were present. Maternal serum 1,2,3,4,7,8-hexaCDF was also associated with an increased hearing threshold (>20 dB) at 4,000 Hz in the left ear, but no other associations were found with this congener.

A general population study found inverse associations between performance on tests for psychomotor development in 6-month-olds and maternal serum 2,3,7,8-tetraCDF, 1,2,3,6,7,8-pentaCDF, and 1,2,3,6,7,8-hexaCDF levels (Nakajima et al. 2006); there were no associations with the mental developmental index scores. In another study by this group (Nakajima et al. 2017), inverse associations between the psychomotor development scores and maternal 2,3,7,8-tetraCDF and 1,2,3,7,8-pentaCDF were observed in males at 6 months, but not in 18-month-olds; an inverse association was found between maternal 1,2,3,4,6,7,8-heptaCDF and mental development index scores in 18-month-old females. Another general population study found associations between neonatal neurological optimality scores and breast milk levels of 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF, but not for other CDF congeners (Huisman et al. 1995). Studies of Vietnamese children in Agent Orange hotspots found associations between breast milk levels of some CDF congeners and performance on tests assessing autism spectrum disorder (Nishijo et al. 2012), eating behaviors (Nguyen et al. 2018), and language skills (Tai et al. 2013). See Table 2-8 for additional information on these studies.

A couple of studies evaluated possible effects on the reproductive system of Yu-Cheng children. An increase in the percentage of abnormal sperm morphology was observed in young men exposed *in utero*; there were no alterations in semen volume or sperm count (Guo et al. 2000). Another study of boys found increased serum estradiol levels at the age of puberty but found no alterations in serum testosterone or follicle stimulating hormone levels at the age of puberty or before puberty (Hsu et al. 2005). In adolescent girls prenatally exposed to Yu-Cheng contaminants, a shorter mean duration of menstrual bleeding per cycle, higher rate of irregular menstrual cycles, and elevated serum estradiol and follicle stimulating hormone levels were found (Yang et al. 2005). In a study of children living in Agent Orange contaminated areas in Vietnam, inverse associations between maternal breast milk levels of several penta-, hexa-, and heptaCDF congeners and levels of serum dehydroepiandrosterone, androstenedione, and testosterone were found (Oanh et al. 2018); see Table 2-8 for additional information.

A few studies evaluated potential impairment of the immune system in the children born after the Yu-Cheng incident. Hsu et al. (1985) reported that approximately 20% of hyperpigmented children exposed perinatally died due to pneumonia, bronchitis, and prematurity (Hsu et al. 1985). Lan et al. (1990) reported that the immune status was normal in the children in the Yu-Cheng cohort 7–9 years old. Another study reported increased frequency of parent reported influenza in children born during or after the Yu-Cheng incident (Yu et al. 1998). No alterations in serum IgA, IgG, or IgM levels, leukocyte subpopulations, T-cell markers, B-cell markers, or natural killer cell markers were found. Chao et al. (1997) reported that children born to the Yu-Cheng cohort had higher incidences of middle ear disease, with the highest incidences occurring in children born closer to the time of the incident. Children with middle ear disease had higher serum levels of 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF.

2,3,7,8-TetraCDF. The developmental toxicity of 2,3,7,8-tetraCDF was examined in mouse studies that examined a limited number of potential endpoints (Weber et al. 1984, 1985). Hydronephrosis was observed in the offspring of mice administered ≥350 μg/kg on gestation day (GD) 10 and at ≥10 μg/kg on GDs 10–13. Cleft palate was also observed at ≥600 μg/kg on GD10 and at ≥50 μg/kg on GDs 10–13. These effects were observed in the absence of overt signs of maternal toxicity, although increases in maternal relative liver weight were noted. Weber et al. (1984) also reported an increase in fetal mortality at ≥250 μg/kg; this finding was not confirmed in a subsequent study in which mice were administered 300–900 μg/kg on GD 10 (Weber et al. 1985).

1,2,3,7,8-PentaCDF. One study evaluated the developmental toxicity of 1,2,3,7,8-pentaCDF. No significant alterations in fetal weight or mortality were observed in the offspring of rats administered ≤200 μg/kg on GDs 10–13 (Birnbaum et al. 1987a). An increased incidence of hydronephrosis was observed at ≥30 μg/kg/day on GDs 10–13; cleft palate was reported at ≥100 μg/kg.

2,3,4,7,8-PentaCDF. Several studies evaluated the developmental toxicity of 2,3,4,7,8-pentaCDF in rodents; observed effects included decreases in fetal/offspring body weight, alterations in thymus weight, increases in the incidence of malformations/anomalies, alterations in the liver, reproductive system alterations, and fetal mortality. Decreases in fetal weight were observed in the offspring of rats administered ≥30 μg/kg on GD 8, 10, or 12 (Couture et al. 1989) and in mice administered ≥30 μg/kg/day on GDs 10–13 (Birnbaum et al. 1987a); a second mouse study did not find significant alterations at 30 μg/kg/day on GDs 10–13 (Birnbaum et al. 1987b). In the male and female offspring of rats administered a single dose of 2,3,4,7,8-pentaCDF on GD 15, ED_{50} values of 56.3±15.7 and 140±860 μg/kg, respectively, were estimated for decreases in fetal weights (Taura et al. 2014). This study

also found decreases in growth hormone levels in female (ED_{50} of 12.6 μg/kg) and male (ED_{50} of 27.4 μg/kg) fetuses (Taura et al. 2014); the investigators suggested that this may have contributed to the observed growth retardation. Another rat study reported decreases in offspring body weight on postnatal days (PNDs) 10, 15, and 20 in the offspring of rats administered 10 μg/kg on GD 15 and at PND 140 in the 1 and 10 μg/kg groups (Salisbury and Marcinkiewicz 2002).

Most of the available developmental studies on 2,3,4,7,8-pentaCDF examined a limited number of endpoints and exposures were limited to the critical developmental time period for the examined endpoint. A 14% decrease in neonatal thymus weight (14%) was observed in the offspring of rats administered 2 μg/kg on GD 16 (Madsen and Larsen 1989). A cross-fostering experiment in which dams were administered 10 μg/kg 2,3,4,7,8-pentaCDF on GD 16 demonstrated a similar decrease in thymus weight in 1-week-old pups exposed *in utero* and in pups exposed via lactation only (Madsen and Larsen 1989); a greater decrease was observed in pups exposed *in utero* and via lactation. Administration of 80 μg/kg/day on GDs 10–13 resulted in impaired embryonic erythropoiesis in the liver, an increase in the number of hepatocytes, and a reduction in the size and number of sinusoids in the liver, and a narrowed central lobular vein (Khera 1992).

Two studies conducted by Birnbaum et al. (1987a, 1987b) reported increased incidences of hydronephrosis in the offspring of mice administered ≥5 μg/kg/day on GDs 10–13 and cleft palate at ≥30 μg/kg/day. An increase in mortality was noted in the fetuses of rats administered 100 μg/kg on GD 8, 10, or 12 (Couture et al. 1989); there were no alterations in fetal mortality at ≤80 μg/kg/day on GDs 10–13 (Birnbaum et al. 1987a, 1987b).

Impaired development of the reproductive system has been observed in male and female offspring. A decrease in the number of days spent in estrus (approximately 30% decrease) with a concomitant increase in diestrus length was observed in the offspring of rats administered 1 μg/kg on GD 15 (Salisbury and Marcinkiewicz 2002). Decreases in ovulation rate were also observed in the offspring at 1 (60% decrease in the number of ova/rate) and 10 μg/kg (90%). In a second study, decreases in luteinizing hormone levels were observed in the male and female fetuses of rats administered 2,3,4,7,8-pentaCDF on GD 15; the ED_{50} values were 56.3 and 140 μg/kg, respectively (Taura et al. 2014). Taura et al. (2014) also evaluated development and sexual maturation in male offspring of rats administered 2,3,4,7,8-pentaCDF on GD 15. Prolonged mount latency, decreased mount frequency, increased intromission latency, and decreased intromission frequency were reported at 50 μg/kg. The investigators suggested that exposure to

2,3,4,7,8-pentaCDF disrupts testicular steroidogenesis in fetuses due to the reduction in the expression of pituitary luteinizing hormone, which imprints defects in sexual behavior (Taura et al. 2014).

1,2,3,4,7,8-HexaCDF. Increases in mean fetal weights were observed in the offspring of mice administered ≥100 μg/kg 1,2,3,4,7,8-hexaCDF on GDs 10–13 (Birnbaum et al. 1987a); edema was noted in the fetuses in the 1,000 μg/kg group. There were no significant alterations in fetal mortality at ≤1,000 μg/kg (Birnbaum et al. 1987a, 1987b). An increase in the incidence of hydronephrosis was observed at ≥100 μg/kg (Birnbaum et al. 1987a, 1987b). Cleft palate was also reported at ≥300 μg/kg in the Birnbaum et al. (1987a) study but was not observed at 300 μg/kg in the second study by this group (Birnbaum et al. 1987b).

Mechanisms. It is well documented that orally administered 2,3,7,8-substituted tetra-, penta-, and hexaCDF congeners induce hydronephrosis and cleft palate in mice at doses that are not maternally toxic and that hydronephrosis is induced at lower doses than cleft palate (Birnbaum et al. 1987a, 1987b; Weber et al. 1984, 1985). The kidney and palate were the only tissues examined in mice because studies with 2,3,7,8-TCDD showed that morphogenesis in these tissues is selectively affected (ATSDR 1998). The strain of mouse (C57BL/6N) tested in these oral studies is known to be Ah-responsive (Morrissey and Schwetz 1989). A single intraperitoneal dose of 0.6 mg/kg 2,3,7,8-tetraCDF on GD 12 induced high incidences of cleft palate and hydronephrosis were found in the Ah-responsive inbred mouse strains, but no cleft palates and few fetuses with hydronephrosis were found in the Ah-nonresponsive strains (Hassoun et al. 1984). Ah-nonresponsive mice appear to have a defective Ah receptor (Goldstein and Safe 1989). This evidence and studies of 2,3,7,8-TCDD (ATSDR 1998; Morrissey and Schwetz 1989) indicate that developmental toxicity of CDFs is mediated by the Ah receptor (see Section 2.20). Studies with 2,3,7,8-TCDD indicate that the *in utero* development of hydronephrosis induced by CDFs may be caused by hyperplasia of the ureteral epithelium (Abbot et al. 1987). Both 2,3,4,7,8-pentaCDF and 2,3,7,8-TCDD can cause hemorrhages in placental tissues (embryo-maternal vascular barrier, visceral yolk sac membrane, maternal vascular spaces of the placenta periphery) of mice at teratogenic doses (Khera 1992). It is not known, however, if these hemorrhagic lesions play a role in the induction of cleft palate or hydronephrosis.

Summary. The developmental toxicity of CDFs has been demonstrated in humans and laboratory animals. Perinatal exposure to high levels resulted in skin lesions similar to those observed in adults, decreases in birth weight, delays in cognitive development, and impairment of immune function. A number of effects have been observed in laboratory animals including increases in the prevalence of

hydronephrosis and cleft palate, decreases in fetal weight, fetal mortality, and impaired development of the reproductive system. Birnbaum et al. (1987a) compared the potential of 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, and 1,2,3,4,7,8-hexaCDF to induce hydronephrosis and cleft palate. For both endpoints, 2,3,4,7,8-pentaCDF was the most toxic, followed by 1,2,3,4,7,8-hexaCDF. The ED_{50} values for hydronephrosis were 36, 133, and 342 μg/kg for 2,3,4,7,8-pentaCDF, 1,2,3,7,8-pentaCDF, and 1,2,3,4,7,8-hexaCDF, respectively.

2.18 OTHER NONCANCER

Epidemiological studies evaluated several other noncancer endpoints including tooth and gum alterations, pancreatitis, and metabolic syndrome. Members of the Yusho cohort reported increased prevalences of periodontal disease, gingivitis, pigmentation of the gingiva, and hypersensitivity of teeth (Akahane et al. 2018). Increased prevalence of gum pigmentation was also reported in another study of the Yusho cohort (Imamura et al. 2007) and the Yu-Cheng cohort (Guo et al. 1999). Other noncancer effects examined in only one study of the Yusho cohort included an increased prevalence of pancreatitis (Akahane et al. 2018) and high uric acid levels (Imamura et al. 2009; Matsumoto et al. 2010).

Two studies evaluated the possible association between CDF serum levels and the prevalence of metabolic syndrome (see Table 2-9). Five criteria are used to assess metabolic syndrome: obesity, high blood pressure, high serum triglycerides, low HDL cholesterol levels, and elevated blood glucose. In a study of residents living near a highly dioxin-contaminated site in Taiwan, associations were found between individual CDF congeners, expressed as TEQs, and metabolic syndrome scores (Chang et al. 2010). In the second study of individuals living in Japan, total CDFs TEQ, 2,3,4,7,8-pentaCDF TEQ, and 1,2,3,6,7,8-hexaCDF TEQ serum levels were associated with a higher prevalence of metabolic syndrome (defined as meeting three or more of the five criteria) (Uemura et al. 2009). Both studies reported dose-related trends between CDF congener TEQ levels and metabolic syndrome prevalence.

Table 2-9. Results of Epidemiological Studies Evaluating Exposure to CDFs and Other Noncancer Effects

Reference, study type, and population	Biomarker[a]	Outcome evaluated	Result
Chang et al. 2010	Serum 2,3,7,8-tetraCDF TEQ (levels not reported)	Metabolic syndrome[b]	↑ 4th quintile
	Serum 1,2,3,7,8-pentaCDF TEQ (levels not reported)	Metabolic syndrome[b]	↑ 4th quintile

Table 2-9. Results of Epidemiological Studies Evaluating Exposure to CDFs and Other Noncancer Effects

Reference, study type, and population	Biomarker[a]	Outcome evaluated	Result
Cross-sectional; 1,490 adults living near a highly dioxin-contaminated site (Taiwan)	Serum 2,3,4,7,8-pentaCDF TEQ (levels not reported)	Metabolic syndrome[b]	↑ 2nd quintile
	Serum 1,2,3,4,7,8-hexaCDF TEQ (levels not reported)	Metabolic syndrome[b]	↑ 3rd quintile
	Serum 1,2,3,6,7,8-hexaCDF TEQ (levels not reported)	Metabolic syndrome[b]	↑ 3rd quintile
	Serum 2,3,4,6,7,8-hexaCDF TEQ (levels not reported)	Metabolic syndrome[b]	↑ 3rd quintile
	Serum 1,2,3,7,8,9-hexaCDF TEQ (levels not reported)	Metabolic syndrome[b]	↔
	Serum 1,2,3,4,6,7,8-heptaCDF TEQ (levels not reported)	Metabolic syndrome[b]	↔
	Serum 1,2,3,4,7,8,9-heptaCDF TEQ (levels not reported)	Metabolic syndrome[b]	↔
	Serum octaCDF TEQ (levels not reported)	Metabolic syndrome[b]	↔
	Serum total CDF TEQ (levels not reported)	Metabolic syndrome[b]	↑ 5th quintile
Uemura et al. 2009 Cross sectional, 1,374 adults (Japan)	Serum median 2,3,4,7,8-pentaCDF TEQ 3.5 pg/g lipid	Metabolic syndrome[c]	↑ 2nd quintile
	Serum median 1,2,3,6,7,8-hexaCDF TEQ median 0.3 pg/g lipid	Metabolic syndrome[c]	↑ 2nd quintile
	Serum total CDF TEQ 2nd quintile ≥2.90–4.50 pg/g lipid	Metabolic syndrome[c]	↑ 2nd quintile

[a]TEQs were calculated using the WHO 1998 TEF values.
[b]Metabolic syndrome defined at having at least three factors: waist circumference >90 cm in men and 80 cm in women; blood pressure >130/85 mmHg, triglycerides >150 mg/dL; HDL cholesterol levels <40 mg/dL; and fasting blood glucose >100 mg/dL.
[c]Metabolic syndrome defined at having at least three factors: BMI ≥25 kg/m^2; serum triglycerides >150 mg/dL; serum HDL cholesterol levels <40 mg/dL; systolic blood pressure >130 mmHg and/or diastolic blood pressure ≥85 mmHg, or self-reported history of physician-diagnosed hypertension; and HbA1C ≥5.6% or self-reported physician diagnosed diabetes.

↑ = association between biomarker level and outcome; ↓ = inverse association between biomarker level and outcome; ↔ = no association between biomarker level and outcome; BMI = body mass index; CDF = chlorodibenzofuran; HDL = high-density lipoprotein; TEF = toxic equivalency factor; TEQ = toxic equivalency; WHO = World Health Organization

2,3,7,8-TetraCDF. Degranulation of exocrine pancreatic cells were observed in rhesus monkeys dying early after administration of 1,000 μg/kg 2,3,7,8-tetraCDF (Moore et al. 1979).

2,3,4,7,8-PentaCDF. In rats chronically administered ≥0.044 μg/kg 2,3,4,7,8-pentaCDF, squamous hyperplasia of the gingiva was observed (NTP 2006).

2.19 CANCER

Several retrospective mortality studies evaluated the Yusho and Yu-Cheng cohorts and found increases in cancer deaths (Kuratsune et al. 1987; Onozuka et al. 2009) in the Yusho cohort and no increases in risk of death from all cancers in the Yu-Cheng cohort (Tsai et al. 2007; Yu et al. 1997). A meta-analysis of the Onozuka et al. (2009) Yusho data and unpublished data on the Yu-Cheng cohort reported an association with a pooled SMR of 1.3 (95% CI 1.1–1.6) among male members (Li et al. 2015a); no association was found among females.

Several studies also examined possible associations for specific tumor sites among the Yusho and Yu-Cheng cohorts, in workers, and in the general population. In the Yusho cohorts, increases in the prevalence of bowel cancer (Akahane et al. 2018), deaths from lung cancer, and deaths from liver cancer (Kuratsune et al. 1987; Onozuka et al. 2009) were observed. In the Yu-Cheng cohort, Li et al. (2013) found increases in the prevalence of neoplasms of the stomach, lymphatic, and hematopoietic tissues among males. The Li et al. (2015a) meta-analysis also examined specific tumor types (cancers of the stomach, rectum, liver, pancreas, lung, female breast, uterus, and leukemia). The only associations found were for lung cancer in males (SMR 1.7, 95% CI 1.2–2.3) and lung cancer for males and females combined (SMR 1.5, 95% CI 1.1–2.1).

In a study of subjects with known exposure to phenoxyacetic acids or potential exposure to CDDs/CDFs, higher levels of 2,3,4,7,8-pentaCDF were found in the seven cases with malignant lymphoproliferative diseases (Hardell et al. 1995). Two general population case-control studies found no differences in levels of CDF congeners in breast adipose tissue in breast cancer cases (Hardell et al. 1996) or in abdominal adipose tissue in non-Hodgkin lymphoma cases (Hardell et al. 2001), as compared to controls. A third general population study found no association between breast tissue adipose levels of 2,3,4,7,8-pentaCDF, 1,2,3,6,7,8-hexaCDF, or 1,2,3,4,6,7,8-heptaCDF levels and the risk of breast cancer (Reynolds et al. 2005). The results of the Hardell et al. (1996, 2001) and Reynolds et al. (2005) studies are summarized in Table 2-10.

Table 2-10. Results of Epidemiological Studies Evaluating Exposure to CDFs and Cancer Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
Hardell et al. 1996 Case control; 22 patients with invasive breast cancer and 19 controls (Sweden)	Breast tissue median 2,3,7,8-tetraCDF 5.9 pg/g lipid in cases and 4.1 pg/g lipid in controls	Breast cancer	↔
	Breast tissue median 1,2,3,7,8-pentaCDF 1.1 pg/g lipid in cases and 0.6 pg/g lipid in controls	Breast cancer	↔
	Breast tissue median 2,3,4,7,8-pentaCDF 23.8 pg/g lipid in cases and 21.6 pg/g lipid in controls	Breast cancer	↔
	Breast tissue median 1,2,3,4,7,8-hexaCDF 5.3 pg/g lipid in cases and 3.4 pg/g lipid in controls	Breast cancer	↔
	Breast tissue median 1,2,3,6,7,8-hexaCDF 4.2 pg/g lipid in cases and 3.2 pg/g lipid in controls	Breast cancer	↔
	Breast tissue median 1,2,3,7,8,9-hexaCDF .1 pg/g lipid in cases and 0.9 pg/g lipid in controls	Breast cancer	↔
	Breast tissue median 1,2,3,4,7,8,9-heptaCDF 0.6 pg/g lipid in cases and 0.7 4.1 pg/g lipid in controls	Breast cancer	↔
	Breast tissue median octaCDF 2.3 pg/g lipid in cases and 1.9 pg/g lipid in controls	Breast cancer	↔
Hardell et al. 2001 Case control; 33 patients with non-Hodgkin lymphoma and 39 controls (Sweden)	Abdominal fat mean 2,3,7,8-tetraCDF 0.94 pg/g lipid in cases and 1.5 pg/g lipid in controls	Non-Hodgkin lymphoma	↔
	Abdominal fat mean 1,2,3,7,8-pentaCDF 0.73 pg/g lipid in cases and 0.99 pg/g lipid in controls	Non-Hodgkin lymphoma	↔
	Abdominal fat mean 2,3,4,7,8-pentaCDF 21 pg/g lipid in cases and 21 pg/g lipid in controls	Non-Hodgkin lymphoma	↔
	Abdominal fat mean 1,2,3,4,7,8-hexaCDF 4.0 pg/g lipid in cases and 3.5 pg/g lipid in controls	Non-Hodgkin lymphoma	↔

Table 2-10. Results of Epidemiological Studies Evaluating Exposure to CDFs and Cancer Effects

Reference, study type, and population	Biomarker	Outcome evaluated	Result
	Abdominal fat mean 1,2,3,6,7,8-hexaCDF 3.3 pg/g lipid in cases and 3.1 pg/g lipid in controls	Non-Hodgkin lymphoma	↔
	Abdominal fat mean 1,2,3,7,8,9-hexaCDF 0.93 pg/g lipid in cases and 0.97 pg/g lipid in controls	Non-Hodgkin lymphoma	↔
	Abdominal fat mean 1,2,3,4,6,7,8-heptaCDF 9.2 pg/g lipid in cases and 4.3 pg/g lipid in controls	Non-Hodgkin lymphoma	↔
	Abdominal fat mean 1,2,3,4,7,8,9-heptaCDF 0.39 pg/g lipid in cases and 0.53 pg/g lipid in controls	Non-Hodgkin lymphoma	↔
	Abdominal fat mean octaCDF 0.83 pg/g lipid in cases and 0.91 pg/g lipid in controls	Non-Hodgkin lymphoma	↔
Reynolds et al. 2005 Case control; 79 women with invasive breast cancer and 52 controls with benign breast cancer (United States)	Breast tissue median 2,3,4,7,8-pentaCDF 8 pg/g lipid in cases and 8 pg/g lipid in controls	Invasive breast cancer	↔
	Breast tissue median 1,2,3,4,7,8-hexaCDF 5 pg/g lipid in cases and 4 pg/g lipid in controls	Invasive breast cancer	↔
	Breast tissue median 1,2,3,6,7,8-hexaCDF 4 pg/g lipid in cases and 3 pg/g lipid in controls	Invasive breast cancer	↔
	Breast tissue median 1,2,3,4,6,7,8-heptaCDF 7 pg/g lipid in cases and 8 pg/g lipid in controls	Invasive breast cancer	↔

↑ = association between biomarker level and outcome; ↓ = inverse association between biomarker level and outcome; ↔ = no association between biomarker level and outcome; CDF = chlorodibenzofuran

2,3,7,8-TetraCDF. In a tumor promotion study using 2,3,7,8-tetraCDF, hairless mice were initiated with a single 5 µmol dermal dose of methylnitronitrosoguanidine (MNNG) in acetone or just acetone followed by twice weekly dermal applications of ≈33.3 µg 2,3,7,8-tetraCDF/kg in acetone for 20 weeks (Poland et al. 1982). Skin papillomas developed in 100% of the mice initiated with MNNG and in 5% of the mice initiated with acetone, compared to 0% in the control group. These findings indicate that 2,3,7,8-tetraCDF had skin tumor promotion activity.

2,3,4,7,8-PentaCDF. The carcinogenic potential of 2,3,4,7,8-pentaCDFs following oral exposure was examined in a study of female rats administered 2,3,4,7,8-pentaCDF via gavage 5 days/week for 2 years (NTP 2006). In rats administered 0.2 µg/kg, increased incidences of hepatocellular adenoma (4/53 compared to 1/53 in controls), cholangiocarcinoma (2/53 compared to 0/53 in controls), and gingival squamous cell carcinoma (3/53 compared to 1/53 in controls) were observed. Although the increases were not statistically significant, NTP considered them to be treatment-related. The investigators noted that these types of neoplasms were also observed in studies of 2,3,7,8-TCDD and PCB 126, which supported the conclusions that the lesions were due to 2,3,4,7,8-pentaCDF exposure. Nonsignificant increases in neoplastic lesions were also observed in the lungs, pancreas, and uterus; some of these lesions were 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 (administered 2,3,4,7,8-pentaCDF for 30 weeks and allowed to recover for the remainder of the 2-year study); and uterine carcinoma in the 0.092 and 0.2 µg/kg groups. Overall, NTP (2006) considered that the study provided some evidence of the carcinogenicity of 2,3,4,7,8-penta-CDF in female Sprague-Dawley rats. The investigators noted that these types of neoplasms were also observed in studies of 2,3,7,8-TCDD and PCB 126, which supported the conclusions that the lesions were due to 2,3,4,7,8-pentaCDF.

Studies also evaluated the carcinogenicity of 2,3,4,7,8-pentaCDF following dermal exposure. Initiation-promotion studies were performed in which a single 5 µmol dose of MNNG initiator was applied to intact uncovered skin of hairless (hr/hr) mice followed by promotion with twice weekly dermal doses of 0.08–3.3 µg/kg 2,3,4,7,8-pentaCDF for 20 weeks (Hebert et al. 1990). Acetone was used as the vehicle for the MNNG and CDFs. Studies were also conducted in which acetone was used as the control initiator and the mice were exposed to 3.3 µg/kg 2,3,4,7,8-pentaCDF 2 times/week for 20 weeks. There were no significant increases in proliferative lesions of the skin in the mice pretreated with acetone and followed by 2,3,4,7,8-pentaCDF, although there was an observation period following treatment. However, proliferative skin lesions developed in 77.8–94.4% of the mice initiated with MNNG and promoted with ≥0.08 µg/kg 2,3,4,7,8-pentaCDF, compared to 10.5% in the control groups. Most of the lesions were hyperproliferative nodules and squamous cell papillomas.

1,2,3,4,7,8-HexaCDF. The carcinogenicity of 1,2,3,4,7,8-hexaCDF was also evaluated in initiation-promotion studies conducted by Hebert et al. (1990) (see 2,3,4,7,8-pentaCDF section for study details).

There were no significant increases in proliferative lesions of the skin in the mice pretreated with acetone and followed by 8.3–33.3 μg/kg 1,2,3,4,7,8-hexaCDF. Proliferative skin lesions developed in 47.1–89.5% of the mice initiated with MNNG and promoted with ≥8.3 μg/kg 1,2,3,4,7,8-hexaCDF, compared to 10.5% in the control groups. Most of the lesions were hyperproliferative nodules and squamous cell papillomas.

Cancer Assessments. IARC (2012) concluded that 2,3,4,7,8-pentaCDF is carcinogenic to humans (Group 1). Other CDF congeners are not classifiable as to their carcinogenicity to humans (Group 3) (IARC 1997). HHS (NTP 2016) and EPA (IRIS 2020) have not conducted carcinogenicity assessments.

2.20 MECHANISM OF ACTION

Many CDFs, CDDs, PCBs, and other structurally related halogenated aromatic hydrocarbons are believed to share a common mechanism of action intimately related to similarities in their structural configuration. Most of what is known regarding the mechanism of action of these compounds is based on three main lines of information (i.e., structure-receptor binding relationships, structure-induction relationships, and structure-toxicity relationships) (Goldstein and Safe 1989; Safe 1990a, 1991). Most of the studies providing this information investigated compounds other than CDFs, particularly 2,3,7,8-TCDD and other CDDs, and used parenteral routes of exposure and/or *in vitro* test systems. The concept of a common mechanism explains why all of these compounds, including CDFs, elicit the same responses and differ only in their relative potency. Most, if not all, of the health effects of CDFs and related compounds are mediated by binding to the Ah receptor, which regulates the synthesis of a variety of proteins via alterations in gene expression. This receptor was identified in the cytosol of mouse liver cells (Poland et al. 1976) and, subsequently, in extrahepatic tissues of laboratory animals, mammalian cell cultures, and human organs and cell cultures. The structure-binding relationships for a series of CDFs were estimated *in vitro* using rat hepatic cytosol preparations (Bandiera et al. 1984b; Mason et al. 1985). Not all CDF congeners showed the same affinity for the Ah receptor; affinity was found to be determined by the chlorine substitution pattern. Those congeners that are isostereomers of 2,3,7,8-TCDD bind with the highest affinity. Tetra- to hexaCDFs that are fully substituted in the lateral two, three, seven, and eight positions are the most active congeners. Affinity constants for CDFs span over range of 4 orders of magnitude, with 2,3,4,7,8-pentaCDF having the highest affinity (EC_{50}=1.5x10^{-8} M, compared to 1.0x10^{-8} M for 2,3,7,8-TCDD). All CDFs tested exhibited saturable binding with the Ah receptor and cooperativity was not a factor in these binding interactions (Farrell et al. 1987). The stereospecific nature

of the binding strongly suggests the existence of a biological receptor as a mediator in the responses caused by CDFs.

Structure-toxicity relationships for several CDFs have been studied in immature male Wistar rats *in vivo* and in rat cell cultures *in vitro* (Bandiera et al. 1984b; Holcomb et al. 1988; Mason et al. 1985; Safe et al. 1986). Determination of ED_{50} values for hepatic microsomal AHH induction, inhibition of body weight gain, and thymic atrophy showed that the potencies of CDF congeners were structure-dependent, and that the *in vivo* structure-activity relationships for the toxic endpoints closely matched those observed for their *in vitro* AHH induction potencies (Mason et al. 1985). However, CDF congeners containing vicinal unsubstituted carbon atoms deviated from the linear correlation. A similar CDF congeneric pattern of toxicity was found in splenic response assays in C57BL/6 mice (Davis and Safe 1988; Dickerson et al. 1990) and in thymic atrophy and liver hypertrophy in male Wistar rats (Yoshihara et al. 1981). These results, along with results obtained with other halogenated aromatic hydrocarbons (summarized in Safe 1990a), are consistent with, and provide support for, the common receptor-mediated mechanism of action.

CDFs, as well as the other related halogenated aromatic hydrocarbons, induce a variety of microsomal enzyme activities such as cytochrome P-450IAl-dependent monooxygenases primarily in the liver. The most widely studied of these responses are induction of hepatic AHH and EROD both in mammalian cell cultures and in laboratory rodents (Bandiera et al. 1984b; Brewster et al. 1988; DeVito et al. 1993; Goldstein and Safe 1989; Goldstein et al. 1978; Holcomb et al. 1988; Kawano and Hiraga 1978; Mason et al. 1985; Nebert et al. 1975; Safe 1990a; Safe et al. 1986). Results from a study in male Wistar rats in which the inductive potency of 13 CDF congeners was tested following intraperitoneal dosing showed that only those congeners substituted in carbon positions 2, 3, 7, and 8 exhibited typical 3-methyl-cholanthrene (MC)-type induction (Yoshihara et al. 1981). Those congeners having two or less chlorine substitutions in the lateral positions did not induce EROD activity. Results from a similar study showed that the structure-activity relationships for liver enzyme inductive potency of a series of CDFs were comparable to those reported for the structure-binding relationships (Mason et al. 1985). Furthermore, a linear correlation was observed between AHH induction *in vitro* and *in vivo*, providing further support to a common receptor-mediated mechanism of action for CDFs.

The dioxin-like compounds bound to the cytosolic Ah receptor translocates to the cell nucleus and dimerize with the Ah receptor nuclear translocator (ARNT) protein (Denison et al. 2011; Safe 2001; Zeytun et al. 2002). The Ah receptor-ARNT heterodimer binds with dioxin responsive elements (DREs) which are specific DNA recognition sites (Denison et al. 2011; Safe 2001). The array of genes that can

be affected is large with diverse functions (Sutter and Greenlee 1992; Zeytun et al. 2002). The most extensively studied is cytochrome P450 1A1 (CYP1A1) (Kurachi et al. 2002; Sutter and Greenlee 1992; Whitlock 1999). Studies with 2,3,7,8-TCDD have identified other gene products that are induced or repressed. Over 290 genes in the liver can be altered by 2,3,7,8-TCDD (Boutros et al. 2009); these genes are associated with responses to chemical stress/xenobiotics (e.g., CYP1A1, glutathione S-transferase, glucose-6-phosphate dehydrogenase), lipid and cholesterol metabolism (e.g., fatty acid binding protein, lipase, fatty acid synthase, retinol binding protein), nitrogen and amino acid metabolism (e.g., aspartate aminotransferase, alanine aminotransferase, ornithine transcarbamylase), carbohydrate metabolism (e.g., glucokinase, glucose-6-phosphate transfer protein, pyruvate carboxylase), bile acid synthesis, and bile transport (Boverhof et al. 2006; Fletcher et al. 2005; Kurachi et al. 2002). Ah receptor target genes are located in a number of tissues other than the liver including the kidneys, thymus, and spleen (Boutros et al. 2009; Zeytun et al. 2002). Ultimately, newly synthesized enzymes and macromolecules resulting from the pleiotropic response to the CDF-receptor complex are responsible for many of the effects caused by CDFs and other halogenated aromatic hydrocarbons.

Studies with 2,3,7,8-TCDD provide *in vitro* evidence of a nongenomic mechanisms involving the Ah receptor, but not requiring ARNT (Matsumura 2009). These mechanisms appear to contribute to the inflammatory response via cytosolic phospholipase A2 (cPLA2), Cox-2, Src kinase, and other protein kinases and phosphatases.

Oxidative stress is another proposed mechanism for the toxicity of CDFs. Significant increases in the production of superoxide anion and lipid peroxidation were identified in the liver and brain tissues of rats administered 2,3,4,7,8-pentaCDF 5 days/week for 13 weeks (Hassoun et al. 2000) or 30 weeks (Hassoun et al. 2002). The increases in the biomarkers of oxidative stress were dose-related. The responses in the brain and liver were similar. In the 30-week study, increases in lipid peroxidation plateaued between 0.02 and 0.092 μg/kg and increased again at the highest dose (0.2 μg/kg) (Hassoun et al. 2002).

2.21 GENOTOXICITY

A small number of *in vitro* and *in vivo* studies have evaluated the genotoxicity of CDFs. The mutagenicity of several CDF congeners was evaluated in microorganisms; the results are summarized in Table 2-11. In assays with several strains of *Salmonella typhimurium* bacteria, octaCDF and 2,3,7,8-tetraCDF were not mutagenic with or without metabolic activation (Schoeny 1982). In assays

with the yeast, *Saccharomyces cerevisiae*, without exogenous metabolic activation, 2,3,7,8-tetraCDF did not induce forward mutations or inter- or intragenic recombinations (Fahrig et al. 1978).

Table 2-11. Genotoxicity of Chlorodibenzofurans (CDFs) *In Vitro*

			Results		
			Activation		
Species (test system)	CDF congener	Endpoint	With	Without	Reference
Salmonella typhimurium (TA98, TA100, TA1535, TA1537, TA1978)	2,3,7,8-tetraCDF	Gene mutation	–	–	Schoeny 1982
Saccharomyces cerevisiae	2,3,7,8-tetraCDF	Forward mutations	NT	–	Fahrig et al. 1978
S. cerevisiae	2,3,7,8-tetraCDF	Recombinations	NT	–	Fahrig et al. 1978
Human peripheral lymphocytes	1,2,4,7,8-pentaCDF	Sister chromatid exchange	–	–	Lundgren et al. 1988
Human peripheral lymphocytes	1,2,4,7,8-pentaCDF	Chromosome aberrations	–	–	Lundgren et al. 1988
Human peripheral lymphocytes	2,3,4,6,7-pentaCDF	Sister chromatid exchange	–	–	Lundgren et al. 1988
Human peripheral lymphocytes	2,3,4,6,7-pentaCDF	Chromosome aberrations	–	–	Lundgren et al. 1988
Human peripheral lymphocytes	2,3,4,7,8-pentaCDF	Sister chromatid exchange	–	–	Lundgren et al. 1988
Human peripheral lymphocytes	2,3,4,7,8-pentaCDF	Chromosome aberrations	–	–	Lundgren et al. 1988
Human peripheral lymphocytes	1,2,3,4,7,8-hexaCDF	Sister chromatid exchange	–	–	Lundgren et al. 1988
Human peripheral lymphocytes	1,2,3,4,7,8-hexaCDF	Chromosome aberrations	–	–	Lundgren et al. 1988
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1978, TA92, TS24, TA2322, TA2637)	octaCDF	Gene mutation	–	–	Schoeny 1982

[a]Results were only positive in assays conducted by one of three laboratories.
[b]Results were positive when assay was conducted in a desiccator; results were negative when tested in standard assay.

+ = positive results; (+) = weakly positive results; – = negative results; NT = not tested

Limited information was located regarding genotoxic effects of CDFs in humans or animals. The levels of sister chromatid exchanges and chromosome aberrations were examined in peripheral lymphocytes of 35 Yu-Cheng women nonsmokers 5 years after they consumed the contaminated rice oil (Lundgren et al. 1988). As compared to a control group of 24 women nonsmokers, no significant alterations in

frequencies of sister chromatid exchange or chromosomal aberrations in lymphocytes were observed. Oxidative stress, which may have resulted from DNA-single strand breaks, was examined in hepatic and brain tissues in rats administered via gavage 2,3,4,7,8-pentaCDF 5 days/week for 13 weeks (Hassoun et al. 2000). There was a significant dose-related increase in DNA single-strand breaks in hepatic and brain tissues after exposure to 2,3,4,7,8-pentaCDF (Hassoun et al. 2000).

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- Quantitative information regarding absorption of inhaled CDFs in humans and animals was not located; however, CDFs were detected in blood and adipose tissue following inhalation exposures in humans. Absorption of ingested CDFs was estimated to be >90% in adults and nursing infants. Studies conducted in animals demonstrate that CDFs can be absorbed through the skin.

- CDFs are lipid soluble and tend to accumulate in tissue lipid. Tissues that accumulate the highest concentrations of CDFs are adipose and liver. Accumulation of CDFs in liver is facilitated by an inducible binding protein, CYP1A2.

- CDFs are metabolized by the inducible CYP450 enzyme system. Factors that influence metabolism (e.g., chlorine substitution, animal species differences) contribute to variability in toxic potencies of CDFs.

- The major pathways of excretion of absorbed CDFs are feces and urine. Studies conducted in monkeys, mice, and rats indicate that feces are the dominant pathway for excretion of absorbed CDFs.

3.1.1 Absorption

Absorption of Inhaled CDFs. Quantitative information regarding absorption of inhaled CDFs in humans and animals were not located. However, absorption of CDFs can be inferred from detection of CDFs in blood and tissues following accidental or occupational exposure to airborne CDFs (Schecter and Ryan 1989; Schecter et al. 1991a). Subjects were exposed to soot or dust containing CDFs during cleanup operations following a PCB transformer fire or associated with municipal solid waste incineration. The relative contribution of the inhalation, dermal, and oral routes of absorption in these individuals cannot be determined.

Absorption of Ingested CDFs. Several human fecal mass balance studies estimated absorption of dietary CDFs based on short-term measurements of the difference between dietary intake and fecal excretion of CDFs (Abraham et al. 1994; Dahl et al. 1995; Jödicke et al. 1992; Körner et al. 1993; McLachlan 1993; Moser and McLachlan 2001; Pluim et al. 1993; Schlummer et al. 1998; Schrey et al. 1998). These studies cannot distinguish fecal excretion of absorbed CDFs from excretion of unabsorbed CDFs and, as a result, these studies can only estimate net absorption. Studies conducted in monkeys and rodents demonstrate that fecal excretion is a major pathway of excretion for absorbed CDFs; therefore, fecal balance studies are likely to underestimate the absorbed fraction of the ingested dose. In some human studies, fecal

excretion has been found to exceed measured dietary intakes of CDFs (negative balance) suggesting that at least some of the fecal CDF was derived from body stores (Moser and McLachlan 2001; Schrey et al. 1998). Net absorption was found to correlate with concentrations of CDFs in blood lipid, which also suggests a relationship between fecal excretion and body burden (Schlummer et al. 1998). Based on these human studies, net absorption of tetraCDFs, pentaCDFs, and hexaCDFs was estimated to be >90% in adults.

Several fecal mass balance studies evaluated the absorption of CDFs from breast milk; each study evaluated a small number of infants (n=1–4). Based on the amounts of CDFs in the feces, the studies estimated that at least 90% of the lower chlorinated CDFs (tetraCDF, pentaCDF, and hexaCDF) in breast milk was absorbed (Abraham et al. 1994; Dahl et al. 1995; Jödicke et al. 1992; Körner et al. 1993; McLachlan 1993; Pluim et al. 1993). The highly chlorinated CDFs (e.g., heptaCDFs and octaCDF) had the highest excretion rates, likely indicative of lower absorption efficiencies (Abraham et al. 1994; Dahl et al. 1995; Jödicke et al. 1992; Körner et al. 1993). One study of a 5-month-old infant reported that the percentage of ingested CDFs in the stool ranged from 2 to 10% for 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, 1,2,3,6,7,8-hexaCDF, and 2,3,4,6,7,8-hexaCDF and from 40 to 100% for 1,2,3,4,6,7,8-heptaCDF and octaCDF (Abraham et al. 1994). Another study reported estimated absorption of 97–100% for 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, and 2,3,4,7,8-pentaCDF; 88–100% for 1,2,3,4,7,8-hexaCDF and 1,2,3,6,7,8-hexaCDF; and 59–82% for 1,2,3,4,6,7,8-heptaCDF (Dahl et al. 1995).

Studies conducted in rodents have shown that guinea pigs and rats absorbed >80% of the ingested CDF dose (Birnbaum et al. 1980; Brewster and Birnbaum 1987; Decad et al. 1981a; Van den Berg et al. 1989). In male Hartley guinea pigs, >90% of a single oral dose of 6 µg of ^{14}C-2,3,7,8-tetraCDF/kg in Emulphor/ethanol/water was absorbed over a 3-day period (Decad et al. 1981a). In female Sprague-Dawley rats administered single doses of three different CDFs mixed in food pellets at 3.5–6.3 µg/kg body weight, 80% of the 2,3,4,7,8-pentaCDF dose was retained in the liver in 24 hours, compared to 34% for 1,2,3,7,8-pentaCDF and 43% for 1,2,3,6,7,8-hexaCDF (Van den Berg et al. 1989). In this study, liver retention was used as an indirect measure of absorption. When similar doses of the CDFs were administered in peanut oil, the amount of retained 1,2,3,7,8-pentaCDF doubled, the amount of retained 2,3,4,7,8-pentaCDF was unchanged, and the amount of retained 1,2,3,6,7,8-hexaCDF increased to 58%. Excretion data showed that male Fischer-344 rats administered single oral doses of 34, 169, or 338 µg ^{14}C-2,3,4,7,8-pentaCDF/kg in corn oil absorbed >70% of the dose over a 3-day period, regardless of the dose; absorption rate was not dose-related over the dose range tested (Brewster and Birnbaum 1987).

High absorption (≥90%) was also reported for 2,3,7,8-tetraCDF in male Fischer-344 rats administered a single gavage dose of the CDF in Emulphor/ethanol (Birnbaum et al. 1980).

Relative bioavailability of CDF congeners in soil was estimated in rats and swine (Budinsky et al. 2008; Finley et al. 2009; Wittsiepe et al. 2007a). Relative bioavailability was measured as the ratio of tissue congener levels following oral dosing with the congener in soil or in a reference vehicle (soil/reference), typically corn oil or some other lipid. These studies showed that the relative bioavailability of CDF congeners was <100% in rats and swine and varied across soil compositions. For example, in rats, the relative bioavailability of 2,3,7,8-tetraCDF in five different soils ranged from 27 to 89% (Budinsky et al. 2008; Finley et al. 2009). Relative bioavailability also varied with congener chlorination; increasing with increasing chlorine content in swine and decreasing with increasing chlorine content in rats (EPA 2010).

The limited data regarding oral absorption of CDFs in animals suggest that, in general, these compounds are absorbed and absorption efficiency depends on the vehicle and the chlorine substitution pattern. However, clear relationships between structure and absorption cannot be established from the available data, since, for example, peanut oil appeared to facilitate absorption of 1,2,3,7,8-pentaCDF and 1,2,3,6,7,8-hexaCDF, but not of 2,3,4,7,8-pentaCDF (Van den Berg et al. 1989).

Dermal Absorption of CDFs. Quantitative data regarding dermal absorption of CDFs in humans after controlled dermal exposure to CDFs were not located. However, absorption of CDFs can be inferred from detection of CDFs in blood and tissues following accidental exposure (Schecter and Ryan 1989). These subjects were exposed to soot or dust containing CDFs derived from a PCB transformer fire. Exposure occurred during clean-up operations that followed the fire. In such cases, the relative contribution of the inhalation, ingestion, or dermal routes cannot be determined.

Limited information is available regarding dermal absorption of CDFs in animals. In a dermal absorption study in male Fischer 344 rats, ^{3}H-1,2,3,7,8-pentaCDF, ^{14}C-2,3,4,7,8-pentaCDF, and ^{14}C-2,3,7,8-tetra-CDF in acetone were applied to the clipped back skin at several dose levels (Brewster et al. 1989). At doses of 34 µg/kg, 25, 34, and 49% of 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, and 2,3,7,8-tetraCDF, respectively, were absorbed over a 3-day period. For these three CDFs, the percentage of the administered dose absorbed decreased as the applied dose increased. For doses near 300 µg/kg of the three CDFs tested, about 80% of the radioactivity associated with the application site could be removed by swabbing with an acetone-soaked cotton, indicating that the remaining radioactivity had not penetrated through the dermis (Brewster et al. 1989). In another study of male Fischer-344 rats, the percentage of

the administered dose (34 µg/kg) of ^{14}C-2,3,4,7,8-pentaCDF absorbed through the skin over a 3-day period decreased with age of the animal (Banks et al. 1990). The greatest decrease was observed between 10- and 36-week-old rats (22% of the administered dose compared to 15% for the adult rats). When absorption rate was expressed as a function of the applied surface area, in order to eliminate the body weight variable, the mass of 2,3,4,7,8-pentaCDF absorbed by the 10-week-old rats was greater than that observed in 36- and 120-week-old animals. A subsequent study by this group reported that approximately 37% of the 34 µg/kg administered dose of 1,2,3,7,8-pentaCDF was absorbed through the skin (Jackson et al. 1993).

The available information indicates that over a 3-day period, the percentage of the dermal dose absorbed for tetra- and pentaCDFs in animals is less than or equal to half of the percentage observed for oral absorption.

3.1.2 Distribution

Tissue Distribution in Humans. Absorbed CDFs tend to distribute and accumulate in tissue lipid because of their relatively high lipid solubility (octanol/water partition coefficients ranging from 10^7 to 10^8) (Jackson et al. 1993; Maruyama et al. 2002). Studies of postmortem concentrations of CDFs have found CDFs in a variety of tissues including blood, bile, adipose, kidney, liver, pancreas, skeletal muscle, and spleen (Bajanowski et al. 2002; Iida et al. 2007; Maruyama et al. 2002; Ryan et al. 1985a, 1986; Schecter et al. 1989a; Watanabe et al. 2013). On a whole weight basis, adipose tissue had the highest concentrations of CDFs, followed by liver, muscle, and kidney (Ryan et al. 1985a). The most prevalent CDFs were 2,3,4,7,8-pentaCDF 1,2,3,4,7,8-hexaCDF, 1,2,3,6,7,8-hexaCDF and 1,2,3,4,6,7,8-heptaCDF (Iida et al. 2007; Ryan et al. 1985a). When the results were expressed on a lipid basis, the concentration of total CDFs was at least twice as great in liver compared to other tissues, consistent with most of the tissue CDFs associated with tissue lipid content (Iida et al. 2007; Ryan et al. 1985a).

Distribution of CDFs in humans has been studied in deceased patients from the Yusho and Yu-Cheng incidents, in which individuals consumed rice oil contaminated predominantly with PCBs and CDFs. The concentration of total CDFs in adipose tissue and liver of deceased Yusho patients ranged from 3 to 25 ppb (Masuda et al. 1985). No CDFs were detected in unexposed individuals in that study; however, subsequent studies using more sensitive analytical methods detected CDFs in tissues of unexposed Japanese and Chinese individuals (Ryan et al. 1987a). In general, the congeners identified in the tissue and blood of Yusho patients consisted of elevated levels of 2,3,4,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF,

and 1,2,3,6,7,8-hexaCDF, the most prevalent of which was 2,3,4,7,8-pentaCDF (Ryan et al. 1987a). The least prevalent was 2,3,7,8-tetraCDF. Similar results were obtained by analyzing adipose and liver tissues of an infant born to a Yu-Cheng mother (indicating *in utero* transfer or through nursing, or both) and in blood of Yu-Cheng patients (Kashimoto et al. 1985; Masuda et al. 1985). Since ≈40 different CDF congeners were identified in the contaminated rice oil, these results suggest preferential metabolism and retention for certain CDF congeners (see Section 3.1.3). Analyses of tissues of a Yu-Cheng patient who died 2 years after poisoning revealed that the liver had the highest concentration of CDFs (≈35 ppb); the concentration in other tissues was 1 or >1 order of magnitude lower than in the liver (Chen et al. 1985a). The major CDF congeners retained in the liver were 1,2,4,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, and 1,2,3,4,7,8-hexaCDF. The congeneric profile for tissues other than the liver was essentially similar to that of the liver.

Maternal-Fetal-Infant Transfer in Humans. Maternal fetal transfer of CDFs occurs based on detection of CDFs in tissues and correlations between maternal blood concentrations and concentrations of CDFs in cord blood, placenta, and fetal tissue (Abraham et al. 1996, 1998; Schecter et al. 1995; 1998; Tsukimori et al. 2013; Wang et al. 2002, 2004). Concentrations of CDFs in maternal blood and breast milk were correlated (Boda et al. 2018; Todaka et al. 2010; Tsukimori et al. 2011). The rate of transfer to breast milk was sufficient to decrease the blood maternal CDF body burden and increase the blood elimination half-time (Abraham et al. 1998; Milbrath et al. 2009; Schecter et al. 1996; Wittsiepe et al. 2007b). Breast milk concentrations of CDFs decline during nursing as a result of the decline in maternal CDF stores (Beck et al. 1994; Vigh et al. 2013); see Section 5.6 for breastmilk monitoring data. Intake-fecal mass balance studies conducted on nursing infants found that CDFs ingested by nursing infants are absorbed to varying degrees depending, in part, on degree of chlorination (Abraham et al. 1994, 1996; Jödicke et al. 1992; Körner et al. 1993; McLachlan et al. 1993; Pluim et al. 1993). Absorption of hepta- and octaCDFs were estimated to range from 80 to 90%, whereas absorption of less chlorinated CDFs was >90%.

CDFs were reported in the liver and adipose tissue of a breastfed infant born to a mother in the Yu-Cheng cohort (Masuda et al. 1985). Beck et al. (1990a) detected CDFs in the brain, adipose tissue, thymus, spleen, and liver of three infants who died of sudden infant death syndrome (SIDS) before reaching 1 year of age. Maternal exposures were not reported. Of the three infants, only one had been breastfed for a significant period of time (≈6 months). The congeners identified in most tissues of the three infants were 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,6,7,8-hexaCDF, and 1,2,3,4,6,7,8-heptaCDF. The most prevalent were 2,3,4,7,8-pentaCDF and 1,2,3,6,7,8-hexaCDF. On a fat weight basis, the brain and adipose tissue had relatively low levels of CDFs, whereas the liver had

the highest levels, in particular in the infant who had nursed. The congeneric composition did not differ among tissues or across infants. Unequivocal placental transfer of CDFs was demonstrated by detecting CDFs in the liver of stillborn infants (Schecter et al. 1990a).

Tissue Distribution in Laboratory Animal Models

Distribution in Monkeys. In rhesus monkeys, following a single intravenous dose of 30.7 µg ^{14}C-labeled 2,3,7,8-tetraCDF/kg, the ^{14}C was rapidly cleared from the blood (Birnbaum et al. 1981). A two-component exponential elimination from blood was observed, with half-times of 1.5 minutes and 1 hour, respectively. Terminal components of the removal of ^{14}C from the blood were not determined in the study. After 21 days, <10% of the ^{14}C remained in the body. When the concentration of ^{14}C was expressed as CDF per gram of tissue, the concentrations in liver and fat were 4 times that observed in skin and 12 times that observed in muscle and blood. Of the ^{14}C extracted from liver and adipose tissue at day 21 and from blood just after dosing, ~90% appeared to be parent compound. However, 67% of the ^{14}C remaining in blood at day 21 seemed to correspond to metabolites. In marmoset monkeys subcutaneously administered a mixture of CDDs and CDFs, elimination half-times from adipose tissue and hepatic tissue increased with the degree of chlorination (Neubert et al. 1990). The location of the chlorines also influenced the elimination half-times with 2,3,7,8-substituted congeners having longer half-times. The half-times for the CDF congeners tested are presented in Table 3-1.

Table 3-1. Half-Times of Various CDF Congeners in Hepatic and Adipose Tissues of Marmoset Monkeys Subcutaneously Administered a Single Dose of a CDD/CDF Mixture[a]

	Half-times (weeks)	
Congener	Hepatic tissue	Adipose tissue
2,3,7,8-TetraCDF	<0.87 (6 days)	1.39
1,2,3,7,8-/1,2,3,4,8-PentaCDF	0.93 (6.5 days)	1.46
2,3,4,7,8-PentaCDF	8.8	12.3
1,2,3,4,7,8-/1,2,3,4,7,9-HexaCDF	23	68
1,2,3,6,7,8-HexaCDF	14.3	24
1,2,3,7,8,9-HexaCDF	8.2	Not calculated
2,3,4,6,7,8-HexaCDF	18.6	38
1,2,3,4,6,7,8-HeptaCDF	37	Apparently infinite
1,2,3,4,7,8,9-HeptaCDF	79	660
OctaCDF	174	Apparently infinite

CDD = chlorodibenzo-*p*-dioxin; CDF = chlorodibenzofuran

Table 3-1. Half-Times of Various CDF Congeners in Hepatic and Adipose Tissues of Marmoset Monkeys Subcutaneously Administered a Single Dose of a CDD/CDF Mixture[a]

	Half-times (weeks)	
Congener	Hepatic tissue	Adipose tissue

Source: Neubert et al. 1990

A study in marmoset monkeys compared tissue concentrations of CDF congeners in maternal and offspring tissues (Hagenmaier et al. 1990). The concentrations of pentaCDF, hexaCDF, heptaCDF, and octaCDF congeners were considerably lower in fetal (pooled sample from 18-week twins) liver tissue compared to maternal liver tissue. For example, fetal concentrations of 2,3,4,7,8-pentaCDF, 1,2,3,6,7,8-hexaCDF, and 1,2,3,4,6,7,8-heptaCDF were approximately 30, 300, and 700 times, respectively, lower than maternal concentrations. At birth, CDF concentrations in the liver were much lower than adults exposed for a similar duration; the sum of CDF congener concentrations were 1,059 pg/g wet weight in the newborns compared to 54,584 pg/g wet weight in adults. However, the concentration of CDF congeners in adipose tissue were similar in the newborn and adult monkeys. On PND 33, the sum of CDF congener concentrations in infants was approximately 4 times lower than in adults (20,266 versus 87,929 pg/g wet weight). The largest differences were found for the higher chlorinated congeners; the ratios of infant to mother were 0.1, 0.2, and 0.7 for octaCDF, heptaCDF, and hexaCDF, respectively. In contrast, the tetraCDF and pentaCDF congener concentrations in the liver were similar in the infants and adults (ratios of 1.1 and 1.0, respectively) (Hagenmaier et al. 1990).

***Distribution in Mice*.** Distribution of absorbed CDFs has been extensively studied in mice (Aozasa et al. 1995; Decad et al. 1981b; De Jongh et al. 1993; DeVito et al. 1995, 1997, 1998; Diliberto et al. 1999; van Ede et al. 2013; Weber and Birnbaum 1985). Following a single intravenous dose of 30.6 µg ^{14}C-labeled 2,3,7,8-tetraCDF/kg, ^{14}C was concentrated in the liver, adipose tissue, skin, and muscle of C57BL/6J and DBA/2J male mice; these tissues accounted for >75% of the injected dose (Decad et al. 1981b). At all times over a 10-day period (except at day 10), the livers of C57BL/6J mice had more ^{14}C than livers of DBA/2J mice (the opposite was observed for fat tissue and muscle); however, the elimination half-time of the ^{14}C from this organ was 1.8 days in both strains. Elimination half-times from adipose tissue were 6 times longer in DBA/2J mice than in the C57BW6J strain, reflecting the higher fat tissue content in the former strain. Greater than 95% of the ^{14}C detected in tissues represented unmetabolized CDF. Four days following an oral dose of ^{14}C-labeled 2,3,4,7,8-pentaCDF, approximately 50% of the ^{14}C dose was in liver, 4–5% was in adipose, ~1% was in skin, and 1% was in skeletal muscle of C57BL/6N and 129/Sv

mice (Diliberto et al. 1999). During the 4-day period following dosing, 26–33% of the dose was excreted; therefore, the liver accounted for approximately 60–80% of the body burden.

Hepatic uptake of pentaCDF in mice was shown to be dependent on expression of CYP1A2, which acts as an inducible binding protein for CDFs and CDDs (DeVito et al. 1997, 1998; Diliberto et al., 1995, 1997, 1999). Hepatic uptake of CDF congeners increases with CYP1A2 induction potency (DeVito et al. 1998; van Ede et al. 2013). Knockout of CYP1A2 decreased hepatic uptake by >10-fold and increased uptake in adipose by a factor of 5 (Diliberto et al. 1999). In mice expressing CYP1A2, observed liver/adipose concentration ratios ranged from 5 to 50, with the highest ratio observed for 2,3,4,6,8-pentaCDF, a relatively potent inducer of CYP1A2 (DeVito et al. 1998; Diliberto et al. 1999; van Ede et al. 2013). Retention of CDFs in liver in mice varies with chlorination. Liver elimination half-times of 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF were 1.5 days (Weber and Birnbaum 1985) and 65 days (De Jongh et al. 1992), respectively.

The distribution of CDFs in pregnant C57BW/6N mice and in the embryos was examined after oral administration of 800 µg ^{14}C-labeled 2,3,7,8-tetraCDF/kg in corn oil to the dams on GD 11 (Weber and Birnbaum 1985). Approximately 30 and 0.41% of the radioactivity per gram of tissue was found in the maternal liver and blood, respectively (only maternal liver and blood were analyzed), on GD 12; these percentages declined by half in both tissues on subsequent days (GD 14 and GD 13, respectively). The elimination half-time from the liver was estimated to be 1.5 days. Less than 0.01% of the radioactivity dose was detected in whole embryos at day 12, and no radioactivity could be detected at later times.

Distribution in Rats. Studies conducted in rats have also shown liver and adipose to be the major sites of uptake and retention of absorbed CDFs (Banks et al. 1990; Birnbaum et al. 1980; Brewster and Birnbaum 1987; Brewster et al. 1989; Golor et al. 1993; Körner et al. 2002; Van Ede et al. 2014; Vanden Heuvel et al. 1994; Weber and Birnbaum 1985). After a single dose of 30.6 µg/kg of ^{14}C-labeled 2,3,7,8-tetraCDF to male Fischer-344 rats, the blood, liver, fat, skin, and muscle accounted for >90% of the retained ^{14}C dose at various times after dosing (Birnbaum et al. 1980). Nearly all of the ^{14}C detected in tissues was unchanged CDF. Loss of radioactivity from tissues could be described by exponential curves with one or more components. Half-times for the early components ranged from 0.02 days for blood and muscle to 0.45 days for skin. Late components had half-times ranging from 0.72 days for muscle to 11.1 days for skin. Clearance from fat showed a single component with a half-time of 3.7 days. In other tissues, such as adrenals, kidneys, thymus, heart, and lungs, 90% of the radioactivity was cleared within 24 hours; in contrast, the specific activity in the liver decreased only 50% in the same time period. Following oral

dosing, liver/adipose concentration ratios of 2,3,4,7,8-pentaCDF ranged from 21 to 41 (Golor et al. 1993; Körner et al. 2002; Van Ede et al. 2014). Retention of CDFs in liver in rats varies with chlorination. Liver retention of 2,3,4,7,8-pentaCDF was >50% of the dose, whereas retention of 2,3,7,8-tetraCDF ranged from 3 to 5% of the dose (Birnbaum et al. 1980; Brewster and Birnbaum 1987). Chlorine in substitution in position 4 appears to delay metabolic transformation (Burka et al. 1990). The liver retention half-time of 1,2,3,7,8-pentaCDF was 3.3 days, whereas the half-time for 2,3,4,7,8-pentaCDF was 108 days (Van den Berg et al. 1989). No significant age-related changes in the distribution of 2,3,4,7,8-pentaCDF in rats were observed (Banks et al. 1990). For the most part, changes in tissue distribution reflected age-related changes in the total mass of specific tissues and organs.

Tissue distribution of CDFs was studied in male Fischer rats 3 days after receiving single applications of 31–340 µg/kg of ^{14}C-labeled 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, or 2,3,4,7,8-pentaCDF in acetone applied on a clipped area of the back (Brewster et al. 1989). For example, following the lowest dose, the liver had the most radiolabel per tissue (5.4% for 2,3,7,8-tetraCDF, 4.1% for 1,2,3,7,8-pentaCDF, 14.9% for 2,3,4,7,8-pentaCDF), followed by adipose tissue, skin, and muscle. All other tissues (other than liver, adipose, skin, and muscle) had <0.01% of the dose. The relative amounts of the dose in tissue decreased as dose increased, indicating decreased absorption at higher administered doses. The percentages of the administered 2,3,4,7,8-pentaCDF dose detected in the liver and adipose tissue were 72 and 6.7%, respectively, when expressed as a percentage of body burden. On a gram of tissue basis, the greatest concentration of radiolabel was detected in the liver. Of the three congeners evaluated, 2,3,4,7,8-pentaCDF had the highest concentration in the liver, followed by 2,3,7,8-tetraCDF and 1,2,3,7,8-pentaCDF. Consistent with oral exposure, these results indicate that liver retention is significant and congener-specific, with significantly higher amounts of the pentaCDF substituted in position 4 retained.

Distribution in Guinea Pigs. After a single intravenous injection of ^{14}C-labeled 2,3,7,8-tetraCDF in guinea pigs (6 µg/kg) ^{14}C accumulated in liver, fat, muscle, and skin (Decad et al. 1981a). Analysis of these tissues suggested the presence of only parent compound. Three hours after dosing, a loss of ^{14}C from the liver could be accounted for by increases in adipose tissues and skin. After 1 day, mobilization of fat stores resulted in redistribution of radioactivity into the liver. Accumulation of radioactivity in other tissues was minimal over a 9-day period. Experiments conducted in guinea pigs administered 6 µg of labeled ^{14}C-labeled 2,3,7,8-tetraCDF/kg by gavage showed that most of the radioactivity (46%) accumulated in adipose tissue 3 days after dosing (Decad et al. 1981a). Liver, muscle, and skin accounted for about 16% each. After six or seven weekly oral doses of 2,3,7,8-tetraCDF at 1 µg/kg, the distribution

of radiolabel in the tissues of guinea pigs was similar to that observed after a single oral dose (Decad et al. 1981a).

Mechanisms of Distribution. The mechanism by which CDFs cross biological membranes is not known. A contributing mechanism of distribution is partitioning into tissue lipids (Jackson et al. 1993; Maruyama et al. 2002). Accumulation of CDFs in liver has been shown to depend on expression of CYP1A2, which acts as an inducible binding protein for CDFs (DeVito et al. 1997, 1998; Diliberto et al., 1995, 1997, 1999).

3.1.3 Metabolism

Information on the metabolism of CDFs in humans can be derived from Yusho and Yu-Cheng patients since these subjects ingested contaminated rice oil in which ≈40 different CDF congeners were identified. Analysis of hepatic adipose tissues of some patients revealed the presence of highly chlorinated congeners and congeners that lacked adjacent unsubstituted carbon atoms (Chen et al. 1985a; Masuda et al. 1985).

The metabolic disposition of CDFs in animals has not been extensively studied. However, some generalizations can be made based on the available data. It is generally accepted that biotransformation of CDFs occurs primarily in the liver (Birnbaum 1985; Olson et al. 1994; Van den Berg 1989). The major metabolic reactions include hydroxylation with or without dechlorination or migration of substituents from the site of hydroxylation to the adjacent carbon, and oxygen bridge cleavage, followed by glucuronidation. Cytochrome P450 isoenzymes appear to catalyze the metabolic reactions (Olson et al. 1994; Tai et al. 1993; Van den Berg 1989).

The major possible metabolic products (specific compounds were not identified) of several CDFs found in rat bile after oral and intravenous dosing of CDFs have been described (Poiger et al. 1989). Female Sprague-Dawley rats were administered a single oral dose of several tetra- and pentaCDFs in corn oil. In addition, 1,2,3,6,7,8-hexaCDF and 1,2,3,4,7,8-heptaCDF were injected intravenously. The doses ranged between 0.4 and 3.7 mg/kg. Samples of bile were analyzed for 3–7 days starting 2 hours after dosing. The tetra-substituted CDFs (1,3,7,8-, 2,3,7,8-, and 2,3,6,8-tetraCDF) exhibited a fairly high rate of metabolic conversion (no quantitative data reported), and each gave rise to tri- and tetra-hydroxylated and dihydroxylated derivatives. No ring-opened compounds were detected, suggesting that substitution of *ortho* atoms to the oxygen is not important for cleavage of the ether bond in tetraCDFs. A study by Burka

et al. (1990) identified glucuronide and sulfate conjugates of 4-hydroxy-2,3,7,8-tetraCDF and 3-hydroxy-2,7,8-triCDF as the major biliary metabolites in rats dosed intravenously with 2,3,7,8-tetraCDF.

Among the pentaCDFs, the rate of transformation of 1,2,3,4,8-, 1,2,3,7,8-, and 2,3,4,7,8-pentaCDF was high, moderate, and low, respectively (Poiger et al. 1989). The predominant metabolite (out of seven compounds found) of 1,2,3,7,8-pentaCDF was a hydroxy-pentaCDF. According to investigators, formation of 6,7-dihydroxy-pentaCDF may also have occurred. Tetrachlorinated compounds were also identified, indicating dehalogenation. The major metabolite (out of 12 compounds found) of 1,2,3,7,8-pentaCDF was a dihydroxy-pentaCDF; other derivatives included monohydroxy-tetra- and pentaCDFs and a trichloro-dihydroxyCDF. Metabolism of 2,3,4,7,8-pentaCDF led to two major compounds (out of 10 compounds found), a methoxy-pentaCDF and a dimethoxy-pentachlorobiphenyl; the latter formed by ether cleavage. A sulfur-containing metabolite was also present. Unmetabolized pentaCDFs were also excreted in the bile. Only a small amount of a hydroxy-pentaCDF was identified from 1,2,3,6,7,8-hexaCDF, whereas no metabolites were detected from 1,2,3,4,6,7-heptaCDF.

No metabolites were detected in urine, feces, liver, and adipose tissue of male Wistar rats given a single gavage dose of 250 mg/kg octaCDF in peanut oil (Veerkamp et al. 1981).

The main conclusions regarding metabolic transformation of CDFs are that chlorine substituents in positions four or six, in addition to the lateral positions, inhibit metabolism more than chlorines in positions one and nine, and that metabolic rate strongly decreases as the number of chlorine atoms increases.

Mechanisms of Metabolism. Studies conducted in microsomes from rat and human liver indicate that hydroxylation of 2,3,7,8-tetraCDF is mediated by the microsomal enzyme, CYP1A1. 2,3,7,8-tetraCDF was metabolized to 4-hydroxy-2,3,7,8-tetraCDF in human liver microsomes and recombinant yeast microsomes expressing CYP1A1, but not in yeast microsome expressing CYP1A2 (Tai et al. 1993). 2,3,7,8-TetraCDF was metabolized in liver slices, isolated hepatocytes, and liver microsomes from rats induced by pre-treatment with 2,3,7,8-tetraCDD (Olson et al. 1994; Tai et al. 1993). Hydroxylation of 2,3,7,8-tetraCDF in rat liver microsomes was inhibited by inhibitors or antibodies to CYP1A1, but not by inhibitors or antibodies to CYP1A2 (Tai et al. 1993).

3.1.4 Excretion

Excretion in Humans. Quantitative information on the routes of excretion of absorbed CDFs in humans was not available. Fecal excretion of CDFs can be measured in humans; however, these measurements represent the contributions of absorbed and unabsorbed CDFs (Jödicke et al. 1992; McLachlan et al. 1993; Moser and McLachlan 2001; Schlummer et al. 1998; Schrey et al. 1998). In some studies, fecal excretion was found to exceed measured dietary intakes of CDFs (negative balance) suggesting that at least some of the fecal CDF was derived from body stores (Moser and McLachlan 2001; Schrey et al. 1998). Dietary intake-fecal excretion balance (net absorption) was found to correlate with concentrations of CDFs in blood lipid, suggesting a relationship between fecal excretion and body burden (Schlummer et al. 1998).

Numerous studies estimated rates of elimination of CDFs from longitudinal measurements of CDFs in serum or blood lipid (Table 3-2). Elimination rates reported in these studies do not necessarily distinguish elimination by metabolism or excretion of CDFs. These studies used a variety of approaches to estimate the half-times. Most studies estimated the half-times by fitting longitudinal data on observed blood CDFs to single exponential models, from which a half-time can be calculated as follows:

$$t_{1/2} = \frac{t \cdot \ln(2)}{\ln(\frac{C_0}{C_t})}$$

where t is time, C_0 is the concentration at time=0 and C_t is the concentration at time t. Several factors can affect these estimates, including the observation time (epoch) over which the half-times were estimated, ongoing exposures that occur during the epoch (e.g., baseline dietary exposures), age and body fat levels, measurement error, and statistical and/or kinetics models used in estimating half-times (Matsumoto et al. 2016; Milbrath et al. 2009). After cessation of a period of elevated exposure (e.g., occupational), blood CDF concentrations will decrease towards a value determined by current baseline exposure. As a result, measured half-times will depend on the epoch in which the blood concentrations are measured and its displacement from the period of elevated exposure (Matsumoto et al. 2009, 2016). Half times measured in epochs closer to the period of elevated exposure will reflect elimination of the body burden accumulated during the exposure, whereas half-times measured in epochs that are distant from the period of elevated exposure will be more greatly influenced by variations in baseline exposures (e.g., time trends in dietary intakes). For example, relatively long half-times ranging from 22 to 44 years were estimated for 2,3,4,7,8-pentaCDF based on blood measurements made 32 years after the Yusho incident. Half-times also appear to vary with the blood CDF concentration, which, in some studies, may have resulted

Table 3-2. Estimated Blood Elimination Half-Lives for Chlorodibenzofuran (CDF) Congeners in Humans

CDF congener	Subject[a]	Epoch[b] (years)	Interval[c] (years)	Half-life[d] (years)	Range	Reference
2,3,4,7,8-PentaCDF	Adult, occupational (n=43)	6	1	19.6[d]	NR	Flesch-Janys et al. 1996
1,2,3,4,7,8-HexaCDF				6.2[d]	NR	
1,2,3,6,7,8-HexaCDF				6.0[d]	NR	
2,3,4,6,7,8-HexaCDF				5.8[d]	NR	
1,2,3,4,6,7,8-HeptaCDF				3.0[d]	NR	
1,2,3,4,7,8,9-HeptaCDF				3.2[d]	NR	
2,3,4,7,8-PentaCDF	Adult, occupational (n=6)	6	16	13.9	4.6–23.1	Rohde et al. 1999
1,2,3,4,7,8-HexaCDF				8.7	4.1–17.3	
1,2,3,6,7,8-HexaCDF				5.8	3.6–9.2	
2,3,4,6,7,8-HexaCDF				9.9	8.7–12.6	
1,2,3,4,6,7,8-HeptaCDF				3.9	2.5–4.6	
2,3,4,7,8-PentaCDF	Adult, occupational (n=1)	6	2	7.2	NR	Schecter et al. 1990b
1,2,3,4,7,8-HexaCDF				4.4	NR	
1,2,3,6,7,8-HexaCDF				4.3	NR	
1,2,3,4,6,7,8-HeptaCDF				4.1	NR	
2,3,4,7,8-PentaCDF	Adult, Yusho (n=10)	8	22	9.6[e]	5.7–36	Ryan et al. 1993
1,2,3,4,7,8-HexaCDF				7.8[e]	4.3–54	
2,3,4,7,8-PentaCDF	Adult, Yusho (n=5)	15	14	7.7	5.2, 14.3	Masuda 2001
1,2,3,4,7,8-HexaCDF				5.1	3.9–6.9	
1,2,3,4,6,7,8-HeptaCDF				3.5	2.6–6.6	
2,3,4,7,8-PentaCDF	Adult, Yusho, >0.5 ppb (n=22)	5	32	21.7	NR	Matsumoto et al. 2009
2,3,4,7,8-PentaCDF	Adult, Yusho, 0.2–0.5 ppb (n=63)	5	32	44.0	NR	
2,3,4,7,8-PentaCDF	Adult, Yusho, 0.1–0.2 ppb (n=40)	5	32	25.6	NR	
2,3,4,7,8-PentaCDF	Adult, Yu-Cheng (n=3)	15	1	2.9	2.7–3.6	Masuda 2001
1,2,3,4,7,8-HexaCDF		15	1	3.5	2.7–3.6	
1,2,3,4,6,7,8-HeptaCDF		15	1	2.5	2.2–2.6	
2,3,4,7,8-PentaCDF	Adult, Yu-Cheng (n=3)	19	14	3.4	3.18–3.95	Ryan et al. 2001
1,2,3,4,7,8-HexaCDF		19	14	3.7	3.19– 4.01	

Table 3-2. Estimated Blood Elimination Half-Lives for Chlorodibenzofuran (CDF) Congeners in Humans

CDF congener	Subject[a]	Epoch[b] (years)	Interval[c] (years)	Half-life[d] (years)	Range	Reference
2,3,4,7,8-PentaCDF	Adult, Yu-Cheng (n=3)	9	1	2.2	1.9–2.3	Ryan et al. 1993
1,2,3,4,7,8-HexaCDF		9	1	2.6	2.1–2.9	
1,2,3,4,6,7,8-HeptaCDF		9	1	2.3	2.0–2.9	
2,3,4,7,8-PentaCDF		SS[g]	SS[g]	4.9	3.3–7.1[h]	Ogura 2004
1,2,3,4,7,8-HexaCDF	Adults, general (n=253)[f]	SS[g]	SS[g]	9.9	6.6–15[h]	
1,2,3,6,7,8-HexaCDF		SS[g]	SS[g]	17	11–26[h]	
1,2,3,4,6,7,8-HeptaCDF		SS[g]	SS[g]	4.8	3.2–7.2[h]	
2,3,4,7,8-PentaCDF	Infant (n=1)	1	0.1	0.30		Leung et al. 2006
2,3,4,7,8-PentaCDF		1	0.1	0.23		

[a]Studies are longitudinal in design, unless specified.
[b]Observation time for estimating half-times.
[c]Interval between end of high level exposure and start of observations epoch.
[d]Mean, unless specified.
[e]Median.
[f]Cross-sectional study design.
[g]Estimated assuming steady-state blood concentration and estimated absorption rate from diet.
[h]95% confidence interval.

NR = not reported; SS = steady state

from effects of body burden on elimination or that the body burdens were approaching a new steady state governed by recent exposures (Leung et al. 2005; Matsumoto et al. 2009).

Some studies estimated the half-time based on cross-sectional blood CDF concentrations and estimates CDF intakes:

$$t_{1/2} = \frac{\ln(2)}{AF \cdot I}$$

where *AF* is an assumed absorption fraction for ingested CDF and *I* is the rate of intake of CDFs (Ogura 2004). Several factors can affect these estimates, including error in estimating long-term intake from short-term intake studies, subjects not being in steady state (which cannot be verified from cross-section observations), age and body fat levels, measurement error; and statistical models used in estimating parameters.

Table 3-2 includes several studies that estimated half-times for multiple congeners, of which the largest (n=43 adults) showed a trend for decreasing half-time with increasing chlorination (Flesch-Janys et al. 1996). This trend is also evident in several smaller studies (Masuda 2001; Rohde et al. 1999). In each of these studies, half-times were estimated from longitudinal measurements of blood CDF concentrations following cessation of a period of elevated exposure. The largest multiple-congener comparison (n=253) showed no consistent trend with chlorination (Ogura 2004). However, the Ogura (2004) study estimated half-times from cross sectional data on blood CDF concentrations and dietary CDF intakes, rather than longitudinal measurements of blood CDF concentrations. This calculation assumes that the individuals were in a steady state and that the cross-sectional estimates of dietary intakes reflected long-term intakes of each individual, an assumption that is unlikely to be accurate for CDFs that have long half-times.

Excretion in Animals. Studies conducted in monkeys and rodents have shown that the primary routes of excretion of absorbed CDFs are feces and urine, with feces being the dominant route in monkeys, mice, and rats.

Excretion in Monkeys. In rhesus monkeys, during a 21-day period following a single intravenous dose of ^{14}C-labeled 2,3,7,8-tetraCDF/kg (30.7 µg/kg), 43% of the ^{14}C dose was excreted in feces and 8% was excreted in urine (Birnbaum et al. 1981). Fecal and urinary ^{14}C consisted of polar metabolites.

Excretion in Mice. Feces are the dominant route of excretion of CDFs in mice (Decad et al. 1981b; Diliberto et al. 1999). In C57BL/6J mice, during a 10-day period following a single intravenous dose of ^{14}C-labled 2,3,7,8-tetraCDF (30.6 µg/kg), 82% of the ^{14}C dose was excreted in feces and 13% was excreted in urine (Decad et al. 1981b). In DBA/2J mice, 56% of the dose was excreted in feces and 20% was excreted in urine (Decad et al. 1981b). Excreted ^{14}C in feces and urine consisted of parent compound and polar metabolites. In C57BL/6N and 129/Sv mice, during a 4-day period following a gavage dose of ^{14}C-labeled 2,3,7,8-tetraCDF (300 µg/kg) fecal excretion ranged from 21 to 30% of the of ^{14}C dose and urinary excretion ranged from 2 to 5% of the dose (Diliberto et al. 1999). Knockout of CYP1A2 expression in mice decreased hepatic retention of ^{14}C-labeled 2,3,7,8-tetraCDF and increased urinary excretion (25% of the ^{14}C dose; Diliberto et al. 1999). Pregnant C57BL/6N mice administered a single dose of 800 µg ^{14}C-labeled 2,3,7,8-tetraCDF/kg by gavage on GD 11 excreted 80% of the administered dose in the feces over a 3-day period; urinary excretion accounted for 5.4% of the dose (Weber and Birnbaum 1985).

Excretion in Rats. In rats, during a 5-day period following a single intravenous dose of ^{14}C-2,3,7,8-CDF (30.6 µg/kg) approximately 80% of the ^{14}C dose was excreted in feces and 5% in urine (Birnbaum et al. 1980). Bile was the major source of ^{14}C in feces. Fecal and urinary ^{14}C consisted of polar metabolites. In rats that received a gavage dose of ^{14}C-2,3,7,8-tetraCDF (31 or 306 µg/kg), approximately 70% of the ^{14}C dose was excreted in feces and approximately 1.5% was excreted in urine over a 3-day period (Birnbaum et al. 1980). Excretion of CDFs was studied in male Fischer-344 rats after receiving single dermal applications (3–340 µg/kg) of labeled ^{14}C-labeled 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, or 2,3,4,7,8-pentaCDF in acetone to a clipped area on their backs (Brewster et al. 1989). Elimination of ^{14}C occurred almost exclusively through the feces. For each congener, the relative amount of ^{14}C detected in the excreta decreased as the dose increased. At the lowest dose tested, fecal excretion accounted for 27% of the ^{14}C dose for 2,3,7,8-tetraCDF, 8% for 1,2,3,7,8-pentaCDF, and 0.7% for 2,3,4,7,8-pentaCDF. Within 3 days of dosing, 56, 32, and 2% of the respective body burden of ^{14}C from 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, and 2,3,4,7,8-pentaCDF had been excreted. Two or more polar metabolites were detected in the feces of rats administered 31 µg 2,3,7,8-tetraCDF/kg and 34 µg 1,2,3,7,8-pentaCDF/kg. Approximately 90% of the 2,3,4,7,8-pentaCDF-derived fecal ^{14}C appeared to be parent compound. Excretion parameters for 2,3,4,7,8-pentaCDF-derived ^{14}C did not change as a function of age in male Fischer-344 rats (Banks et al. 1990). These results are consistent with the view that CDF congeners with chlorine substitution in position 4 (2,3,4,7,8-pentaCDF) are excreted slower than those unsubstituted in position 4 (2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF). A contributing factor to this difference may be slower metabolism of CDFs with chlorine substitution in position 4; only parent compound was found in the

feces of rats given 2,3,4,7,8-pentaCDF, whereas polar metabolites could be detected in feces of those given 2,3,7,8-tetraCDF and 1,2,3,7,8-pentaCDF.

Excretion in Guinea Pigs. Unlike monkeys, mice, and rats, fecal excretion was not the dominant excretory pathway for 2,3,7,8-tetraCDF in guinea pigs. In guinea pigs, during a 9-day period following a single intravenous dose of ^{14}C-labeled 2,3,7,8-tetraCDF (6 μg/kg), approximately 7% of the ^{14}C dose was excreted in feces and approximately 7% was excreted in urine. More than 90% of excreted ^{14}C was parent compound (Decad et al. 1981a). Over the same time period, following an oral dose of ^{14}C-labeled 2,3,7,8-tetraCDF (6 μg/kg), guinea pigs excreted 11% of ^{14}C dose in the feces and 3.3% in urine (Decad et al. 1981a). Slower elimination (metabolism and excretion) of 2,3,7,8-tetraCDF in the guinea pig compared to rats and mice, contributes to the higher toxic potency of 2,3,7,8-tetraCDF in guinea pigs (Decad et al. 1981a).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

Much of the research on modeling the toxicokinetics of CDFs has focused on one-compartment models or statistical models for estimating elimination half-times (Campbell et al. 1996; Flesch-Janys et al. 1996; Kerger et al. 2007a, 2007b; Leung et al. 2007; Ogura et al. 2001; Portier et al. 1999; Rohde et al. 1999; Ryan et al. 2001; Schecter et al. 1990b; Tuomisto et al. 2016). Multicompartment models of varying complexity have also been developed simulating absorption, distribution, and elimination CDFs (Carrier et al. 1995a, 1995b; Maruyama et al. 2002, 2003).

Carrier et al. (1995a, 1995b) developed a three-compartment model simulating the absorption, distribution, and elimination of CDF congeners in humans and mammalian species. The model includes compartments representing blood, adipose, and liver tissues. The liver compartment simulates the

nonlinear relationship between the fraction of the body burden in liver (f_hC_b), which increases with increasing body burden (C_b; Carrier et al. 1995a). This is achieved by simulating binding of CDFs to an inducible protein in liver (e.g., CYP1A2) using parameters that can be adjusted to reproduce the observed dose relationships for the liver fraction of the body burden (f_hC_b), the adipose fraction of the body burden ($f_{at}C_b$), and the liver/adipose tissue concentration ratio (C_h/C_{at}) relationships. The model assumes instantaneous quasi-steady state for the absorbed dose, exchanges of free (unbound) CDF between all lipid fractions of compartments, and binding in the liver. Saturable binding in the liver is simulated as an instantaneous equilibrium:

$$C_x = \frac{C_x}{C_x \cdot K_D}$$

where C_x is the free (unbound) concentration and K_D is the binding dissociation constant. Induction of binding is assumed to have limited capacity with respect to the liver CDF concentration. This limitation is simulated with a Michaelis-Menten function of the liver fraction of the body burden:

$$f_h C_b = f_h^{min} + \frac{(f_h^{max} - f_h^{min}) \cdot C_b}{K + C_b}$$

where K is the induction constant and f_h^{min} and f_h^{max} are minimum and maximum (saturating) liver fractions, respectively. Elimination is assigned to the liver and governed by a first-order rate coefficient (day^{-1}). The model was evaluated with data on adipose concentrations of pentaCDF in Yu-Cheng patients (Ryan et al. 1993).

Maruyama et al. (2002, 2003) developed a six-compartment model for simulating absorption, distribution, and elimination of CDF congeners in humans. The model includes compartments representing blood, fat kidney, liver, muscle, skin, and a lumped compartment representing all other richly perfused tissues. Gastrointestinal absorption was governed by congener-specific absorption fractions that ranged from 87 to 99%. Exchanges of congeners between blood and tissues was assumed to be flow-limited; governed by tissue plasma flows (L/hour), the tissue-plasma partition coefficient, and the concentration gradient between blood and tissue venous blood. Elimination of congeners occurs via bile to feces, and kidney to urine; both are governed by first order-rate constants (day^{-1}), the concentration of congener in liver or kidney, and volume flow rates for bile or urine (L/day). The model does not simulate metabolism as a separate elimination pathway. The model was evaluated with data on blood and tissue congener levels in Yusho and Yu-Cheng patients (Iida et al. 1999a, 1999b).

3.1.6 Animal-to-Human Extrapolations

There are limited data on CDFs that allow for evaluating species differences. Potential differences have been more extensively investigated for CDDs; in particular, 2,3,7,8-TCDD. As discussed in ATSDR (2012), species differences in Ah receptor binding affinities have been reported between humans, rats, and mice. These data suggest that humans have approximately one-tenth the binding capacity compared to laboratory species. Comparisons of the EROD activity between humans and rats also suggest that 10-fold higher doses of 2,3,7,8-TCDD are needed to elicit the same response as observed in rats. Similarly, it appears that a higher 2,3,7,8-TCDD body burden is needed to induce increases in CYP1A1 gene expression in humans as compared to laboratory rodents. Although species differences have been found for 2,3,7,8-TCDD that suggest that humans may be less sensitive than rodents, it is not known whether these differences would also be found for CDF congeners. Comparisons of the endpoints of toxicity between those reported in the Yusho and Yu-Cheng cohorts and those reported in laboratory animals exposed to single CDF congeners or mixtures of congeners suggest a similarity in their toxicities. However, data are not available that would allow for dose-response comparisons.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health, nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high levels of CDFs are discussed in Section 5.7, Populations with Potentially High Exposures.

There are limited data on the toxicity of CDFs in children, and the toxicity is assumed to be similar to adults. As discussed in Section 2.16, *in utero* and/or lactational exposure to CDFs results in developmental effects. Adverse effects have been observed in the children of women exposed to CDFs in the Yusho and Yu-Cheng incidents. These effects included skin, nail, gingival hyperpigmentation, deformed nails, conjunctivitis, and acne (Funatsu et al. 1971; Gladen et al. 1990; Hsu et al. 1985, 1993; Rogan et al. 1988; Taki et al. 1969; Yamaguchi et al. 1971; Yoshimura 1974). These effects are similar to those observed in adults. Other reported effects in these children include decreases in birth weight (Funatsu et al. 1971; Lan et al. 1987; Rogan 1989; Taki et al. 1969; Yamaguchi et al. 1971), decreased muscular development (Guo et al. 1994a), cognitive delays (Chen et al. 1992; Guo et al. 1995), and possibly reproductive effects (Guo et al. 2000; Hsu et al. 2005; Yang et al. 2005). Studies in laboratory animals report several developmental effects including hydronephrosis, cleft palate, fetal mortality, decreases in fetal weight, decreases in thymus weight, and impaired development of the reproductive system (Birnbaum et al. 1987a, 1987b; Couture et al. 1989; Madsen and Larsen 1989; Salisbury and Marcinkiewicz 2002; Taura et al. 2014; Weber et al. 1984, 1985).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to CDFs are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for CDFs from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of

tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by CDFs are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

CDFs are pervasive environmental contaminants found in body tissues and fluids of the general population. Because they are lipophilic and have long half-lives, certain CDF congeners containing the 2,3,7,8-chlorine substitution pattern (particularly 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF) preferentially accumulate in lipid-rich tissues, especially adipose tissues, and are present in whole blood, serum, plasma, and human milk. High amounts of CDFs are also found in the liver. In general, CDFs have been found at lower concentrations in all other tissues examined to date. Serum and adipose tissue CDF levels are indicators of exposure that can provide an estimate of body burden because, as discussed in Section 3.1.2, some studies have reported that levels of CDFs and congener patterns are similar in serum, adipose, and other tissues when expressed on a fat weight basis (Ryan et al. 1985a; Schecter and Ryan 1989). However, concentrations of CDFs on a fat weight basis are higher in liver than in adipose tissue (Beck et al. 1990a; Thoma et al. 1990). A study of PCB exposure suggests that measurement in both serum and adipose may be more predictive of body burden than each parameter by itself, because concentration in serum varies with the concentration of lipids in serum (Brown and Lawton 1984). Measurements of CDFs in human milk have been used in general monitoring studies and provide some information on previous exposures; no reports were located that used these data to estimate body burden or environmental exposure levels. Quantitative exposure to CDFs can be estimated if the steady-state body burden and elimination half-lives of congeners are known. An elimination half-time from blood of ≈2–2.5 years was estimated for 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF in Yu-Cheng victims (Ryan et al. 1993). Sampling was conducted over a 8-year period starting 2 years after the incident. The same investigators (Ryan et al. 1993) calculated a median elimination half-time of 10 years for the same

congeners in Yusho victims. In this case, sampling was conducted over an 8-year period, but starting 14 years after the poisoning had occurred.

Hair analysis can be a useful method for identifying recent exposure to CDFs in ambient air (Schramm et al. 1992). Hair levels appear to reflect body burden and atmospheric burden (Nakao et al. 2002; Tirler et al. 2001). When the concentrations in blood were compared to hair levels in a study of six adults, a correlation between the two was only found for 2,3,4,7,8-pentaCDF; no correlations were found for the other congeners (Nakao et al. 2002). Another study found that the congener profile in hair differed from that of blood or breast milk levels (Tirler et al. 2001). For example, the ratio of 1,2,3,7,8-pentaCDF to 2,3,4,7,8-pentaCDF in blood is at least 1:10, but in hair the ratio was approximately 1:2. The congener pattern in hair was similar to skin lipid, environmental samples, and spruce needles.

3.3.2 Biomarkers of Effect

Chloracne and changes in the Meibomian glands of the eyelid are effects clearly associated with significant exposure to CDFs based on outcomes of the Yusho and Yu-Cheng incidents. Although chloracne and lesions of the eyelid are biomarkers that are distinct and easily observed, they may not be the most sensitive indicators of human exposure. Additionally, these effects are not associated specifically with CDFs, as they can also be induced by other chloroaromatic compounds (e.g., CDDs) that act by a common Ah receptor-mediated mechanism (see Section 2.20). As discussed in Section 3.3.2, chloracne in Yu-Cheng victims was associated with an estimated body burden of 4.0 µg/kg/day of 2,3,4,7,8-pentaCDF equivalent (PEQ), or about 300 µg (PEQ) in an adult (Ryan et al. 1990).

Biochemical changes (e.g., increased serum levels of hepatic enzymes, disorders of lipid and carbohydrate metabolism, unbalanced porphyrin metabolism), and/or changes in liver size, ultrastructure, or histology can indicate effects induced by CDFs, but are not specific for these or other chemicals. Biochemical changes in the placenta of women exposed during the Yu-Cheng incident were evaluated for possible use as biomarkers (Lucier et al. 1987, 1990; Sunahara et al. 1987). Decreased placental epidermal growth factor receptor phosphorylation capacity was associated with decreased birth weights, but this is likely to be a general effect of similarly structured chloroaromatic compounds.

3.4 INTERACTIONS WITH OTHER CHEMICALS

Since concurrent exposure to mixtures of CDFs, CDDs, and other chloroaromatics is common in the general environment, studies regarding interactions of CDFs with other substances have aimed almost exclusively at determining possible changes in the relative potency of individual congeners in the presence of other congeners or 2,3,7,8-TCDD. This is largely because in using the TEF approach to risk assessment of CDFs and CDDs, which assumes additivity of toxic responses, it is important to know whether or not interactions between congeners play a role in the final expression of a particular mixture's toxicity. Therefore, it is of vital importance to elucidate whether interactions occur and their nature, so that toxicity of mixtures is appropriately estimated, including mixtures associated with hazardous waste sites as well as the Yusho and Yu-Cheng incidents. The validity of the TEF approach for assessing mixtures of CDFs and CDDs has been investigated using both environmental (Eadon et al. 1986) and experimental mixtures (DeVito et al. 1993; Pluess et al. 1988a) with varying results depending upon the endpoint assessed (Eadon et al. 1986; Nagao et al. 1993; Pluess et al. 1988a).

Additive effects, as well as the usefulness of the TEF approach, have also been demonstrated in long-term feeding studies. Rats were fed a diet containing a mixture of 2,3,7,8-TCDD, 1,2,3,7,8-pentaCDF, and 1,2,3,6,7,8-hexaCDF for 13 weeks (Pluess et al. 1988a). This mixture, which contained 1.5 ppb of 2,3,7,8-TCDD equivalents, induced toxic lesions in the thymus and liver of comparable severity to that caused by a dose of 2 ppb of 2,3,7,8-TCDD alone, indicating that the single compounds additively contribute to the toxicity of the mixture as predicted for whole animals.

Administration of a mixture of 25 nmol 2,3,7,8-TCDD/kg and 200 nmol 2,3,7,8-tetraCDF/kg as a single subcutaneous injection to pregnant mice on GDs 9–11 resulted in an incidence of 80% cleft palate in the fetuses examined at day 18 (Krowke 1986). When each chemical, at the same concentrations, were administered separately, the incidence of cleft palate was 34% for 2,3,7,8-TCDD and 40% for 2,3,7,8-tetraCDF, suggesting an additive whole animal response for the mixture. Weber et al. (1985) had previously reported a more adequate analysis of similar results by showing dose additivity (by probit model analysis) between 2,3,7,8-tetraCDF and 2,3,7,8-TCDD on cleft palate incidence after oral administration to mice. Also, mixtures of 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF and of 2,3,4,7,8-pentaCDF and 2,3,4,5,3',4'-hexachlorobiphenyl had additive teratogenic effects (cleft palate and hydronephrosis) when administered orally to pregnant C57BL/6N mice (Birnbaum et al. 1987b). Probit analysis of the data revealed parallel dose-response curves, which is compatible with a common and additive mechanism of action for whole animal data.

Co-treatment of DBA/2J mice with single intraperitoneal injections of 200 nmol 2,3,7,8-TCDD/kg and 50, 200, or 800 µmol 1,3,6,8-tetraCDF/kg inhibited AHH induction 13, 39, and 18%, and EROD induction 17, 34, and 21%, respectively, compared to 2,3,7,8-TCDD alone (Bannister and Safe 1987). Therefore, the maximum partial antagonist activity of 1,3,6,8-tetraCDF was obtained at an agonist/ antagonist ratio of 1,000/1. In C57BL/6J mice, co-treatment with 15 nmol 2,3,7,8-TCDD/kg and 10, 50, 100, 200, and 500 µmol 1,3,6,8-tetraCDF/kg significantly inhibited both AHH and EROD only at 200 µmol 1,3,6,8-tetraCDF/kg. In this case, the maximum partial antagonist activity occurred at an agonist/antagonist ratio of 13,300/l. The investigators suggested that the antagonist activity depends on the strain and the relative concentration ratios of agonist and antagonist.

Administration of single intraperitoneal doses of 1,3,6,8-tetraCDF and 2,3,7,8-TCDD to mice resulted in significant antagonism of the immunotoxic effects of 2,3,7,8-TCDD, as monitored by the splenic plaque-forming cell response to SRBCs (Davis and Safe 1988). Similar results were reported for the combination of 1,3,6,8-tetraCDF and 2,3,4,7,8-pentaCDF. These results are consistent with previously published data showing that 1,3,6,8-tetraCDF has a high affinity for the cytosolic Ah receptor (Keys et al. 1986).

The viability of lymphocytes derived from mice fetal thymus organ culture was reduced by a combination of 3,4,3’,4’-tetrachloroazoxybenzene and 2,3,7,8-tetraCDF in an additive manner (Hassoun 1987). While each compound induced a 25–350% reduction in cell viability, an equimolar combination reduced viability by 75%. The results suggest a common mechanism of action for the two chemicals, which is consistent with the fact that both substances bind to the Ah receptor.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Dibenzofuran is an organic compound that contains two benzene rings fused to a central furan ring. CDFs are a class of organic compounds in which one to eight chlorine atoms are attached to the benzene ring positions of a dibenzofuran structure.

Based on the number of chlorine substituents (one to eight) on the benzene rings, there are eight homologues of CDFs (monochlorinated through octachlorinated). Each homologous group contains one or more isomers. There are 135 possible CDF isomers, including 4 monoCDFs, 16 diCDFs, 28 triCDFs, 38 tetraCDFs, 28 pentaCDFs, 16 hexaCDFs, 4 heptaCDFs, and 1 octaCDF. Each one of these compounds is called a congener. Because of molecular asymmetry, CDFs have 135 congeners, compared to 75 for CDDs.

The synonyms, chemical formulas, chemical structure, and identification numbers of selected CDFs are reported in Table 4-1. CDFs that are known or suspected to be most toxic (2,3,7,8-substituted congeners) and other CDFs, for which health effects data are discussed in Chapter 2, have been selected for inclusion in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

CDFs have been synthesized in quantities <1 g. The methods needed to separate the isomeric compounds in a congener series make the isolation of an individual congener difficult. Therefore, data pertaining to the simplest physical and chemical properties of the individual congener are not generally available. The extremely low water solubilities and vapor pressures contribute to the difficulty in determining these and related physico-chemical properties (e.g., K_{ow} and Henry's law constant) of these compounds. In general, the melting point increases and the vapor pressures and water solubilities of the CDFs decrease as the number of chlorine substituents increases (see Table 4-2). These hydrophobic compounds are generally colorless solids and are soluble in nonpolar organic solvents (Gray et al. 1976). The CDFs are relatively stable towards acid and alkali attack, but they start to decompose at 700°C (Van den Berg et al. 1985). The physical and chemical properties of CDFs are given in Table 4-2.

Table 4-1. Chemical Identity of Chlorodibenzofurans (CDFs)

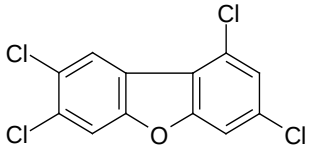
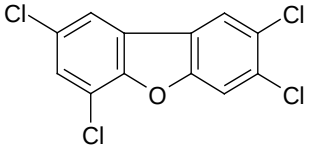
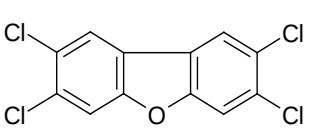
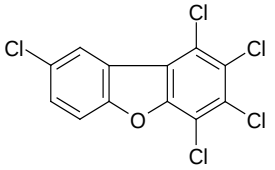
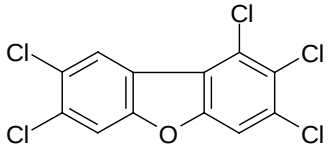
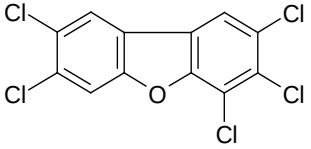
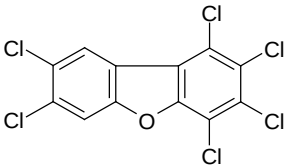
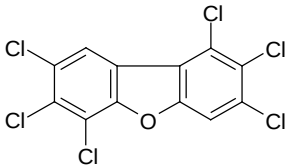
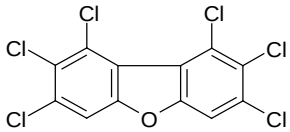
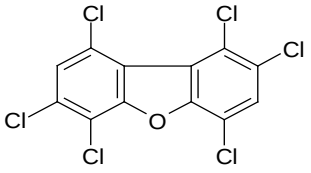
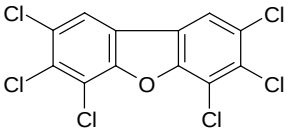
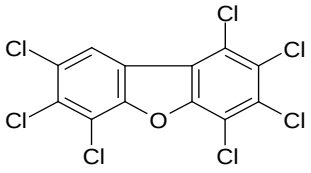
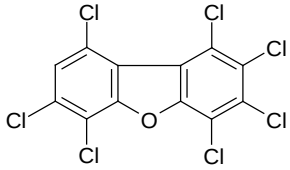
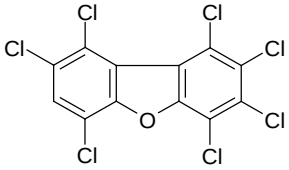
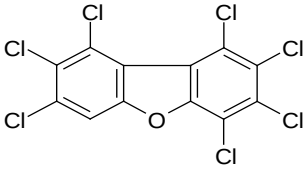
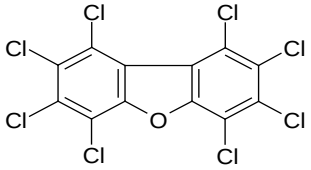
Characteristic	Information			
Chemical name	1,3,7,8-TetraCDF	2,3,6,8-TetraCDF	2,3,7,8-TetraCDF	1,2,3,4,8-PentaCDF
Registered trade name(s)	No data	No data	No data	No data
Chemical formula	$C_{12}H_4Cl_4O$	$C_{12}H_4Cl_4O$	$C_{12}H_4Cl_4O$	$C_{12}H_3Cl_5O$
Chemical structure				
CAS Registry Number[a]	57117-35-8	57117-37-0	51207-31-9	67517-48-0
Characteristic	Information			
Chemical name	1,2,3,7,8-PentaCDF	2,3,4,7,8-PentaCDF	1,2,3,4,7,8-HexaCDF	1,2,3,6,7,8-HexaCDF
Registered trade name(s)	No data	No data	No data	No data
Chemical formula	$C_{12}H_3Cl_5O$	$C_{12}H_3Cl_5O$	$C_{12}H_2Cl_6O$	$C_{12}H_2Cl_6O$
Chemical structure				
CAS Registry Number[a]	57117-41-6	57117-31-4	70648-26-9	57117-44-9
Chemical name	1,2,3,7,8,9-HexaCDF	1,2,4,6,7,9-HexaCDF	2,3,4,6,7,8-HexaCDF	1,2,3,4,6,7,8-HeptaCDF
Registered trade name(s)	No data	No data	No data	No data
Chemical formula				
Chemical structure	$C_{12}H_2Cl_6O$	$C_{12}H_2Cl_6O$	$C_{12}H_2Cl_6O$	$C_{12}HCl_7O$
CAS Registry Number[a]	72918-21-9	75627-02-0	60851-34-5	67562-39-4

Table 4-1. Chemical Identity of Chlorodibenzofurans (CDFs)

Characteristic	Information			
Chemical name	1,2,3,4,6,7,9-HeptaCDF	1,2,3,4,6,8,9-HeptaCDF	1,2,3,4,7,8,9-HeptaCDF	1,2,3,4,6,7,8,9-OctaCDF
Registered trade name(s)	No data	No data	No data	No data
Chemical formula	$C_{12}HCl_7O$	$C_{12}HCl_7O$	$C_{12}HCl_7O$	$C_{12}Cl_8O$
Chemical structure				
CAS Registry Number[a]	70648-25-8	69698-58-4	55673-89-7	39001-02-0

[a]EPA 1985

CAS = Chemical Abstracts Services

Table 4-2. Physical and Chemical Properties of Chlorodibenzofurans (CDFs)

Property	1,3,7,8-TetraCDF	2,3,6,8-TetraCDF	2,3,7,8-TetraCDF	1,2,3,4,8-PentaCDF
Molecular weight	305.9	305.9	305.9	340.42
Color[a]	No data	Colorless[b]	Colorless	No data
Physical state[c]	Solid	Solid	Solid	Solid
Melting point, °C[a]	No data	197–198	219–221	177–178
Boiling point °C	No data	No data	No data	No data
Density at 20°C	No data	No data	No data	No data
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water[d]	No data	No data	1.37×10^{-9} mol/L (0.43 µg/L)	No data
Organic solvents[e]	Soluble in toluene	Soluble in toluene and chloroform	Soluble in toluene	Soluble in toluene
Partition coefficients:				
Log K_{ow}[f]	6.73	6.73	6.53	6.79
Log K_{oc}[h]	No data	No data	5.61 (estimated)	No data
pKa	Not applicable	Not applicable	Not applicable	Not applicable
Vapor pressure at 25°C[i]	1.95×10^{-8}[j]	1.95×10^{-8}[j]	9.21×10^{-7}	No data
Henry's law constant[k]	1.48×10^{-5}	1.48×10^{-5}	1.48×10^{-5}	2.63×10^{-5}
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors				
Air[a] Water Soil	1 ppb = 12.72 µg/m^3 1 ppb = 1 µg/L 1 ppb = 1 µg/kg	1 ppb = 12.72 µg/m^3 1 ppb = 1 µg/L 1 ppb = 1 µg/kg	1 ppb = 12.72 µg/m^3 1 ppb = 1 µg/L 1 ppb = 1 µg/kg	1 ppb = 14.15 µg/m^3 1 ppb = 1 µg/L 1 ppb = 1 µg/kg
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Chlorodibenzofurans (CDFs)

Property	1,2,3,7,8-PentaCDF	2,3,4,7,8-PentaCDF	1,2,3,4,7,8-HexaCDF	1,2,3,6,7,8-HexaCDF
Molecular weight	340.42	340.42	374.87	374.87
Color[a]	Colorless	No data	No data	No data
Physical state[c]	Solid	Solid	Solid	Solid
Melting point °C[a]	225–227	196–16.5	225.5-226.5	232–234
Boiling point °C	No data	No data	No data	No data
Density at 20°C	No data	No data	No data	No data
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water[d]	No data	6.92×10^{-10} mol/L (0.24 µg/L)	2.20×10^{-11} mol/L (0.008 µg/L)	4.72×10^{-11} mol/L (0.018 µg/L)
Organic solvents[e]	Soluble in hexane[a] and toluene	Soluble in toluene	Soluble in toluene	Soluble in toluene
Partition coefficients:				
Log K_{ow}[f]	6.79	6.92	No data	No data
Log K_{oc}[h]	No data	No data	No data	No data
pKa	Not applicable	Not applicable	Not applicable	Not applicable
Vapor pressure at 25°C[i]	2.73×10^{-7}	1.63×10^{-7}	6.07×10^{-8}	6.07×10^{-8}
Henry's law constant[k]	2.63×10^{-5}	2.63×10^{-5}	2.78×10^{-5}	2.78×10^{-5}
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors				
Air[a] Water Soil	1 ppb = 14.15 µg/m^3 1 ppb = 1 µg/L 1 ppb = 1 µg/kg	1 ppb = 14.15 µg/m^3 1 ppb = 1 µg/L 1 ppb = 1 µg/kg	1 ppb = 15.58 µg/m^3 1 ppb = 1 µg/L 1 ppb = 1 µg/kg	1 ppb = 15.58 µg/m^3 1 ppb = 1 µg/L 1 ppb = 1 µg/kg
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Chlorodibenzofurans (CDFs)

Property	1,2,3,7,8,9-HexaCDF	1,2,3,7,8,9-HexaCDF	2,3,4,6,7,8-HexaCDF	1,2,3,4,6,7,8-HeptaCDF
Molecular weight	374.87	374.87	374.87	409.31
Color[a]	No data	No data	No data	No data
Physical state[c]	Solid	Solid	Solid	Solid
Melting point, °C[a]	No data	180–181	239–240	236–237
Boiling point, °C	No data	No data	No data	No data
Density at 20°C	No data	No data	No data	No data
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water[d]	No data	No data	No data	3.31×10^{-12} mol/L (0.014 µg//L)
Organic solvents[e]	Soluble in toluene	Soluble in toluene	Soluble in toluene	Soluble in toluene
Partition coefficients:				
Log K_{ow}[f]	No data	No data	No data	No data
Log K_{oc}[h]	No data	No data	No data	No data
pKa	Not applicable	Not applicable	Not applicable	Not applicable
Vapor pressure at 25°C[i]	3.74×10^{-8}	No data	3.74×10^{-8}	1.68×10^{-8}
Henry's law constant[k]	2.78×10^{-5}	2.78×10^{-5}	2.78×10^{-5}	4.1×10^{-6}
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors				
Air[a] Water Soil	1 ppb = 15.58 µg/m^3 1 ppb = 1 µg/L 1 ppb = 1 µg/kg	1 ppb = 15.58 µg/m^3 1 ppb = 1 µg/L 1 ppb = 1 µg/kg	1 ppb = 15.58 µg/m^3 1 ppb = 1 µg/L 1 ppb = 1 µg/kg	1 ppb = 17.02 µg/m^3 1 ppb = 1 µg/L 1 ppb = 1 µg/kg
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Chlorodibenzofurans (CDFs)

Property	1,2,3,4,6,7,9-HeptaCDF	1,2,3,4,6,8,9-HeptaCDF	1,2,3,4,7,8,9-HeptaCDF	1,2,3,4,6,7,8,9-OctaCDF
Molecular weight	409.31	409.31	409.31	443.76
Color[a]	No data	No data	No data	No data
Physical state[c]	Solid	Solid	Solid	Solid
Melting point, °C[a]	No data	211–212	212–223	25[c]
Boiling point, °C	No data	No data	No data	537[c]
Density at 20°C	No data	No data	No data	No data
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water[d]	No data	No data	No data	2.61lx10^{-12} mol/L (0.0012 µg/L) (3.0 µg/L)[l]
Organic solvents[e]	Soluble in toluene	Soluble in toluene	Soluble in toluene	Soluble in toluene
Partition coefficients:				
Log K_{ow}[f]	No data	No data	No data	8.20 (7.97)[i]
Log K_{oc}[h]	No data	No data	No data	8.57 (estimated)
pKa	Not applicable	Not applicable	Not applicable	Not applicable
Vapor pressure at 25°C[i]	No data	No data	9.79x10^{-9}	No data
Henry's law constant[k]	4.1x10^{-6}	4.1x10^{-6}	4.1x10^{-6}	1.7x10^{-6}
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors				
Air[a]	1 ppb = 17.02 µg/m^3	1 ppb = 17.02 µg/m^3	1 ppb = 17.02 µg/m^3	1 ppb = 18.45 µg/m^3
Water	1 ppb = 1 µg/L	1 ppb = 1 µg/L	1 ppb = 1 µg/L	1 ppb = 1 µg/L
Soil	1 ppb = 1 µg/kg	1 ppb = 1 µg/kg	1 ppb = 1 µg/kg	1 ppb = 1 µg/kg

Table 4-2. Physical and Chemical Properties of Chlorodibenzofurans (CDFs)

Property	1,2,3,4,6,7,9-HeptaCDF	1,2,3,4,6,8,9-HeptaCDF	1,2,3,4,7,8,9-HeptaCDF	1,2,3,4,6,7,8,9-OctaCDF
Explosive limits	No data	No data	No data	No data

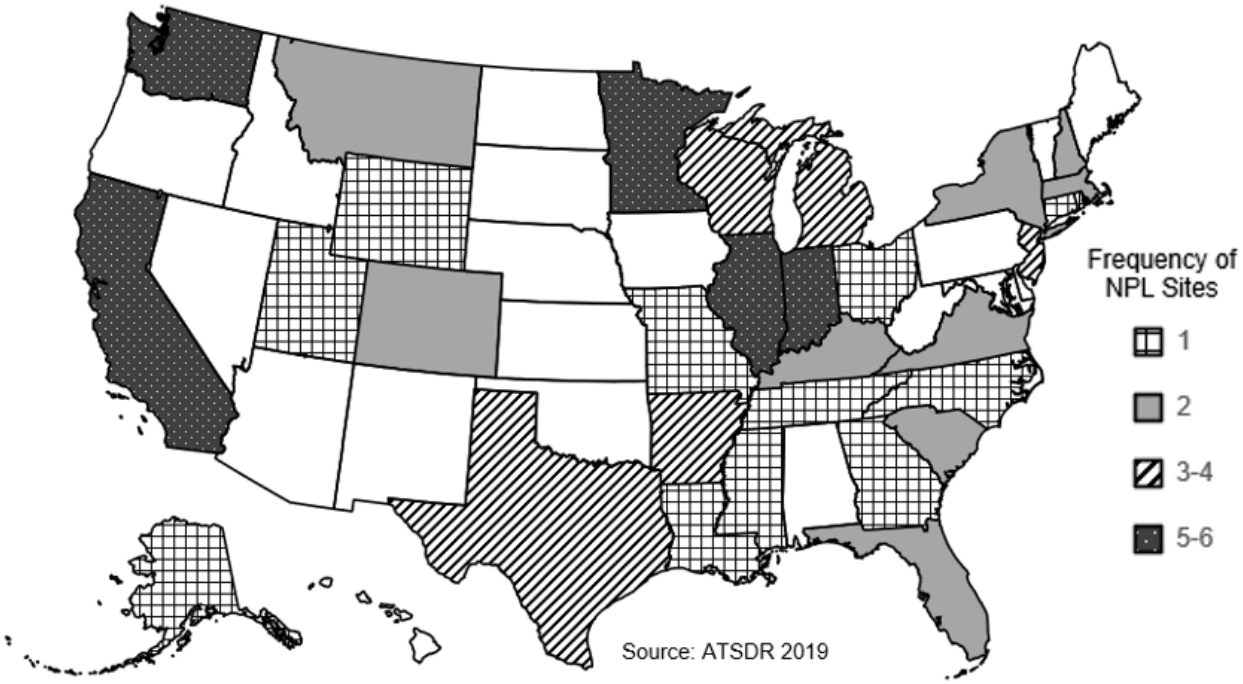
[a]Kuroki et al. 1984 unless otherwise stated.
[b]The polychlorinated dibenzofurans are present predominantly in the particulate phase in ambient air (Hunt and Maisel 1990).
[c]WHO 2000.
[d]Friesen et al. 1990 unless otherwise stated.
[e]Ryan et al. 1991 unless otherwise stated.
[f]Sijm et al. 1989 unless otherwise stated; some of the values are for two isomers that could not be separated.
[g]Burkhard and Kuehl 1986.
[h]EPA 1985.
[i]Eitzer and Hites 1988.
[j]Rordorf 1989.
[k]Eitzer and Hites 1989a; the values are for unseparated isomers of each homologous series.
[l]Frank and Schrap 1990.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

CDFs have been identified in at least 76 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which CDFs have been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

Figure 5-1. Number of NPL Sites with Chlorodibenzofuran (CDF) Contamination



- The most important human exposure route is through the ingestion of foods containing CDFs
- Inhalation of ambient air, as well as ingestion of drinking water, are minor routes of human exposure to CDFs; exposure can also occur from certain consumer products.
- The lower chlorinated CDFs are semi-volatile; however, the tetra-, penta-, hexa-, and octa-congeners are considered nonvolatile.
- The lower chlorinated CDFs degrade in the atmosphere by reaction with atmospheric oxidants in a matter of days; however, the higher chlorinated congeners are more persistent and subject to long range transport.
- Direct photolysis of CDFs is an important degradation process; however, biodegradation occurs slowly for the higher chlorinated CDFs and they are considered persistent in the environment.

- CDFs have large soil adsorption coefficients and possess low mobility in soil surfaces.
- Higher chlorinated CDFs bioconcentrate in aquatic organisms.

Low levels of CDFs occur as contaminants in certain chemical products and during combustion of certain precursors of CDFs. The processes that are responsible for the production of CDFs in the environment form a mixture of congeners. In addition, many of the combustion processes that produce CDFs also produce structurally similar compounds, such as CDDs and chlorinated dibenzothiophenes (CDTs). Due to the similarity in their physicochemical properties, including low water solubility, high lipid solubility, low vapor pressure, and multiple chlorine substitution, these compounds are generally found together in environmental samples. Therefore, environmental exposures to CDFs occur not only from a mixture of CDFs, but also from CDDs, CDTs, and other structurally similar compounds and other structurally similar compounds present as co-contaminants. To simplify the assessment of human health risk of a mixture of CDDs and CDFs, EPA has recommended the toxic equivalent (TEQ) approach. The TEQ is a weighted quantity of measure based on the toxicity of each member of the dioxin and dioxin-like compounds category relative to the most toxic member of the category, 2,3,7,8-TCDD. TEQs are calculated by multiplying the mass or concentration of each dioxin-like compound by a TEF and summing across all of the compounds present.

The sources of CDFs in the environment are combustion processes mainly involving municipal and industrial incineration; combustion of fossil fuels by power plants, home heating, and fireplaces; automobile exhaust; medical waste incineration; yard waste composting; accidental fires or malfunction of PCB-filled transformers and capacitors; improper disposal of chlorinated chemical wastes; use of certain chemical products (e.g., chlorinated phenols); certain high temperature industrial processes, such as copper smelting, electrical arc furnaces in steel mills, and production of metallic magnesium and refined nickel; chlorine bleaching of pulp and paper (this is not a relevant source of CDFs in the United States); and photochemical processes involving certain products, such as chlorinated diphenyl ethers. Some of these sources emit CDFs in the air, while others discharge CDFs as effluents in surface water. The source of these compounds in soil is disposal of chemical wastes containing CDFs as contaminants. The deposition of atmospheric CDFs is also an important source of these compounds in surface water and soil.

In the atmosphere, the higher chlorinated CDFs are present predominantly in the particulate phase, but tetra- and pentaCDFs may be present in the vapor phase as well. Due to higher atmospheric temperatures, the concentrations of CDFs in the vapor phase increase during summer. The most important chemical

process in determining the fate of CDFs in air is the reaction with hydroxyl radicals. The lifetime of CDFs due to this process is >10 days, and increases with higher chlorinated CDFs, which allows these compounds to be transported long distances in air. Wet and dry deposition of atmospheric CDFs may also be important for the removal of these compounds from air. CDFs will be present in water mainly in the particulate-sorbed phase. Significant loss of CDFs in water, either due to chemical reactions including photochemical reactions or biodegradation processes, has not been observed. CDFs in water partition into the particulate phase and settle into the sediment. Sediment is the ultimate sink of atmospheric and aquatic CDFs. CDFs bioconcentrate in aquatic organisms. CDFs are very persistent in soils. They also strongly adsorb to soil; consequently, very little vertical movement of these compounds has been observed in soil (e.g., leaching to groundwater).

The concentrations of CDFs in air usually increase in the following order: rural < suburban < urban < industrial/auto tunnel. The concentrations of total tetra-, penta-, hexa-, hepta-, and octaCDF in ambient urban/suburban air were 0.13–7.34, 0.09–5.10, <0.09–12.55, 0.08–12.71, and 0.13–3.78 pg/m^3, respectively. CDFs were detected in 1 of 20 water supplies in New York State. The only congener groups detected in this water were tetraCDF at a concentration 2.6 ppq (pg/L) and octaCDF at a concentration of 0.8 ppq. The levels of CDFs in contaminated water, such as effluents from a kraft pulp mill, can be 3 orders of magnitude higher than the levels in drinking water. The levels of CDF in various foods consumed in Germany, Japan, Canada, and the United States are also available, and the level in individual food products is on the order of pg/kg.

The general population is exposed to CDFs by inhaling air, ingesting food, soil, and water, and from consumer products (e.g., paper towels, tampons). The estimated total intake of CDDs/CDFs from all these sources in a Canadian background population is 2.4 pg toxic equivalent to 2,3,7,8-TCDD/kg body weight/day. The intake from food constitutes ≈96% of the total toxic intake. Fish and fish products, milk and milk products, and meat and meat products each constitute ≈30% of CDF food intake in Germany. Because of this CDF body burden in background populations and the tendency of CDFs to bioconcentrate in fat, the levels of CDFs in adipose tissue, human milk, and the lipid portion of blood in both background and exposed populations have been determined.

Workers in sawmills, in the textile industry, in the leather industry, in the pulp and paper industries, in certain chemical manufacturing, and in PCB user industries (repairing transformers or capacitors, using casting waxes containing PCBs) may be exposed to a higher level of CDFs than the background population. Among the general population, groups who consume high amounts of fatty fish, people who

are exposed to accidental fires involving PCBs, and nursing babies are potentially exposed to higher levels of CDFs. People living near incinerators or incinerator ash dump sites may be exposed to elevated levels of CDFs. The levels will depend on the nature of the waste being incinerated. People who live adjacent to uncontrolled landfill sites containing high concentration of CDFs or landfill fires may also be exposed to higher concentrations of CDFs. Diverse studies indicate that the levels of CDFs in the adipose tissue of exposed populations are higher than those in unexposed or background populations.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Table 5-1 lists the facilities in each state that unintentionally produce, store, dispose of, or process dioxin-like substances, including CDFs, and the range of maximum amounts that are stored onsite. This is a special category in the Toxics Release Inventory (TRI) and includes 17 CDFs and chlorinated dioxins. The data from the TRI listed in Table 5-1 should be used with caution, however, since only certain types of facilities were required to report (EPA 2005). This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use Dioxin-like Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	5	0	1	1, 5, 12
AL	48	0	99,999	1, 3, 5, 12, 13, 14
AR	20	0	100,000,000	1, 5, 12, 13, 14
AZ	11	0	99	1, 5, 13
CA	31	0	10	1, 2, 5, 6, 11, 12, 13, 14
CO	12	0	1	1, 4, 5, 13
CT	1	0	–	1, 5
DE	3	0	1	1, 5, 10, 13, 14
FL	20	0	10	1, 5, 12, 13, 14
GA	32	0	99,999	1, 2, 5, 12, 13, 14
GU	1	0.1	1	1, 5
HI	5	0	–	1, 5
IA	18	0	10	1, 5, 13, 14
ID	3	0	99	1, 5, 13, 14
IL	26	0	999	1, 5, 12, 13
IN	31	0	99	1, 5, 6, 12, 13, 14
KS	8	0	1	1, 5, 13

Table 5-1. Facilities that Produce, Process, or Use Dioxin-like Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
KY	30	0	9,999	1, 5, 13, 14
LA	47	0	99,999	1, 5, 10, 12, 13, 14
MD	7	0	10	1, 5, 14
ME	4	0	1	1, 5, 9
MI	23	0	9,999	1, 2, 5, 12, 13, 14
MN	21	0	99,999	1, 2, 5, 9, 12, 13, 14
MO	27	0	9,999	1, 2, 5, 12, 13, 14
MS	17	0	99,999	1, 5, 8, 13, 14
MT	5	0	1	1, 5
NC	26	0	99,999	1, 5, 12, 13, 14
ND	12	0	1	1, 5, 12, 13
NE	11	0	999,999	1, 5, 9, 14
NH	2	0	–	1, 5, 12
NJ	7	0	10	1, 5, 13, 14
NM	5	0	–	1, 5, 13, 14
NV	6	0	999,999	1, 5, 13, 14
NY	18	0	100,000,000	1, 5, 12, 13, 14
OH	34	0	999	1, 3, 5, 12, 13, 14
OK	14	0	9,999	1, 5, 8, 13, 14
OR	13	0	999,999	1, 5, 12, 13, 14
PA	35	0	10	1, 2, 5, 12, 13, 14
PR	3	0	1	1, 5, 12
SC	25	0	10	1, 2, 3, 5, 12, 13, 14
SD	3	0	–	1, 5
TN	26	0	99,999	1, 5, 8, 9, 13, 14
TX	72	0	9,999	1, 5, 12, 13, 14
UT	16	0	999,999	1, 2, 3, 4, 5, 9, 12, 13, 14
VA	17	0	10	1, 2, 5, 13, 14
VI	2	0	–	1, 5
WA	23	0	99,999	1, 5, 6, 13, 14
WI	31	0	99,999	1, 2, 5, 12, 13, 14

Table 5-1. Facilities that Produce, Process, or Use Dioxin-like Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
WV	18	0	99	1, 5, 12, 13, 14
WY	9	0	10	1, 5, 13, 14

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI18 2020 (Data are from 2018)

CDFs are not manufactured commercially in the United States or any other country except on a laboratory scale for use in chemical laboratories or for toxicological studies. These compounds are produced as undesired by-products during the manufacture of PCBs, polychlorinated phenols, and herbicides. They are also formed during the pyrolysis of PCBs, polychlorinated diphenyl ethers, polychlorinated phenols, polychlorinated benzenes, and phenoxy herbicides. Municipal and industrial incinerators also produce CDFs. These compounds can also be produced from the photolysis of PCBs, polychlorinated diphenyl ethers, and polychlorinated benzenes (Van den Berg et al. 1985). Chlorine bleaching at paper and pulp mills can also result in CDF formation (Campin et al. 1991; Näf et al. 1992).

Several methods are available for the synthesis of CDFs; all yield mixtures of isomers (EPA 1985; Gara et al. 1981). Two methods that have been used to synthesize a number of structure-specific CDFs are cyclization of diazotized chlorophenoxy-o-aniline and cyclization of chlorinated diphenylethers, promoted by palladium(I1) acetate (Gara et al. 1981; Gray et al. 1976; Humppi 1986; Kuroki et al. 1984; Norstrom et al. 1979). In the first process, chlorophenates and chloronitrobenzene react to form nitrochlorodiphenyl ethers. The latter compounds are reduced to aminochlorodiphenyl ethers, diazotized, and cyclized with isoamyl nitrite to form the CDFs. In the second method, chlorinated diphenyl ethers are produced by refluxing chlorinated diphenyl iodonium salt with chlorophenolate. The chlorinated diphenyl ethers are cyclized with palladium acetate in the presence of acetic acid and methane sulfonic acid (Kuroki et al. 1984).

Another method that has been used to synthesize 22 high purity CDF isomers is the cyclization of o-hydroxyl PCBs by refluxing with dimethyl sulfoxide and potassium hydroxide (Safe and Safe 1984).

The o-hydroxyl PCBs are produced either by a diazo coupling of chlorinated anisidines and symmetrical chlorinated benzenes or by diazo coupling of chlorinated anilines with chlorinated anisoles.

The pyrolysis of PCBs, commercial chlorobenzenes, and chlorinated diphenyl ethers yields CDF mixtures. Although the pyrolysis method produces mixtures of isomeric CDFs, it has been used frequently to prepare qualitative CDF standards, because it is fast and safe (Buser 1979; EPA 1985; Groce et al. 1989). Similarly, qualitative standard mixtures of CDFs have also been produced by the ultraviolet and gamma irradiation of octaCDF (Buser 1976).

5.2.2 Import/Export

Because there is no commercial use of CDFs, there are no import or export volumes of these substances in the United States.

5.2.3 Use

There is no commercial use of CDFs other than small amounts used in toxicology, chemical, and biochemical laboratories.

5.2.4 Disposal

Several methods for disposing CDFs have been proposed; some of these have been put into field use to decontaminate wastes containing CDFs. The most commonly used methods for disposal or decontamination of CDF-containing wastes are photolysis, incineration, chemical destruction, microbial degradation, and landfilling. Each of these methods has limitations, but some may be preferable to others. The common methods for CDF waste disposal/decontamination are discussed below.

In the photolytic process, CDDs/CDFs are destroyed by dechlorination of the compounds by ultraviolet light most efficiently in the presence of hydrogen donors. The most commonly used hydrogen donor is isopropyl alcohol (des Rosiers 1983). TCDD-contaminated soil was decontaminated by ultraviolet treatment of the soil in the presence of olive oil emulsion as a hydrogen donor. A total reduction in excess of 60% was observed after 48 hours of irradiation. The decontamination efficiency of CDFs by ultraviolet radiation was reported to be 90% after 48 hours irradiation of the walls and ceiling of a building contaminated during a PCB fire (Borwitzky and Schramm 1991). When CDFs were extracted

from a contaminated soil in hexane and irradiated with ultraviolet light in the presence of a hydrogen donating solvent (propanol), the decontamination efficiency reached 99.9% in 4 hours (Drechsler 1986). The destruction efficiencies of CDFs by liquid phase photolysis are faster than CDDs (Muto and Takizawa 1991). The advantage of photolytic destruction is that it poses only a small risk to workers. The notable disadvantages of the photolysis process are that it is time consuming (when a large area is involved or solvent extraction is performed) and may not be universally applicable to other contaminants (Borwitzky and Schramm 1991).

Incineration is a preferred method for disposing of CDF-containing wastes. In this process, the waste is burned in a stationary or rotary kiln incinerator at temperatures between 900 and 1,000°C and a minimum residence time of 1.8 seconds; however, the destruction of particle bound CDFs may require higher temperatures and longer retention times. Higher temperatures can be attained by adding a secondary combustion chamber to a rotary kiln incinerator. Land-based and at-sea incineration facilities are available. Investigators have postulated the following combustion criteria for land-based incineration of CDF wastes: a 2-second dwell time at 1,200°C or 15-second dwell time at 1,600°C, a combustion efficiency in excess of 99.99%, and a scrubber system to control flue gas emission (Almemark et al. 1991; des Rosiers 1983). EPA considers CDFs as Principal Organic Hazardous Constituents (POHCs) and requires them to be incinerated, in order to achieve a destruction and removal efficiency of 99.99% (EPA 1990a).

Some of the chemical methods available for the destruction of CDFs include alkaline dehydrochlorination; reduction with hydrogen in the presence of a palladium or platinum catalyst at 100°C; catalytic oxidation with ruthenium tetroxide, chlorolysis in the presence of chlorine gas at 600°C and a pressure of 170 atm; or micellar catalysis with either benzalkonium dichloroiodide or cetylpyridinium dichloroiodide. Disadvantages of these methods are generation of unwanted byproducts requiring high temperatures or pressures and, in some cases, cost. The preferable chemical method is dehydrochlorination in a mixture of alkaline polyethylene glycol and inorganic peroxide at a temperature <100°C (des Rosiers 1983; Drechsler 1986; Hagenmaier et al. 1987; Tiernan et al. 1989). A chemical method employing precipitation by the addition of alum or lime at a concentration of 9,000 mg/L removed >98% of CDDs/CDFs from bleach plant filtrates and combined treated mill effluents from pulp and paper industries (Barton et al. 1990). However, the sludge from this process contains the CDDs/CDFs and requires proper disposal. The destruction of CDFs in aqueous solution at a pH of 10 and temperature of 50°C by ozone was reported to be >90% in 4 hours (Palauschek and Scholz 1987).

Decontamination of CDF-containing wastes by a biodegradation method has also been attempted. *Phanerochuete chrysosporium*, a white rot fungus, which degraded TCDD in laboratory experiments (des Rosiers 1986), may be suitable for biodegrading CDFs. However, no successful biotreatment method exists that can satisfactorily decontaminate CDF wastes.

In the past, land disposal of waste materials contaminated with CDDs and CDFs was considered an option under strict technical conditions. Some of these conditions included use of soil with low water permeability, use of synthetic membrane liners to cover the soil, compatibility with the hydrogeology of the site, maintenance of a leachate monitoring program, and acquisition of waivers from the appropriate EPA or state agency (des Rosiers 1983). However, land disposal of certain CDF wastes is presently prohibited. The Toxic Substances Control Act (TSCA) regulates the use, disposal, and distribution in commerce of process waste-water treatment sludges intended for land application that are derived from pulp and paper industry employing chlorination processes (EPA 1991).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

Table 5-2 contains releases to the environment of the dioxin category of compounds of the TRI.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Dioxin-like Compounds[a]

	Reported amounts released in pounds per year[b]								
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	48	98	75	0	114	0	190	97	287
AK	5	1	0	0	0	0	1	0	1
AR	20	14	19	0	24	2	52	7	58
AZ	11	25	0	0	37	0	25	37	62
CA	31	7	2	0	66	0	9	66	75
CO	12	14	0	0	0	0	14	0	15
CT	1	0	0	0	0	0	0	0	0
DE	3	2	0	0	0	0	2	0	3
FL	20	17	2	0	12	2	31	2	33
GA	32	21	25	0	31	19	76	19	95
GU	1	1	0	0	0	0	1	0	1
HI	5	1	0	0	1	0	1	1	2
IA	18	11	0	0	8	0	11	8	19
ID	3	55	0	0	717	0	408	365	773
IL	25	17	0	0	86	0	17	86	103
IN	31	24	0	0	139	0	24	139	163
KS	8	5	0	0	0	0	5	0	5
KY	30	49	3	0	35,587	0	116	35,522	35,638
LA	47	46	50	0	339	1	122	314	436
MD	7	3	0	0	0	0	3	0	3
ME	4	4	0	0	4	0	4	3	7
MI	22	119	2	0	1,931	0	123	1,929	2,052
MN	21	44	2	0	230	0	47	230	277
MO	27	36	0	0	3	0	39	0	39
MS	17	10	55	0	767	2	831	2	833
MT	5	7	0	0	2	0	7	2	9
NC	26	87	8	0	4	0	95	3	98
ND	11	17	0	0	0	0	17	0	17
NE	11	4	1	0	0	0	4	0	4
NH	2	0	0	0	0	0	0	0	0
NJ	7	2	0	0	42	13	2	55	57
NM	5	3	0	0	0	0	3	0	3
NV	6	3	0	0	2	0	3	2	5
NY	18	11	1	0	4	6	13	9	22
OH	34	39	2	0	1,860	0	1,756	144	1,900
OK	14	20	0	0	48	0	28	41	68
OR	13	4	0	0	13	0	4	13	17

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Dioxin-like Compounds[a]

	Reported amounts released in pounds per year[b]								
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
PA	35	27	0	0	4	0	27	4	31
PR	3	1	0	0	0	0	1	0	1
SC	25	13	7	0	7	0	26	0	26
SD	3	9	0	0	0	0	9	0	9
TN	26	32	5	0	1,771	0	1,791	16	1,808
TX	70	93	908	337	33,757	0	10,934	24,161	35,094
UT	16	64	0	0	14,543	0	14,070	537	14,607
VA	17	9	1	0	12	0	11	11	22
VI	2	0	0	0	0	0	0	0	0
WA	23	10	8	0	183	0	22	180	201
WI	30	29	0	0	543	0	30	543	573
WV	18	13	3	0	32	0	16	32	48
WY	9	19	0	0	0	0	19	0	19
Total	878	1,141	1,178	337	92,922	45	31,044	64,580	95,624

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI18 2020 (Data are from 2018)

CDFs in the environment are primarily of anthropogenic origin (Czuczwa and Hites 1986a, 1986b). Trace amounts of CDFs may come from sources, such as forest fires, which may not be anthropogenic in origin (Bumb et al. 1980). The levels of CDDs and CDFs in archived soil samples collected from the same semi-rural area in southeast England between 1846 and 1986 were found to increase around the turn of the century (A.D. 1900) as anthropogenic sources became more important than natural emissions (Kjeller et al. 1991; Rappe 1991). Higher levels of CDFs are found in human tissue (Ligon et al. 1989;

Rappe 1991) and river silt (Schecter 1991) samples collected from industrial countries than those from less industrial countries or from ancient civilization. These results suggest that most CDFs found at present are of anthropogenic origin.

The primary sources of environmental release of CDFs can be divided into the following five categories: thermal reactions, chemical reactions, photochemical reactions, enzymatic reactions, and hazardous waste sites.

Thermal Reactions

Combustion Processes. The combustion processes can be divided into two categories: large systems and small systems. Municipal waste incineration (Bonfanti et al. 1990; Brna and Kilgore 1990; des Rosiers 1987; Hutzinger and Fiedler 1989; Siebert et al. 1987; Tiernan et al. 1985; Tong and Karasek 1986), incineration of industrial and hazardous wastes (des Rosiers 1987; Muto et al. 1991), and power plants with fossil fuels (des Rosiers 1987; Hutzinger and Fiedler 1989) are examples of large systems. Small combustion systems include home heating and fireplaces (Clement et al. 1985; Safe 1990b), household waste incineration (Harrad et al. 1991a), automobile exhaust (Ballschmiter et al. 1986; Marklund et al. 1987), and medical waste incineration (des Rosiers 1987; Glasser et al. 1991; Lindner et al. 1990). Incineration of industrial and hazardous wastes that produce CDFs include wastes containing PCBs (Choudhury and Hutzinger 1982; Hutzinger and Fiedler 1989; Sedman and Esparza 1991), polychlorinated diphenyl ethers (Choudhury and Hutzinger 1982), 2,4,5-trichlorophenol esters (Choudhury and Hutzinger 1982), chlorinated benzenes (Choudhury and Hutzinger 1982; Öberg and Bergstrom 1987), chlorophenols (Narang et al. 1991; Oberg and Bergstrom 1987), waste oil (Taucher et al. 1992), biosludge from paper and pulp mills (des Rosiers 1987; Mantykoski et al. 1989; Someshwar et al. 1990), polyvinyl chloride (Christmann et al. 1989a), municipal sewage sludge (Clement et al. 1987a; des Rosiers 1987), chlorinated fluorenones, and 9,10-anthraquinones (Boenke and Ballschmiter 1989). The typical concentrations of total tetraCDFs, pentaCDFs, hexaCDFs, heptaCDFs, and octaCDF in municipal waste incineration fly ash are 79.5, 120.3, 116.3, 108.2, and 42.9 ppb, respectively (Safe 1990b). The corresponding CDF concentrations are 28.9, 16.6, 6.2, 1.8, and 0.3 ppb, respectively, in soot from home heating oil and 50.8, 30.0, 11.7, 3.2, and 0.5 ppb, respectively, in soot from coal/wood burning for home heating. The concentrations of 2,3,7,8-tetraCDF congener in municipal fly ash, soot from heating oil, and soot from coal/wood burning are 2.5, 1.1, and 1.9 ppb, respectively. The combined bottom and fly ash from five state-of-the-art mass-burn municipal waste combustors, with a variety of pollution control equipment, were analyzed for CDFs. The concentrations of CDFs (ppt) in ash samples

were determined to be: 2,3,7,8-tetraCDF, 176–626; 1,2,3,7,8-pentaCDF, 52-194; 2,3,4,7,8-pentaCDF, 43–171; 1,2,3,4,7,8-hexaCDF, 74–654; 1,2,3,6,7,8-hexaCDF, 131–660; 1,2,3,7,8,9-hexaCDF, 36-479; 2,3,4,6,7,8-hexaCDF, 5–124; 1,2,3,4,6,7,8-heptaCDF, 139–1,842; and 1,2,3,4,7,8,9-heptaCDF, 8–119 (EPA 1990b).

Three mechanisms have been postulated for the formation of CDFs in combustion processes: (1) CDFs are already present in trace amounts within the fuel and are not destroyed during combustion; (2) CDFs are formed during combustion from precursors (e.g., PCBs, polychlorophenols), which are present in the fuel; and (3) *de novo* synthesis from nonchlorinated organic substance and chlorine-containing molecules (Hutzinger and Fiedler 1989). Details about the mechanisms of CDF formation in combustion processes are available (Choudhury and Hutzinger 1982; Hutzinger and Fiedler 1989; Jay and Stieglitz 1991; Stieglitz et al. 1989). Other investigators have studied the control technologies available for the reduction of CDF emissions from municipal waste combustors (Brna and Kilgore 1990; Jordan 1987; Takeshita and Akimoto 1989). A significant reduction of CDF-concentrations in the flue gas from municipal and industrial waste incinerators and fossil fuel-fired power stations can be achieved by either the addition of a mixture of anhydrous calcium hydrate and coke to the flue gas or by treating the flue gas with titanium dioxide catalyst in the presence of ammonia (Hagenmaier et al. 1991). For three hazardous waste incinerators operating in China, it was determined that concentrations of CDDs and CDFs were highest during the start-up/ignition process, and were up to 5.4 times greater than levels measured during the normal operating period (Cao et al. 2018).

Accidental Fires or Malfunction of PCB-filled Transformers and Capacitors. Some of the major fires/ malfunctions involving PCB transformers and capacitors in the United States include a transformer fire inside the state office building in Binghamton, New York, in 1981; a transformer fire inside an office building in Boston, Massachusetts, in 1982; a transformer fire adjacent to a high-rise building in San Francisco, California, in 1983; a transformer fire inside an office building in Chicago, Illinois, in 1983; and a capacitor fire inside an office building in Columbus, Ohio, in 1984 (des Rosiers and Lee 1986; Hryhorczuk et al. 1986; Stephens 1986; Tiernan et al. 1985). CDFs were detected in air, soot, or wipe samples from all of these fire incidents. However, it was determined that in the absence of fire, CDF levels do not appear to increase in PCB fluids in electrical equipment from normal usage (des Rosiers and Lee 1986). The concentrations of total tetraCDFs, pentaCDFs, hexaCDFs, heptaCDFs, and octaCDF in air samples from different locations of a building following a transformer fire in San Francisco ranged from not detected to 53.9, not detected to 11.0, not detected to 1.3, not detected to 3.7, and not detected to 165.0 pg/m^3, respectively (Stephens 1986). A maximum concentration of 2,3,7,8-tetraCDF inside the

building air was 18.5 pg/m^3 (Stephens 1986). The concentration range of 2,3,7,8-tetraCDF in soot samples from other transformer/capacitor fires in the United States was 3–1,000 µg/g (des Rosiers and Lee 1986). The mechanism by which many CDFs form in the production of PCBs has been investigated (Erickson 1989; Hutzinger et al. 1985a). A study examining the impact of landfill fires reported elevated levels of total furans in air samples collected while the fire was burning and while it was being extinguished (Weichenthal et al. 2015).

Certain Industrial Processes. Certain high-temperature industrial processes like copper smelting, electrical arc furnaces in steel mills, and production of metallic magnesium and refined nickel emit CDFs into the atmosphere and process waste waters containing CDFs at concentrations higher than those found in emissions from municipal incineration and automobile exhausts (Oehme et al. 1989; Rappe 1987). It has been theorized that contamination/coating with polyvinyl chloride or polychlorinated paraffins are the precursors for the formation of CDFs in copper smelting and steel production from scrap metals (Rappe 1987). It has been speculated, in the case of magnesium and nickel production, that heavy metals in the presence of chlorine catalyze the formation of CDFs. But the precursors of CDFs have not been identified (Oehme et al. 1989). Solá-Gutiérrez et al. (2019) found that CDFs were formed during the electrochemical oxidation of the antibacterial and antifungal agent triclosan.

Cigarette Smoke. Both mainstream and sidestream cigarette smoke contain CDFs. The smoke contained 2,3,7,8-substituted congeners of CDFs, and the concentrations of total CDFs in mainstream and sidestream smoke of one common commercial brand of Swedish cigarettes were 720 and 1,670 pg per 20 cigarettes, respectively (Lofroth and Zeburh 1992).

Chemical Reactions

Certain Chemical Products. CDFs occur as contaminants in a number of chemical products, such as chlorinated phenols, formerly produced PCBs, phenoxy herbicides, chlorodiphenyl ether herbicides, hexachlorobenzene, tetrachlorobenzoquinones, and certain dyes. These chemical products containing CDFs may be released into the environment during their manufacture, use, or disposal.

The level of CDFs in commercial chlorinated phenols from different countries are given in Table 5-3. The difference in the levels of isomeric congeners is due to different degrees of chlorination and different methods of synthesis. The major CDF isomers identified were 1,2,4,6,8-penta-, 1,2,3,4,6,8-hexa-, 1,2,4,6,7,8-hexa-, 1,2,4,6,8,9-hexa-, 1,2,3,4,6,7,8-hepta-, and 1,2,3,4,6,8,9-heptaCDF (Rappe and Buser

1981). Commercial pentachlorophenol and sodium pentachlorophenate, used extensively for the preservation of wood, contain trace amounts of CDFs (Hagenmaier and Brunner 1987). These substances have the potential to migrate away or volatilize from wood surfaces and contaminate indoor air. The concentrations of CDFs in indoor ambient air of a kindergarten building in West Germany using pentachlorophenol (PCP)-treated wood were as follows: non-2,3,7,8-tetraCDF, 0.27 pg/m^3; 1,2,3,7,8-pentaCDF, 0.1 pg/m^3; non-2,3,7,8-pentaCDFs, 3.51 pg/m^3; 1,2,3,4,7,8-hexaCDF, 0.37 pg/m^3; 1,2,3,6,7,8-hexaCDF, 0.60 pg/m^3; 1,2,3,7,8,9-hexaCDF, 0.16 pg/m^3; non-2,3,7,8-hexaCDFs, 12.3 pg/m^3; 1.2,3,4,6,7,8-heptaCDF, 10.7 pg/m^3; 1,2,3,4,7,8,9-heptaCDF, 0.38 pg/m^3; non-2,3,7,8-heptaCDFs, 12.2 pg/m^3; and octaCDF, 6.0 pg/m^3 (Mukerjee et al. 1989). Therefore, use of certain commercial products can be a source of CDFs in air. From the analysis of air particulates and sediment, it was concluded that the likely source of CDFs in a western Lake Ontario site was a pentachlorophenol production facility (Czuczwa and Hites 1986b).

Table 5-3. Levels of Chlorodibenzofurans (CDFs) in Commercial Chlorinated Phenols (µg/g)

	CDFs						
	Tetra	Penta	Hexa	Hepta	Octa	∑CDFs	∑CDDs
2,4,6-Trichlorophenol, Sweden	1.5	17.5	36	4.8	–	60	<3
2,4,6-Trichlorophenol, United States	1.4	2.3	0.7	<0.02	–	4.6	0.3
2,3,4,6-Tetrachlorophenol, Finland	0.5	10	70	70	10	160	12
Pentachlorophenol, United States	0.9	4	32	120	130	280	1,000
Pentachlorophenol, United States	–	–	30	80	80	190	2,6
Pentachlorophenol, United States	≤0.4	40	90	400	260	790	1,900
Pentachlorophenol, Germany	–	–	0.03	0.8	1.3	2.1	6.8

CDDs = chlorinated dibenzo-*p*-dioxins

Source: Rappe and Buser 1981

The manufacture of PCBs stopped in the United States in the late 1970s; however, they are still widespread in the environment and exposure to CDFs continues through past PCB manufacture and use. In Bowes et al. (1975a), commercial Aroclors (i.e., commercial PCB mixtures, Clophen A-60, and Phenoclor DP-6) were analyzed for CDF concentrations (see Table 5-4). In a preceding study, Bowes et al. (1975b) determined the concentrations of 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF in two Aroclors and two Japanese Kanechlors. Concentrations of CDFs in a number of commercial PCB samples are provided in Table 5-4. The CDF isomers identified in commercial PCBs are 2,3,7,8-tetraCDF, 2,3,6,7-tetraCDF, 2,3,6,8-tetraCDF, 2,3,4,7,8-pentaCDF, 1,2,3,7,8-pentaCDF, 1,2,4,7,8-pentaCDF,

1,2,3,4,7,8-hexaCDF, 1,2,4,6,7,8-tetraCDF, 1,2,4,6,8,9-hexaCDF, 1,2,3,4,5,7,8-heptaCDF, and 1,2,3,4,6,8,9-heptaCDF (Rappe and Buser 1981).

Table 5-4. Levels of Chlorodibenzofurans (CDFs) in Commercial Polychlorinated Biphenyls (PCBs) (µg/g)

Sample	Tri	Tetra	Penta	Hexa	Hepta	Total
Aroclor 1248, 1969[a]	–	0.5	1.2	0.3	–	2.0
Aroclor 1254, 1969[a]	–	0.1	0.2	1.4	–	1.7
Aroclor 1254, 1970[a]	–	0.2	0.4	0.9	–	1.5
Aroclor 1254[b]	0.10	0.25	0.7	0.81	–	1/9
Aroclor 1254 (lot KK 602)[b]	–	0.05	0.1	0.02	–	0.2
Aroclor 1260, 1969[a]	–	0.1	0.4	0.5	–	1.0
Aroclor 1260 (lot AK 3)[a]	–	0.2	0.3	0.3	–	0.8
Aroclor 1260[b]	0.06	0.3	1.0	1.1	1.35	3.8
Aroclor 1016, 1972[a]	–	<0.001	<0.001	<0.001		–
Clophen A 60[a]	–	1.4	5.0	2.2	–	8.4
Clophen A 60[a]	0.10	0.3	1.73	2.45	0.82	5.4
Phenoclor DP-6[a]	–	0.7	10.0	2.9	–	13.6

[a]Bowes et al. 1975a.
[b]Rappe and Buser 1981.

Phenoxy herbicides generally contain higher concentrations of CDDs than CDFs. Therefore, more effort has been spent to determine the levels of CDDs rather than CDFs in study samples. According to an EPA (1985) report, two samples of European 2,4,5-trichlorophenoxyacetic acid contained no 2,3,7,8-tetraCDF. Compost from municipal yard waste was also found to contain CDFs, possibly due to the presence of a PCP-based biocide (Harrad et al. 1991b).

CDFs have been detected as contaminants in commercial samples of diphenyl ether herbicides. Concentrations of tetraCDFs, pentaCDFs, and hexaCDFs in these samples were as high as 0.4, 1.0, and 0.2 ppb, respectively (Yamagishi et al. 1981). Three early commercial hexachlorobenzene preparations were analyzed for CDFs. One sample contained a heptaCDF; all three samples contained octaCDF at concentrations ranging from 0.35 to 58.3 ppm (Villaneueva et al. 1974).

Samples of eight commercially available tetrachlorobenzoquinones (chloranils) from four different producers were analyzed for CDFs. OctaCDF was found in seven of eight samples at a maximum concentration of 6.02 ppm, while 1,2,3,4,6,7,8-heptaCDF was found in four of eight samples at a

maximum concentration of 27 ppb. 1,2,3,4,7,8-HexaCDFs, pentaCDFs, and tetraCDFs were also found in some of the samples (Christmann et al. 1989b).

CDFs are also formed during the bleaching process for the manufacture of pulp and paper (Kitunen and Salinoja-Salonen 1989; Näf et al. 1992; Taucher et al. 1991). Low levels (ppt) of 2,3,7,8-substituted congeners of tetra-, penta-, hexa-, and heptaCDF have been identified in the pulp, finished paper boards, effluents, and sludges from paper mills and 2,3,7,8-TCDF has been found in fish downstream of plant effluent.

The chloroalkali process utilizing graphite electrodes used for the production of chlorine produces CDFs. Total CDF levels as high as 650 ng/g (ppb) of sludge have been detected in sludge samples from graphite electrodes of a chloroalkali plant (Rappe et al. 1991a). The levels of tetra-, penta-, and hexaCDFs in the sludge were found to be approximately the same.

A number of commercial dyes were analyzed for CDFs. These samples contained tetra-, penta-, hexa-, hepta-, and octaCDFs at the ppb level (Heindl and Hutzinger 1989; Remmers et al. 1992; Williams et al. 1992).

Photochemical Reactions

Certain Photochemical Processes Involving Commercial Products. 1,3,7,9-TetraCDF was formed from the photolysis of 2,2',4,4',6,6'-hexachlorobiphenyl in hexane-methanol solution (Safe et al. 1977). The rate of photolysis was markedly higher in oxygen-degassed solutions than in oxygen-saturated solutions, indicating a triplet state as a possible intermediate for the photolysis process (Safe et al. 1977). Photolysis of chlorinated diphenyl ethers at around 300 nm in a degassed methanol solution also produced mono-, di-, tri-, and tetraCDFs (Choudhury et al. 1977). Photodegradation of polychlorobenzenes can also be a source of CDFs (EPA 1985). In addition, dechlorination of higher CDFs can be a source of lower chlorinated CDFs. The relevance of laboratory photolysis to environmental sources of CDFs is unknown.

Enzymatic Reactions. CDFs are formed by enzyme-catalyzed oxidations of 2,4-dichlorophenol, 2,4,5-chlorophenol, 2,3,4,6-tetrachlorophenol, 2,3,5,6-tetrachlorophenol, and PCP (Oberg and Rappe 1992; Svenson et al. 1989a, 1989b). The implication of these investigations is that CDFs may be biogenically formed from wastes containing these chlorophenols, but the significance of the process in contributing to the release of CDFs in the environment has not been assessed.

Hazardous Waste Sites. The improper disposal of CDF-containing wastes in landfill sites will primarily contaminate soils, but the air may also be contaminated by windblown dusts.

5.3.1 Air

Estimated releases of 1,141 pounds (~0.52 metric tons) of dioxin compounds including CDFs to the atmosphere from 878 domestic manufacturing and processing facilities in 2018 accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2020). These releases are summarized in Table 5-2.

CDFs are released to air from combustion processes, accidental fires or malfunction of PCB-filled transformers and capacitors, improper disposal of chlorinated chemical wastes, certain chemical products, certain industrial processes, and certain photochemical processes involving commercial products.

5.3.2 Water

Estimated releases of 1,178 pounds (~0.53 metric tons) of dioxin compounds including CDFs to surface water from 868 domestic manufacturing and processing facilities in 2018, accounted for about 1% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2020). This estimate includes releases to waste water treatment and publicly owned treatment works (POTWs) (TRI18 2020). These releases are summarized in Table 5-2.

CDFs enter water as a result of deposition after these compounds have been emitted to the atmosphere from combustion sources. The concentrations and congener patterns of CDFs found in the sediment of three lakes and in the atmosphere led the authors to conclude that atmospheric deposition is the primary source of these compounds in lakes (Czuczwa and Hites 1986a).

CDFs will enter surface water as a result of the discharge of CDF contaminated waste water, which is generated during the manufacture of chemicals containing CDFs contaminants. 2,3,7,8-TetraCDF has been detected at concentrations ≤4.5 ppb in sediment from estuaries adjacent to an industrial site in which chlorinated phenols were produced (Bopp et al. 1991). The typical waste waters from magnesium and refined nickel production are also examples of such CDF contamination (Oehme et al. 1989). Chemical manufacturing waste contaminated with CDFs that has been improperly disposed of can leach from

landfills into groundwater. CDF contaminated soil sites have been found in Butte, Montana, and Kent, Washington (Tiernan et al. 1989a). Uncontrolled landfills can be sources of CDFs for adjacent surface waters (Clement et al. 1989a).

Historically, an important source of CDFs in surface water is the discharge of effluents from pulp and paper mills that use the bleached kraft process. The concentrations of 2,3,7,8-tetraCDF in the treated effluents from five bleached kraft pulp and paper mills in the United States ranged from not detected (0.007 ppt) to 2.2 ppt with a mean value of 0.54 ppt, but the waste water sludges contained 2,3,7,8-tetraCDF at a mean concentration of 0.37 ppb (Amendola et al. 1989). The effluent from a kraft pulp mill from Jackfish Bay, Lake Superior, contained tetraCDFs in concentrations ranging from 0.3 to 1.3 ng/L (9.3–1.3 ppt) (Sherman et al. 1990). Due to guidelines under the Clean Water Act, this is no longer a source of CDF releases in the United States.

Chlorination of water has been shown to be a source of trace amounts (ppq level [i.e., pg/L level]) of CDFs. Apparently, impurities in the water may form CDFs during chlorination.

5.3.3 Soil

Estimated releases of 92,922 pounds (~42.2 metric tons) of dioxin compounds including CDFs to soil from 878 domestic manufacturing and processing facilities in 2018, accounted for about 97% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2020). An additional 337 pounds (~0.2 metric tons), accounting for about <1% of the total environmental emissions, were released via underground injection (TRI18 2020). These releases are summarized in Table 5-2.

The main sources of CDFs in soil are atmospheric deposition from combustion and manufacturing processes and disposal of CDF-contaminated wastes. Several instances of CDF environmental contamination from improper disposal of hazardous chemical wastes have been associated with the manufacture or use of certain chlorinated organic compounds and wastes from certain bleaching processes (Someshwar et al. 1990; Tiernan et al. 1989). Soil samples around two wood-preserving facilities in Finland that used chlorophenols contained several congeners of CDFs (Kitunen et al. 1987). The concentrations of octaCDF, 1,2,3,4,6,8,9-heptaCDF, 1,2,3,4,6,7,8-heptaCDF, 1,2,4,6,8,9-hexaCDF, 1,2,4,6,7,8-hexaCDF, and 1,2,3,4,6,8-hexaCDF in the top soil from one of these facilities were 210, 840, 1,400, 440, 340, and 550 µg/kg, respectively. In the other facility, the concentrations of CDFs decreased with soil depth, then increased at a depth of 60–80 cm, and tended to decrease at depths ≥100 cm of soil

(Kitunen et al. 1987). Soil contaminated with CDFs from PCP-containing wood preserving waste sites has been found in Butte, Montana, and Kent, Washington, in the United States (Tiernan et al. 1989), and in Finland (Kitunen et al. 1987). Land disposal of treated waste-water sludge from magnesium and nickel production is another source of CDF soil contamination (Oehme et al. 1989). An important source of CDFs in soil is the discharge of waste-water sludge from bleached kraft pulp and paper mills. The sludge from paper mills is known to contain CDFs (Amendola et al. 1989; Sherman et al. 1990; Someshwar et al. 1990). The presence of CDFs in the soil of Superfund sites also indicates that disposal of contaminated waste (e.g., waste from certain combustion processes, chemical wastes) is an important source of CDFs in soil. Biosolids applied to soils may also be a potential source of CDFs (EPA 2007a; Venkatesan and Halden 2014).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. CDFs are present in the atmosphere both in the vapor and particulate phase (Hites 1990). The ratio of the vapor to particulate-phase CDFs in air increases with increasing temperature. The ratio in Bloomington, Indiana was as high as 2 during the warm summer months and <0.5 in the winter. However, it should be recognized that the distribution of CDFs between the vapor and particulate phase will depend on the amount and nature of the particulate matter in the atmosphere, as well as the temperature (Hites 1990). The vapor to particle ratio is also different for the different congeners. In the air, a higher proportion of tetraCDF congeners is present in the vapor phase, whereas heptaCDF and octaCDF congeners are found predominantly in the particulate phase (Hites 1990). The transport of atmospheric CDFs to soil and water occurs by dry and wet deposition. Dry deposition refers to the simple gravitational settling of particles and the removal of vapor phase compounds onto surface materials, such as water and vegetation by impaction. Wet deposition refers to the removal of the atmospheric compounds by rain, fog, or snow.

The overall determined average dry to wet deposition ratio for atmospheric CDFs was 5:1 (Hites 1990). Therefore, dry deposition is more important than wet deposition for removal of atmospheric CDFs. Both particulate- and gas-phase compounds can be removed from the atmosphere by wet deposition. Particle-scavenging is the process by which rainfall removes particles from the atmosphere. About 40% of tetraCDF and pentaCDF homologues and 80% of the hexaCDF through octaCDF homologues in Bloomington, Indiana air were removed by particle scavenging. Therefore, particle scavenging during

wet deposition is generally a more important process than gas scavenging (Eitzer and Hites 1989a; Hites 1990). Wet deposition of vapor-phase CDFs is a relatively minor loss process (Atkinson 1991).

In addition to the intermedia transport of CDFs from air to water and soil, intramedia transport of CDFs is also significant. The long atmospheric lifetimes of tetra- and higher chlorinated congeners and the presence of these CDFs in remote areas far removed from an emission source indicates that these substances are susceptible to long-range atmospheric transport (Atkinson 1991; Czuczwa et al. 1985; Oehme 1991; Rappe et al. 1989).

Water. The two significant processes in the transport of a chemical from water are volatilization and adsorption to sediment. The first process transfers the chemical from water to air and the second process transfers the chemical from water phase to sediment. The volatilization of CDFs from water, as with other chemicals, depends on their Henry's law constants. Since the values of the Henry's law constants for tetra- and higher CDFs are $<1.48 \times 10^{-5}$ atm-m^3/mol (see Table 4-2), the rate of volatilization of these CDFs is slow and is controlled by slow diffusion through air (Thomas 1982). The volatilization rates are further decreased because the CDFs are present in water predominantly in the adsorbed states. The adsorption of CDFs to suspended solids and sediment in water depends on their K_{oc} values. The estimated log K_{oc} values for 2,3,7,8-TCDD and octaCDF are 5.61 and 8.57, respectively (see Table 4-2). Therefore, these compounds strongly adsorb to suspended solids and sediment in water. As a result, almost all of the literature provides concentrations of CDFs in sediment, and not in water; concentration in water is so low that it is rarely measured. Therefore, sediments are the ultimate environmental sinks for CDFs (Czuczwa and Hites 1986b).

The estimated high log K_{ow} values for 2,3,7,8-tetraCDF and octaCDF (see Table 4-2) suggest that the bioconcentration of CDFs in aquatic organisms is high. The experimental bioconcentration factor (BCF) for octaCDF in the guppy (*Poecilia reticulata*) was 589 on wet weight basis and 7,760 on lipid weight basis (Frank and Schrap 1990). Similarly, steady-state concentrations of slightly >0.001 µg/g (wet weight) in tissues were found in guppies after feeding the fish 10.6–40.6 µg/g octaCDF in food (Clark and Mackay 1991). In a static laboratory test, the determined bioconcentration factors for 1,2,3,7,8-pentaCDF and 2,3,4,7,8-pentaCDF in guppies were 2,400 and 5,000, respectively (Opperhuizen and Sijm 1990). In another laboratory experiment, the determination of bioconcentration of 2,3,7,8-tetraCDF in goldfish (*Carassius auratus*) was attempted by exposing the fish to fly ash (containing <1,400 ppt 2,3,7,8-tetraCDF) and contaminated sediment (containing <68 ppt 2,3,7,8-tetraCDF) in aquaria for 10 weeks (O'Keefe et al. 1986). Fish in both tests contained only 0.7 ppt 2,3,7,8-tetraCDF. The BCF

could not be determined because the concentration of 2,3,7,8-tetraCDF in water was too low. Laboratory experiments in fish exposed to contaminated sediments and in Wisconsin River fish showed that residues of 2,3,7,8-substituted congeners of CDFs are selectively enriched in carp (*Cyprinus carpio*) (Kuehl et al. 1987). Since the concentrations of CDF isomers were too low for determination, the authors reported the following bioavailability indices (ratio of concentration of a compound in fish lipid to concentration in sediment based on carbon content): 0.06 for 2,3,7,8-tetraCDF, 0.21 for 2,3,4,7,8-pentaCDF, 0.033 for 1,2,3,6,7,8-hexaCDF, and 0.0033 for 1,2,3,4,6,7,8-heptaCDF (Kuehl et al. 1987). In another study, highest bioavailable indices were achieved for organisms filtering or ingesting organic particles (mussels, chironomids) and those consuming benthic organisms (crayfish suckers) (Muir et al. 1992).

It is clear from the above experiments that the BCFs for CDFs in aquatic organisms are lower than other polychlorinated aromatic compounds such as octachlorobiphenyl (Clark and Mackay 1991). Several explanations have been proposed to explain the lower-than-expected bioconcentration of CDFs in fish. One possible explanation is the rapid depuration (elimination) of the chemicals from fish, probably via biotransformation through a cytochrome P450 system mediated mixed function oxidase with the formation and elimination of polar metabolites, such as hydroxylated compounds (Frank and Schrap 1990; Opperhuizen and Sijm 1990). Another explanation for the lower-than-expected BCF is a low rate of membrane permeation of these highly hydrophobic compounds (Opperhuizen and Sijm 1990). The theory of low permeation is disputed by other investigators (Frank and Schrap 1990). In addition, CDF congeners are present in the water mostly in the adsorbed state and the inability to distinguish between the adsorbed and free CDFs (bioavailability will be lower in the adsorbed state) may have largely overestimated the dissolved CDFs in water. As a result, the BCF derived from the overestimated water concentration may be responsible for underestimating the true bioconcentration potential. Khairy et al. (2019) investigated the uptake and bioaccumulation potential of chlorinated pesticides, perfluoroalkyl acids, CDDs, and CDFs in aquatic organisms in the Passaic River, New Jersey, and determined that uptake occurred more through sediment and pore-water for CDFs rather than the river water itself. Estimated BCFs and bioaccumulation factors (BAFs) were calculated using the EPA Estimation Programs Interface Suite (EPI Suite™) software using the quantitative structure-activity relationships (QSARs) described in Arnot et al. (2009). (See Appendix E for definitions of bioaccumulation and bioconcentration). The results are shown in Table 5-5. These estimated values suggest that bioaccumulation in aquatic organisms is very high for most congeners.

Table 5-5. Estimated BCFs and BAFs for Chlorodibenzofurans (CDFs) in Aquatic Organisms

Congener	Estimated BCF	Estimated BAF
1,3,7,8-TetraCDF	12,800	11,384
2,3,6,8-TetraCDF	12,800	11,384
2,3,7,8-TetraCDF	9,451	2,573
1,2,3,4,8-PentaCDF	14,000	14,993
1,2,3,7,8-PentaCDF	4,732	22,533
2,3,4,7,8-PentaCDF	4,732	54,231
1,2,3,4,7,8-HexaCDF	14,000	239,208
1,2,3,6,7,8-HexaCDF	14,000	239,208
1,2,3,7,8,9-HexaCDF	4,712	12,280
1,2,4,6,7,9-HexaCDF	4,732	45,385
2,3,4,6,7,8-HexaCDF	6,902	64,676
1,2,3,4,6,7,8-HeptaCDF	6,902	64,676
1,2,3,4,6,7,9-HeptaCDF	3,336	93,467
1,2,3,4,7,8,9-HeptaCDF	3,336	93,467
OctaCDF	4,712	12,280

BAF = bioaccumulation factor; BCF = bioconcentration factor

Source: EPA 2020

Compared to other aquatic organism such as fish, crabs lack the ability to metabolize most of the CDF isomers and uptake more of these substances than fish via sediment and tend to have high concentrations of CDFs (Khairy et al. 2019; Oehme et al. 1990). The concentrations of 2,3,7,8-tetra-, 2,3,4,7,8-penta-, and 1,2,3,6,7,8-hexaCDFs in the hepatopancreas of crabs collected from a contaminated river were 2.3, 1.6, and 4.6 ppb. These values are ≈3 orders of magnitude higher than those found in fish (Kuehl et al. 1987). Therefore, bioconcentration of CDFs in crabs will be much higher than in fish that are known to metabolize CDFs, but no values for bioconcentration of CDFs in crabs were provided (Oehme et al. 1990). This is apparently due to a lack of data concerning the concentrations of CDFs in water.

The biomagnification of CDFs in a littoral food chain consisting of phytoplankton → blue mussel (*Mytilus edulis*) → juvenile eider duck (*Somateria mollissima*) and a pelagic food chain consisting of phytoplankton → zooplankton → herring (*Clupea harengus*) → cod (*Gadus morrhua*) was studied (Broman et al. 1992). It was concluded that the total concentrations of 2,3,7,8-substituted CDFs decreased with increasing trophic level, whereas the toxic content of the 2,3,7,8-substituted CDFs increased with increasing trophic level. The result implied a selective enrichment of 2,3,7,8-substituted isomers with high toxic equivalency factors.

Sediment and Soil. The transport of CDFs from soil to air is possible via volatilization and by windblown dusts. The very low vapor pressures and high soil sorption coefficients of those CDFs for which data are available (see Table 4-2) indicate that volatilization of these compounds from soil is insignificant (Hutzinger et al. 1985b). The observation that essentially no loss of 2,3,7,8-TCDD, a structurally similar compound, from the contaminated soil at Times Beach, Missouri, occurred in 4 years (Yanders et al. 1989), strongly suggests that volatilization is insignificant for CDFs as well. No evidence of appreciable loss of CDFs due to volatilization was found in contaminated soils during a period of 8 years (Hagenmaier et al. 1992). CDFs may be transported from soil to water via leaching and runoff. Soil leaching experiments indicate that CDFs remain strongly adsorbed even in sandy soil and leaching of these compounds from soil by rainwater is not significant (Carsch et al. 1986). The vertical movement of CDFs was found to be very slow and >90% of CDFs were found in the top 10 cm after 3 years (Hagenmaier et al. 1992). Therefore, transport of CDF from landfill soil to adjacent land or surface water by runoff water is more likely than leaching. Leaching or vertical movement of CDFs in soil can occur under special conditions, such as saturation of the sorption sites of the soil matrix, presence of organic solvents in the soil facilitating co-solvent action, cracks in the soil, or burrowing activity of animals (Hagenmaier et al. 1992; Hutzinger et al. 1985b). The bioavailability of CDDs and CDFs was studied in soil samples obtained from a former creosote producing hazardous waste site (Roberts et al. 2019). The bioaccessibility percentage of CDFs calculated using the levels in the soil pre- and post-extraction using a physiologically-based extraction fluid ranged from 34.3% (2,3,7,8-tetraCDF) to 60.6% (1,2,3,4,7,8,9-heptaCDF).

Data regarding the translocation of CDFs from the roots to the above-ground parts of plants were not located. Because there is little bioaccumulation of CDDs in plants from soil (EPA 1985), bioaccumulation of CDFs in plants is also probably insignificant. As in the case with CDDs (EPA 1985), due to absorption by underground roots of some plants such as carrots, the roots can accumulate more CDFs, compared to aerial parts. In most plants (plants with higher aerial surface area and leaf surfaces with compounds that enhance adsorption), higher concentrations of CDFs are likely to be found on aerial portions of plants due to deposition of airborne particles and vapor. The estimated accumulation potential of CDFs on pine needles (ratio of CDF concentration in a gram of pine needles or concentration in a gram of air) due to deposition of airborne particles for 10 months was 104 to 105 (Reischl et al. 1989).

Other Media. The biotransfer of CDFs from contaminated soil to grazing animals was studied with chickens as a model (Petreas et al. 1991). Compared to controls, the concentration of CDFs in eggs of

exposed chickens increased 10-fold at low exposure levels (total CDF concentration in soil was 555 ppt) and 100-fold at high exposure levels (total CDF concentration was 11,841 ppt). The biotransfer factors (ratio of concentration in egg fat over concentration in soil) for different congeners of CDFs were <1. However, statistically significant ($p<0.05$) concentration dependence of biotransfer factors, as a result of high and low exposure, were found for only 2,3,7,8-tetraCDF and 1,2,3,4,7,8,9-heptaCDF.

5.4.2 Transformation and Degradation

Air. The loss of vapor-phase CDFs by reactions with hydroxyl radicals, nitrate radicals, and ozone has been estimated to occur slowly for the highly chlorinated congeners (Atkinson 1991). The estimated rate constants for the reactions of vapor phase CDFs with OH radicals are as follows (-10^{-12} cm^3/molecule-second): tetraCDFs, 1.4–8.3; pentaCDFs, 1.0–4.3; hexaCDFs, 0.74–2.6; heptaCDFs, 0.53–0.92; and octaCDFs, 0.39. Using a 12-hour average daytime hydroxyl radical concentration of $1.5x10^6/cm^3$, the estimated tropospheric lifetimes of tetra-, penta-, hexa-, hepta-, and octaCDF are 1.9–11, 3.6–15, 5.9–22, 17–31, and 39 days, respectively. The vapor-phase reaction of CDFs with hydroxyl radicals is the dominant loss process and this loss process is more important for the lower, than the higher, chlorinated congeners, because the lifetimes due to this reaction are shorter for lower chlorinated congeners and the vapor-phase concentrations of lower chlorinated congeners are higher. Based on the available information, the reactions of hydroxyl radicals with particulate-phase CDFs are insignificant and the principal air removal mechanism for particulate-phase CDFs is wet and dry deposition.

Photodegradation of CDFs bound to atmospheric particles is not an important process in removing these compounds from air (Koester and Hites 1992). No data regarding vapor-phase photolysis of CDFs were located. In the absence of data, the half-lives of these compounds in the vapor phase have been estimated from aqueous phase photolysis data and it was concluded that photolysis is relatively unimportant, even when compared to reaction with hydroxyl radicals (with the possible exception of 1,3,6,8-tetraCDF) (Atkinson 1991).

Water. The loss of CDFs in water by abiotic processes such as hydrolysis and oxidation is not likely to be significant (EPA 1985). The photolysis of CDFs in solution indicates that significant photolysis occurs in hydrogen donating solvents. Photolysis was faster in methanol than in hexane. Photolysis in these solvents proceeds with rapid dechlorination and eventual formation of unidentified resinous polymeric products (Hutzinger et al. 1973), and may proceed at a much faster rate at shorter wavelengths (254 nm) than are available from sunlight (>290 nm). In addition, the rate of photolysis in hexane is

faster for CDFs than CDDs and the higher chlorinated congeners photodegrade faster than lower chlorinated congeners (Muto and Takizawa 1991). The rates of photolysis of 2,3,7,8-substituted congeners in solution are faster than the rates of non-2,3,7,8-substituted congeners (Tysklind and Rappe 1991). During the photolysis of octaCDF in dioxane under xenon lamp, hexa- and pentaCDFs were the major products, with small amounts of hepta- and tetraCDFs (Koshioka et al. 2014).

The estimated photolysis lifetimes of CDDs by sunlight in surface waters at 40° latitude range from 0.4 to 225 days, depending upon the specific congener and the season of the year (shorter lifetimes in summer than in winter) (Atkinson 1991). If the photolysis rates of CDFs are assumed to be faster than CDDs (Muto and Takizawa 1991), the photolysis lifetimes of CDFs are expected to be shorter than those for CDDs. However, the persistence of CDFs in natural water (based on a half-life of 1 year for CDDs in a model aquatic ecosystem) (EPA 1985), contradicts the estimated photolytic lifetimes in natural water. This discrepancy is possibly due to the fact that CDDs/CDFs in natural water are present predominantly in particulate-sorbed phase. The rate of photolysis is much slower in the sorbed phase compared to solution phase photolysis (the estimated lifetimes data of Atkinson [1991] is based on solution phase photolysis) (Tysklind and Rappe 1991).

No data in the literature indicate that biodegradation of CDFs in water is significant. Biodegradation studies in sediments of lake water indicate that 2,3,7,8-TCDD resists biodegradation (EPA 1985). Therefore, biodegradation of CDFs in water may also be insignificant.

Sediment and Soil. The photodegradation of thin film CDIs of fly ash bound CDFs under sunlight was much slower than solution phase photolysis (Hutzinger et al. 1973; Tysklind and Rappe 1991). Direct evidence of sunlight-initiated photolysis of CDFs in soil was not located. Given the fact that sunlight cannot penetrate beyond the surface layer of soil and the lack of photolysis of CDFs adsorbed to fly ash (Koester and Hites 1992; Tysklind and Rappe 1991), the photolysis of CDFs in soil and sediment may not be significant. It may be significant for airborne particles.

No significant changes in the concentration patterns of homologous or isomeric CDFs could be detected in contaminated soil samples taken in 1981, 1987, and 1989 at the same sites and from the same depth (Hagenmaier et al. 1992). This underlines the persistence of CDFs in soil. No direct evidence was located in the literature suggesting that biodegradation of CDFs in soil and sediments is significant. The lack of biodegradation of CDDs in soil and sediments (although a few microbes degraded 2,3,7,8-TCDD at a slow rate) (EPA 1985) and the lack of evidence for any degradation of CDFs in dated lake sediments

(Czuczwa and Hites 1986b; Czuczwa et al. 1985) indirectly suggest that biodegradation of CDFs in soil or sediments is not significant.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to CDFs depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of CDFs in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on CDFs levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-6 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-7.

Table 5-6. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	~1 fg/m^{3}[b]	EPA 2013
Drinking water	10-50 pg/L (ppq)	EPA 1994 (Method 1613)
Surface water and groundwater	0.025–1 ng/L (ppt)	Tondeur et al. 1989 (EPA Method 8290)
Soil	0.4–0.8 ng/g (ppb)	Draper et al. 1991
Sediment	~1 ng/g (ppb)	EPA 2007b (Method 8280B)
Whole blood	5 pg/kg (ppq)	Patterson et al. 1987, 1989

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.
[b]Detection limits in air are dependent upon the sampling time/sampling volume. Typical detection limits are in the pg/m^3 range; however, this study had extended sampling times and large volume collections (>150 m^3) ensuring very low detection limits.

Table 5-7. Summary of Environmental Levels of Chlorodibenzofurans (CDFs)

Media	Low	High	For more information
Outdoor air (ppbv)	<LOD	5.2x10^{-4}	Section 5.5.1
Indoor air (ppbv)	<LOD	0.00023	Section 5.5.1
Surface water (ppb)	<LOD	1.5	Section 5.5.2
Groundwater (ppb)	<LOD	445	Section 5.5.2
Drinking water (ppb)	<LOD	0.23	Section 5.5.2

Table 5-7. Summary of Environmental Levels of Chlorodibenzofurans (CDFs)

Media	Low	High	For more information
Food (ppb)	<LOD	0.005	Section 5.5.4
Soil (ppb)	<LOD	21,000	Section 5.5.3

LOD = limit of detection

Detections of CDFs in air, water, and soil at NPL sites are summarized in Table 5-8.

Table 5-8. Chlorodibenzofuran (CDF) Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Tetrachlorodibenzofuran					
Water (ppb)	0.000295	0.00029	1.31	2	2
Soil (ppb)	0.2	0.634	59.9	11	8
Air (ppbv)			No data		
2,3,7,8-Tetrachlorodibenzofuran					
Water (ppb)			No data		
Soil (ppb)	0.32	0.514	22.2	17	12
Air (ppbv)			No data		
Pentachlorodibenzofuran					
Water (ppb)			No data		
Soil (ppb)	4.05	3.83	13.7	14	7
Air (ppbv)			No data		
1,2,3,7,8-Pentachlorodibenzofuran					
Water (ppb)			No data		
Soil (ppb)	0.387	0.207	26.8	6	6
Air (ppbv)			No data		
2,3,4,7,8-Pentachlorodibenzofuran					
Water (ppb)			No data		
Soil (ppb)	1.3	0.553	43.5	5	4
Air (ppbv)			No data		
Hexachlorodibenzofuran					
Water (ppb)			No data		
Soil (ppb)	33	22.2	19.0	18	11
Air (ppbv)			No data		

Table 5-8. Chlorodibenzofuran (CDF) Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
1,2,3,4,7,8-Hexachlorodibenzofuran					
Water (ppb)			No data		
Soil (ppb)	7.8	3.06	77.2	7	6
Air (ppbv)			No data		
1,2,3,6,7,8-Hexachlorodibenzofuran					
Water (ppb)			No data		
Soil (ppb)	5.1	1.32	65.2	8	7
Air (ppbv)			No data		
1,2,3,7,8,9-Hexachlorodibenzofuran					
Water (ppb)			No data		
Soil (ppb)	12.7	6.26	455	6	5
Air (ppbv)			No data		
2,3,4,6,7,8-Hexachlorodibenzofuran					
Water (ppb)			No data		
Soil (ppb)	15	2.12	117	5	4
Air (ppbv)			No data		
Heptachlorodibenzofuran					
Water (ppb)	161	1.11	7,940	3	3
Soil (ppb)	38.9	26.4	27.7	28	16
Air (ppbv)			No data		
1,2,3,4,6,7,8-Heptachlorodibenzofuran					
Water (ppb)	0.0000655	0.0000274	8.56	2	2
Soil (ppb)	114	22.4	58.9	10	8
Air (ppbv)			No data		
1,2,3,4,7,8,9-Heptachlorodibenzofuran					
Water (ppb)			No data		
Soil (ppb)	30	12.0	352	5	4
Air (ppbv)			No data		
1,2,3,4,6,7,8,9-Octachlorodibenzofuran					
Water (ppb)	0.83	0.489	2,600	7	5
Soil (ppb)	65.4	22.0	37.5	31	19
Air (ppbv)			No data		

Table 5-8. Chlorodibenzofuran (CDF) Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Dibenzofurans, chlorinated					
Water (ppb)			No data		
Soil (ppb)	39.4	39.4	1	2	1
Air (ppbv)			No data		

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

The National Dioxin Air Monitoring Network (NDAMN) was established by the EPA in 1998 to determine background air concentrations of CDDs, CDFs, and dioxin-like PCBs in the United States (EPA 2013). Congener-specific data from June 1998 through November 2004 at 34 NDAMN stations (urban 4 stations, rural 23 stations, and remote 7 stations) throughout the United States are shown in Table 5-9. Large sampling times and large volumes of collected air guaranteed low detection limits and a high detection frequency. The maximum concentration of 4,498 fg/m^{3}was observed for 1,2,3,4,6,7,8-heptaCDF .

Table 5-9. Congener-specific Monitoring Data from the NDAMN 1998–2004

Congener	Detection frequency (%)	Mean (fg/m^3)	SD (fg/m^3)
2,3,7,8-TetraCDF	96	2.1	9.6
1,2,3,7,8-PentaCDF	94	2.4	14.1
2,3,4,7,8-PentaCDF	96	4.3	28.8
1,2,3,4,7,8-HexaCDF	98	5.6	41.4
2,3,4,6,7,8-HexaCDF	99	6.4	41.3
1,2,3,7,8,9-HexaCDF	74	1.5	22.3
1,2,3,4,6,7,8-HeptaCDF	100	27.3	178.1
1,2,3,4,7,8,9-HeptaCDF	91	3.5	25.2
OctaCDF	99	21.9	142.8

NDAMN = National Dioxin Air Monitoring Network; SD = standard deviation

Source: EPA 2013

High levels of CDFs and dioxin like substances were observed following the terrorist attacks at the World Trade Center (WTC) complex in New York City on September 11, 2001 (Rayne et al. 2005). Predicted gas-phase concentrations in Manhattan 6 weeks after the attack were estimated to be as high as 9,600 fg/m^3 (9.6 pg/m^3) for 2,3,7,8-tetraCDF.

Lin et al. (2010) studied atmospheric levels of CDDs and CDFs in the air of Taiwan in the vicinity of water treatment facilities. Average atmospheric levels in pg/m^3 were as follows: 2,3,7,8-tetraCDF, 0.082; 1,2,3,7,8-pentaCDF, 0.108; 2,3,4, 7,8-pentaCDF, 0.197; 1,2,3,4,7,8-hexaCDF, 0.230; 1,2,3,6,7,8-hexaCDF, 0.209; 1,2,3,7,8,9-hexaCDF, 0.0.013; 2,3,4, 6,7,8-hexaCDF, 0.241; 1,2,3,4,6,7,8-heptaCDF, 0.729; 1,2,3,4,7,8,9-heptaCDF 0.125; and octaCDF 0.727. Levels were consistently higher in the spring as compared to summer, fall, and winter months.

Levels of CDFs determined in the ambient air in North America are presented in Table 5-10. As expected, the concentrations of CDFs in air show geographical variability based on the sources of emissions. Generally, the levels show the following trend: tunnel > urban > suburban > rural (Eitzer and Hites 1989a). Even in a particular area, the level shows daily and seasonal variability. For example, the concentrations of CDFs are generally higher on rainy days with high humidity and on less windy days (Nakano et al. 1990). The levels are also higher in winter than in summer, due to increases in the contribution from combustion sources (heating) (CARB 1990). Table 5-10 indicates that the concentrations of total tetra-, penta-, hexa-, hepta-, and octaCDFs in ambient urban/suburban air can vary within the ranges of 0.13–7.34, 0.09–5.10, <0.09–12.55, 0.08–12.71, and 0.13–3.78 pg/m^3, respectively. In rural areas, the concentrations of total tetra-, penta-, hexa-, hepta-, and octaCDFs are below their detection limits. It has also been determined that the vapor/particulate phase ratio of the CDFs in ambient air depends on the season of the year and the number of chlorine substituents. Generally, the tetra- and pentaCDFs are present at higher ratios in the vapor phase, while hepta- and octaCDF are present predominantly in the particulate phase in the atmosphere. This ratio of vapor/particulate phase increases during summer, compared to winter (CARB 1990; Eitzer and Hites 1989a; Nakano et al, 1990). The congener profile in the atmosphere follows the congener profile of their sources; that is, if the major source of CDFs in the atmosphere is a municipal incinerator, the congener pattern in the air follows the congener pattern in flue gas from that municipal incinerator (Edgerton et al. 1989; Eitzer and Hites 1989a).

Table 5-10. Concentrations of Chlorodibenzofurans (CDFs) in Ambient Indoor and Outdoor Air in North America and Oceans

Site	Sampling year	CDF	Concentration (pg/m^3)	Reference
Bridgeport, Connecticut (outdoor)	1987–1988	2,3,7,8-TetraCDF	0.078	Hunt and Maisel 1990
		Total tetraCDF	0.856	
		1,2,3,7,8-PentaCDF	0.031	
		2,3,4,7,8-PentaCDF	0.047	
		Total pentaCDF	0.547	
		1,2,3,4,7,8-HexaCDF	0.106	
		1,2,3,6,7,8-HexaCDF	0.039	
		2,3,4,6,7,8-HexaCDF	0.087	
		1,2,3,7,8,9-HexaCDF	0.007	
		Total hexaCDF	0.580	
		1,2,3,4,6,7,8-HeptaCDF	0.212	
		1,2,3,4,7,8,9-HeptaCDF	0.033	
		Total heptaCDF	0.369	
		OctaCDF	0.211	
Toronto Island, Canada (outdoor)	1988–1989	Total tetraCDF	0.404	Steer et al. 1990
		Total pentaCDF	0.118	
		Total hexaCDF	0.204	
		Total heptaCDF	0.240	
		OctaCDF	0.142	
Dorset, Canada (outdoor)	1988–1989	Total tetraCDF	0.064	Steer et al. 1990
		Total pentaCDF	0.200	
		Total hexaCDF	0.074	
		Total heptaCDF	0.52	
		OctaCDF	0.194	
Windsor, Canada (outdoor)	1988–1989	Total tetraCDF	0.733	Steer et al. 1990
		Total pentaCDF	0.383	
		Total hexaCDF	0.333	
		Total heptaCDF	0.550	
		OctaCDF	0.182	
Boston, Massachusetts (indoor)	No data	2,3,7,8-TetraCDF	(0.37)[a]–1.4	Kominsky and Kuoka 1989
		Total tetraCDF	(0.64)[a]–6.2	
		Total pentaCDF	(0.12)[a]–1.9	
		Total hexaCDF	(0.39–(1.5)a	
		OctaCDF	(0.54)–(1.8)[a]	
Albany, New York (outdoor)	1987–1988	Total tetraCDF	3.86	Smith et al. 1990
		2,3,7,8-tetraCDF/unknown isomer	0.89	
		Total pentaCDF	2.00	
		Total hexaCDF	0.28	
		Total heptaCDF	<0.34	
		OctaCDF	<0.50	

Table 5-10. Concentrations of Chlorodibenzofurans (CDFs) in Ambient Indoor and Outdoor Air in North America and Oceans

Site	Sampling year	CDF	Concentration (pg/m^3)	Reference
Binghamton, New York (outdoor)	1988	Total tetraCDF 2,3,7,8-tetraCDF/unknown isomer Total pentaCDF Total hexaCDF Total heptaCDF OctaCDF	0.94 0.18 0.25 <0.09 <0.14 <0.30	Smith et al. 1990
Utica, New York (outdoor)	1988	Total tetraCDF 2,3,7,8-tetraCDF/unknown isomer Total pentaCDF Total hexaCDF Total heptaCDF OctaCDF	7.34 1.15 3.16 <0.36 <0.24 <0.61	Smith et al. 1990
Niagara Falls, New York (outdoor)	1987–1988	Total tetraCDF 2,3,7,8-tetraCDF/unknown isomer Total pentaCDF Total hexaCDF Total heptaCDF OctaCDF	1.53 <0.11 0.98 1.45 1.37 0.51	Smith et al. 1990
United States and Canada ambient air (outdoor)	No data	Total tetraCDF Total pentaCDF Total hexa CDP Total heptaCDF OctaCDF	1.09 0.63 0.72 1.14 0.62	Waddell et al. 1990
Bloomington, Indiana	1986	2,3,7,8-/2,3,4,8-/2,3,4,6-TetraCDF Total tetraCDF 1,2,3,7,8-/1,2,3,4,8-pentaCDF 2,3,4,7,8-/1,2,3,6,9-pentaCDF Total pentaCDF 1,2,3,4,7,8-/1,2,3,4,6,7-HexaCDF 1,2,3,6,7,8-/1,2,3,4,7,9-HexaCDF 2,3,4,6,7,8-HexaCDF 1,2,3,7,8,9-HexaCDF Total hexaCDF 1,2,3,4,6,7,8-HeptaCDF 1,2,3,4,7,8,9-HeptaCDF Total heptaCDF OctaCDF	0.048 0.263 0.017 0.017 0.20 0.023 0.016 0.015 0.0007 0.113 0.039 0.005 0.071 0.28	Eitzer and Hites 1989b
Southern California (outdoor)	1987–1989	2,3,7,8-TetraCDF 1,2,3, 7,8-PentaCDF 2,3,4,7,8-PentaCDF 1,2,3,4,7,8-HexaCDF 1,2,3,6,7,8-HexaCDF 2,3,4,6,7,8-HexaCDF 1,2,3,4,6,7,8-HeptaCDF 1,2,3,4,7,8,9-HeptaCDF	<0.007–0.482 <0.010–1.9 <0.009–0.110 <0.001–0.27 <0.001–0.800 <0.001–0.280 <0.002–1.58 <0.002–0.092	CARB 1990

Table 5-10. Concentrations of Chlorodibenzofurans (CDFs) in Ambient Indoor and Outdoor Air in North America and Oceans

Site	Sampling year	CDF	Concentration (pg/m^3)	Reference
Los Angeles, California (outdoor)	1987	2,3,7,8-TetraCDF	0.021	Maisel and Hunt 1990
		Other tetraCDF	0.30	
		1,2,3,7,8-PentaCDF	0.077	
		2,3,4,7,8-PentaCDF	0.077	
		Other pentaCDF	0.41	
		1,2,3,4,7,8-HexaCDF	0.151	
		1,2,3,6,7,8-HexaCDF	0.25	
		2,3,4,6,7,8-HexaCDF	<0.069	
		1,2,3,7,8,9-HexaCDF	<0.083	
		Other hexaCDF	<0.080	
		1,2,3,4,6,7,8-HeptaCDF	<0.190	
		1,2,3,4,7,8,9-HeptaCDF	<0.018	
		Other heptaCDF	0.26	
		OctaCDF	0.056	
Dayton, Ohio (outdoor, suburban/ roadside)	1988	Total tetraCDF	0.13	Tiernan et al. 1989
		Total pentaCDF	0.24	
		Total hexaCDF	0.14	
		Total heptaCDF	0.11	
		OctaCDF	<0.07	
Dayton, Ohio (outdoor, municipal solid waste incinerator)	1988	Total tetraCDF	1.23	Tiernan et al. 1989
		2,3,7,8-tetraCDF	0.11	
		Total pentaCDF	5.10	
		1,2,3,7,8-pentaCDF/unknown isomer	0.46	
		2,3,4,7,8-pentaCDF	0.53	
		Total hexaCDF	12.55	
		1,2,3,4,7,8-hexaCDF/unknown isomer	1.18	
		1,2,3,6,7,8-hexaCDF	2.27	
		1,2,3,7,8,9-hexaCDF	<0.06	
		2,3,4,6,7,8-hexaCDF	<0.41	
		Total heptaCDF	12.71	
		1,2,3,4,6,7,8-heptaCDF	8.22	
		1,2,3,4,7,8,9-heptaCDF	0.56	
		OctaCDF	3.78	
Dayton, Ohio (outdoor, rural area)	1988	Total tetraCDF	<0.02	Tiernan et al. 1989
		Total pentaCDF	<0.02	
		Total hexaCDF	<0.05	
		Total heptaCDF	<0.07	
		OctaCDF	<0.17	
Windsor, Canada (outdoor)	1987–1988	Total tetraCDF	0.21	Bobet et al. 1990
		Total pentaCDF	0.09	
		Total hexaCDF	0.10	
		Total heptaCDF	0.08	
		OctaCDF	0.13	
Walpole Island, Canada (outdoor)	1987–1988	Total tetraCDF	<0.05	Bobet et al. 1990
		Total pentaCDF	<0.07	
		Total hexaCDF	<0.10	
		Total heptaCDF	<0.07	
		OctaCDF	<0.14	

Table 5-10. Concentrations of Chlorodibenzofurans (CDFs) in Ambient Indoor and Outdoor Air in North America and Oceans

Site	Sampling year	CDF	Concentration (pg/m^3)	Reference
Lake Trout, Wisconsin (outdoor)	1987	Total tetraCDF	0.083	Edgerton et al. 1989
		Total pentaCDF	0.067	
		Total hexaCDF	0.031	
		Total heptaCDF	0.012	
		OctaCDF	0.006	
Akron, Ohio (outdoor)	1987	2,3,7,8-TetraCDF	0.200	Edgerton et al. 1989
		Total tetraCDF	1.23	
		1,2,3,7,8-PentaCDF	0.029	
		2,3,4,7,8-PentaCDF	0.036	
		Total pentaCDF	0.590	
		1,2,3,4,7,8-HexaCDF	0.083	
		1,2,3,6,7,8-HexaCDF	0.065	
		2,3,4,6,7,8-HexaCDF	<0.021	
		1,2,3,7,8,9-HexaCDF	0.032	
		Total hexaCDF	0.620	
		1,2,3,4,6,7,8-HeptaCDF	0.237	
		1,2,3,4,7,8,9-HeptaCDF	<0.029	
		Total heptaCDF	0.383	
		OctaCDF	0.180	
Columbus, Ohio (outdoor)	1987	2,3,7,8-TetraCDF	0.405	Edgerton et al. 1989
		Total tetraCDF	2.85	
		1,2,3,7,8-PentaCDF	0.045	
		2,3,4,7,8-PentaCDF	<0.056	
		Total pentaCDF	0.995	
		1,2,3,4,7,8-HexaCDF	0.165	
		1,2,3,6,7,8-HexaCDF	0.141	
		2,3,4,6,7,8-HexaCDF	<0.02	
		1,2,3,7,8,9-HexaCDF	0.079	
		Total hexaCDF	0.785	
		1,2,3,4,6,7,8-HeptaCDF	0.335	
		1,2,3,4,7,8,9-HeptaCDF	<0.021	
		Total heptaCDF	0.450	
		OctaCDF	<0.260	

Table 5-10. Concentrations of Chlorodibenzofurans (CDFs) in Ambient Indoor and Outdoor Air in North America and Oceans

Site	Sampling year	CDF	Concentration (pg/m^3)	Reference
Waldo, Ohio (outdoor)	1987	2,3,7,8-TetraCDF Total tetraCDF 1,2,3,7,8-PentaCDF 2,3,4,7,8-PentaCDF Total pentaCDF 1,2,3,4,7,8-HexaCDF 1,2,3,6,7,8-HexaCDF 2,3,4,6,7,8-HexaCDF 1,2,3,7,8,9-HexaCDF Total hexaCDF 1,2,3,4,6,7,8-HeptaCDF 1,2,3,4,7,8,9-HeptaCDF Total heptaCDF OctaCDF	0.130 0.890 0.021 <0.033 0.500 0.098 0.014 <0.008 0.097 0.510 0.220 0.019 0.290 0.077	Edgerton et al. 1989
Chicago, Illinois (outdoor)	2004–2007	ΣCDDs/CDFs	1.3±0.10	Venier et al. 2009
Eagle Harbour, Michigan (outdoor)	2004–2007	ΣCDDs/CDFs	0.12±0.013	Venier et al. 2009
Sturgeon Point, New York	2004–2007	ΣCDDs/CDFs	0.74±0.083	Venier et al. 2009
Sleeping Bear Dunes, (outdoor) Michigan	2004–2007	ΣCDDs/CDFs	0.40±0.093	Venier et al. 2009
Calcasieu Parish, Louisiana outdoor)	2001–2002	ΣCDDs/CDFs	0.0027–0.0924	Gibbs et al. 2003
North Atlantic	2010–2011	ΣCDFs	0.008 (gas) 0.0094 (aerosol)	Morales et al. 2014
South Atlantic	2010–2011	ΣCDFs	0.006 (gas) 0.014 (aerosol)	Morales et al. 2014
Indian Ocean	2010–2011	ΣCDFs	0.0061 (gas) 0.0093 (aerosol)	Morales et al. 2014
South Pacific	2010–2011	ΣCDFs	0.0045 (gas) 0.0066 (aerosol)	Morales et al. 2014
North Pacific	2010–2011	ΣCDFs	0.0069 (gas) 0.0094 (aerosol)	Morales et al. 2014

Table 5-10. Concentrations of Chlorodibenzofurans (CDFs) in Ambient Indoor and Outdoor Air in North America and Oceans

Site	Sampling year	CDF	Concentration (pg/m^3)	Reference
Global	2010–2011	ΣCDFs	0.0067 (gas) 0.0100 (aerosol)	Morales et al. 2014

[a]Detection limit.

The majority of CDFs found in the air are non-2,3,7,8-substituted congeners, which are much less toxic than 2,3,7,8-substituted congeners. Among the 2,3,7,8-substituted isomers in the air, the 1,2,3,4,6,7,8-heptaCDF congener dominate, followed by 2,3,7,8-tetraCDF. It has been shown that 2,3,7,8-tetraCDF constitutes ≈9% of total tetraCDFs; 1,2,3,7,8-penta- and 2,3,4,7,8-pentaCDF constitute ≈9 and 10.4%, respectively, of total pentaCDFs; 1,2,3,4,7,8-hexa-, and 1,2,3,6,7,8-hexaCDF constitute ≈9.4 and 18.1%, respectively, of the total hexaCDFs; and 1,2,3,4,6,7,8-heptaCDF and 1,2,3,4,7,8,9-heptaCDF constitute ≈64.7 and 4.4%, respectively, of the total heptaCDFs present in the air near a municipal solid waste incinerator in Dayton, Ohio (Tiernan et al. 1989).

Considerably higher concentrations of CDFs have been detected in the indoor air and wipe samples of buildings after accidental fires involving PCB capacitors/transformers. For example, the concentrations of total CDFs and 2,3,7,8-tetraCDF (plus co-eluting isomers) in wipe samples from the transformer vault after the 1983 transformer fire in Chicago were 12,210 and 410 ng/100 cm^2 (41,000 ng/m^2), respectively (Hryhorczuk et al. 1986). The concentrations of total tetraCDFs in air and wipe samples inside the vault 4 months after the 1983 San Francisco transformer fire were 1,000–3,000 pg/m^3 and 1,000–23,000 ng/100 cm^2 (100,000–2,300,000 ng/m^2), respectively (Stephens 1986). Seven months following the fire, the maximum concentration of 2,3,7,8-substituted CDFs in air of the building that contained the transformer vault was 19.5 pg/m^3. The concentrations of total tetraCDFs, 2,3,7,8-tetraCDF (plus co-eluting isomers) and total pentaCDFs of indoor air in a Binghamton, New York, office building 1.5–2 years after cleanup following a 1981 electric fire were ≤23, 195, and 60 pg/m^3, respectively (Smith et al. 1986). The mean indoor air levels of combined 2,3,7,8-TCDD and 2,3,7,8-tetraCDF was 24.5 pg/m^3 in the melting shop area of an electric arc furnace steelmaking plant (Aries et al. 2008). Concentrations of tetraCDF, pentaCDF, hexaCDF, heptaCDF and octaCDF were ≤0.4, 0.6, 2.2, 4.4, and 4.8 ng/100 cm^2, respectively, present in the wipe samples of a building used for the improper incineration of PCBs (Thompson et al. 1986). Following the attacks on the WTC, CDD/CDF levels of window films within 1 km of the WTC site in lower Manhattan were as large as 630 000 pg/m^2 (630 ng/m^2) (Rayne et al.

2005). Dust samples obtained from 21 homes in Albany, New York had CDF levels ranging from 13 to 5,600 pg/g (Tue et al. 2013).

5.5.2 Water

The concentrations of CDFs in most waters are so low that it is difficult to determine the levels in drinking water and surface water, unless the surface water is sampled close to points of effluent discharge containing CDFs. Because of their low water solubilities and high K_{oc} values, the CDFs partition from the water to sediment in environmental water or in sludge during the treatment of waste waters. Therefore, more monitoring data are available for CDFs levels in the latter two media.

A drinking water sample in Sweden contained 2,3,4,7,8-pentaCDF at a concentration of 0.002 ppq (Rappe 1991). The levels of CDFs in drinking water from 20 communities in New York state were measured (Meyer et al. 1989). Total tetraCDFs at a concentration of 2.6 ppq (pg/L) and octaCDF at a concentration 0.8 ppq were the only two congener groups detected in 1 of 20 water supplies (Lockport, New York). The concentration of 2,3,7,8-tetraCDF in water from Lockport was 1.2 ppq. The raw water that served as the source of this drinking water contained several CDFs at the following concentrations (ppq): total tetraCDF, 18.0; 2,3,7,8-tetraCDF, not detected (detection limit 0.7); 1,2,3,7,8-pentaCDF, 2.0; total pentaCDF, 27.0; 1,2,3,4,7,8-hexaCDF, 39.0; 1,2,3,6,7,8-hexaCDF, 9.2; total hexaCDF, 85.0; 1,2,3,4,6,7,8-heptaCDF, 210; total heptaCDF, 210; and octaCDF, 230. Since the finished drinking water contained 2,3,7,8-tetraCDF, and the raw water did not contain any detectable level of this compound, the source of 2,3,7,8-tetraCDF in the drinking water must be the chlorination process. Considerably higher concentrations of CDFs were detected in the sediment of the raw water. This provides more indirect evidence that chlorination may be partially responsible for the in situ production of CDFs.

Lin et al. (2010) studied concentrations of CDFs in drinking water in Taiwan to better understand how atmospheric deposition of CDFs influence these concentrations. Tap water levels in pg/L were as follows: 2,3,7,8-tetraCDF, 0.021; 1,2,3,7,8-pentaCDF, 0.0023; 2,3,4, 7,8-pentaCDF, 0.0026; 1,2,3,6,7,8-hexaCDF, 0.0019; 1,2,3,7,8,9-hexaCDF, 0.0005; 2,3,4, 6,7,8-hexaCDF, 0.0021; 1,2,3,4,6,7,8-heptaCDF, 0.0071; 1,2,3,4,7,8,9-heptaCDF 0.0017; octaCDF 0.0256. The authors found tap water levels for total CDDs/CDFs to be approximately 55% less than that in source water and that atmospheric deposition to uncovered water treatment facilities likely increase the levels in finished water.

Because of CDFs high soil adsorption, leaching to groundwater is unlikely with an exception for buried wastes or highly contaminated sites. CDFs have been detected in groundwater at several NPL sites with octaCDF being detected at a concentration of 445 ppb (µg/L) at a former wood production facility (ATSDR 2017).

Effluents from bleached kraft and sulfite mill pulp in the United States, Canada, and Europe contained total tetraCDFs in the concentration range of <0.01–4,100 ppt, whereas the concentrations of 2,3,7,8-tetraCDF varied from <0.002 to 8.4 ppt. The octaCDF levels in these effluents ranged from <0.05 to 0.5 ppt. The sludge from the treated effluents from paper mills contained much higher concentrations of CDFs. In one case, the sludge from a chloralkali process contained ≤52,000 ppt of 2,3,7,8-tetraCDF and 81,000 ppt of octaCDF (Clement et al. 1989b, 1989c; Rappe et al. 1990a; Waddell et al. 1990; Whittemore et al. 1990).

Surface water adjacent to a landfill near Tonawanda, New York, contained the following concentrations of CDFs (ppt): total tetraCDFs, 0.2–77; total pentaCDFs, 0.3–130; total hexaCDFs, 0.8–200; total heptaCDFs, 1.0–980; and octaCDF, 1.2–1,500 (Clement et al. 1989a). Leachates from bottom and fly ash disposal facilities of five state-of-the-art mass burn municipal waste combustors, with a variety of pollution control equipment, were analyzed for CDFs. With the exception of the leachate from one facility, leachates from the other four facilities contained CDFs below the detection level (0.01–0.06 ppb). HeptaCDF at a concentration of 0.076 ppb was detected in the remaining leachate sample (EPA 1990b).

The level of CDFs has also been measured in rainwater. The concentrations of total tetraCDFs, total pentaCDFs, total hexaCDFs, total heptaCDFs and octaCDF in rainwater from Bloomington, Indiana; Dorset, Canada; and Toronto, Canada, were <0.6–5.7, 0.2–6.0, 0.7–6.0, <0.8–2.4, and <0.8–0.8 ppq, respectively (Eitzer and Hites 1989b; Reid et al. 1990). As expected, the concentrations of CDFs were lower in rainwater from the rural site (Dorset) than from the urban site (Toronto) (Reid et al. 1990). The levels of CDFs in fog have also been measured, and the congener profile was similar to rainwater; however, the concentrations of CDFs were higher in fog than in rainwater, due to enhanced particle scavenging by fog (Czuczwa et al. 1989).

5.5.3 Sediment and Soil

The maximum 2,3,7,8-tetraCDF and 2,3,7,8-substituted CDF concentrations of 0.3 ppt (ng/kg) and 11.0 ppt, respectively, were determined for sediments from an uncontaminated river (Elk River) in

Minnesota (Reed et al. 1990). The maximum concentrations of total pentaCDFs, hexaCDFs, heptaCDFs, and octaCDF in sediment samples from the same river were 25.0, 12.0, 30.0, and 23.0 ppt, respectively. In all cases, the analyte was not detected in some samples. The concentrations of 2,3,7,8-tetraCDF in sediment from the lower Hudson River (New York), Cuyahoga River (Ohio), Menominee River (Wisconsin), Fox River (Wisconsin), Raisin River (Michigan), and Saginaw River (Wisconsin) ranged from 5 to 97 ppt (O'Keefe et al. 1984; Smith et al. 1990b). The concentration of 2,3,7,8-tetraCDF in sediment from an uncontaminated lake (Lake Pepin) in Wisconsin was <l ppt, while its concentration in sediment from Lake Michigan in Green Bay (Wisconsin) was 24 ppt (Smith et al. 1990a). The concentrations of 2,3,7,8-tetraCDF in estuarine sediment varied from 15.0 ppt for an uncontaminated sediment in Long Island Sound (New York) to 4,500 ppt in sediment from an estuary adjacent to a 2,4,5-trichlorophenoxyacetic acid production facility in Newark, New Jersey (Bopp et al. 1991; Norwood et al. 1989). A concentration ≤1,400 ppt was also detected in sediment from New Bedford Harbor (Massachusetts) near a Superfund site (Norwood et al. 1989). The concentrations of 2,3,7,8-tetraCDF and other 2,3,7,8-substituted congeners of pentaCDF were higher in contaminated sediments than uncontaminated sediments (Norwood et al. 1989). In a survey of harbor sediment near a wood treatment facility at Thunder Bay (Ontario), the concentration of tetraCDFs and pentaCDFs were below the detection limit, while the levels of the higher congeners increased with the degree of chlorination (maximum of 6.5 ng/g [6,500 ppt] for hexaCDF to 400 ng/g for octaCDF) (McKee et al. 1990). Iyer et al. (2018) compiled data on levels of CDDs and CDFs in the San Jacinto River and Houston Ship Channel. The maximum concentration for CDFs occurred for octaCDF, 12 ng/g (12,000 ppt) in the Buffalo Bayou in August 2005.

The concentrations (ppt) of CDFs in uncontaminated soils from the vicinity of Elk River, Minnesota were as follows (detection limit in parentheses): 2,3,7,8-tetraCDF, not detected (0.8); total tetraCDF, not detected (0.8) to 1.2; total hexaCDFs, 6.7–150; 1,2,3,4,6,7,8-heptaCDF, 26–72; total heptaCDFs, 30–260; and octaCDF, not detected (3) to 270 (Reed et al. 1990). The concentrations (ppt) of CDFs in soils adjacent to a refuse incineration facility in Hamilton, Ontario, were as follows (detection limit in parenthesis): total tetraCDFs, not detected (0.3) to 71; total pentaCDFs, not detected (1.3) to 6.0; total hexaCDFs, not detected (1.3); total heptaCDFs, not detected (1.3) to 180; and octaCDF, not detected (0.8) to 811 (McLaughlin et al. 1989). These levels were not elevated compared to urban control samples. Similarly, the levels of CDFs in soils adjacent to a municipal incinerator in England were indistinguishable from background levels (Mundy et al. 1989). On the other hand, much higher levels of CDFs were detected in soils from a PCP-containing waste landfill in Germany. For example, the concentrations (ppt) of CDFs in the landfill soil were as follows: 1,2,3,7,8/1,2,3,4,8-pentaCDF, 17,000;

2,3,4,7,8-pentaCDF, 7,000; 1,2,3,4,7,8/1,2,3,4,7,9-hexaCDF, 152,000; 1,2,3,6,7,8-hexaCDF, 48,000; 1,2,3,7,8,9-hexaCDF, 3,000; and 2,3,4,6,7,8-hexaCDF, 24,000 (Hagenmaier and Berchtold 1986). High levels of CDFs may be detected at hazardous waste sites. For example, 1,2,3,7,8,9-hexaCDF was detected at a concentration of 21 ppm (soil depth unspecified) at a hazardous waste site in Illinois (ATSDR 2017).

Biosolids obtained from waste water or sewage treatment facilities are applied to agricultural lands in order to add nutrients to the soils used for commercial farming applications. CDFs were detected in biosolids collected in 32 U.S. states and the District of Columbia from 94 waste water treatment plants by the EPA in its 2001 national sewage sludge survey (EPA 2007a). Minimum levels of CDFs ranged from about 0.1 (2,3,7,8-tetraCDF) to1 ng/kg (octaCDF).

5.5.4 Other Media

The Food and Drug Administration (FDA) conducts Total Diet Studies and Market Basket Surveys (MBS) to determine if certain toxic substances are in the U.S. commercial food supply. The TDS is FDA's ongoing market basket survey of approximately 280 food staples in the food supply of America. It can be used to estimate exposures of substances in representative diets of specific age-gender groups in the nation. Typically, four market baskets are collected each year, once in each of four geographic regions of the nation. For each market basket, food samples are collected from commercial grocery stores and fast food restaurants in three cities within the region, and also prepared table-ready foods (i.e., as they would be consumed). In 2000, the FDA began monitoring for dioxin-like substances including CDFs. Data from the 2004 TDS indicated that CDFs were detected in food items at or above the detection limits in 269 out of 3,944 food items tested (FDA 2007). The highest concentration of CDFs occurred in liver (beef/calf), pan-cooked with oil, which had a concentration of 2.8 pg/g for octaCDF. 2,3,7,8-TCDF was detected in 28 items tested with a maximum concentration of 0.13 pg/g in baked salmon steaks/fillets.

The concentrations of CDFs in meat, fish, and dairy products purchased from a supermarket in upstate New York were 0.14–7.0, 0.07–1.14, and 0.3–5 ppt (pg/g) (wet weight), respectively (Schecter et al. 1993). The concentrations of 2,3,7,8-TCDF in these meat, fish, and dairy products were 0.01–0.1, 0.02–0.73, and 0.02–0.15 ppt (wet weight), respectively (Schecter et al. 1993).

A large number of data concerning the levels of CDFs in fish collected from different waters are available (De Vault et al. 1989; Gardner and White 1990; O'Keefe et al. 1984; Pagano et al. 2018; Petty et al. 1983;

Smith et al. 1990b; Zacharewski et al. 1989) and representative data on the concentrations of CDFs, particularly the 2,3,7,8-substituted congeners are presented in Table 5-11. It is evident from the table that 2,3,7,8-tetraCDF is the prevalent CDF congener present in fish, followed by 2,3,4,7,8-pentaCDF. The concentrations of CDFs are significantly higher in the hepatopancreas than in the meat of crabs and lobster. The levels of CDFs in fish obtained from the Great Lakes have been dropping over the past decades. Pagano et al. (2018) analyzed the trend in 2,3,7,8-tetraCDF concentrations in fish caught in the Great Lakes from 2004 to 2014 and noted a 51.8% decrease in concentrations found in walleye and lake trout over this time frame. A retrospective analysis using data collected over the period of 1977−2014 showed a decrease of 94% for 2,3,7,8-tetraCDF levels in lake trout from Lake Ontario. Levels of 2,3,7,8-tetraCDFs in eggs from mature Chinook and Coho salmon decreased 61.4% between 2004 and 2014 from the Salmon River fish hatchery in Altmar, New York (Garner and Pagano 2019). Levels of 2,3,7,8-tetraCDF decreased from 285±136 pg/g (1989) to 1.31±0.67 pg/g (2012) in white sucker collected from Jackfish Bay and Mountain Bay, Lake Superior following engineering controls applied to a pulp mill, which discharged to these areas (Dahmer et al. 2015). The mean level of total 2,3,7,8-substituted CDFs in gutted whole fish from the St. Maurice River, Quebec, caught immediately downstream of a kraft mill was 260 pg/g (ppt), but the level declined to 112 ppt at 95 km downstream (Hodson et al. 1992). Data on 2,3,7,8-substituted CDF congeners in aquatic fauna were analyzed by principal component analysis. In this method, the congener profile in aquatic fauna can be used to predict the principal source of contamination such as pulp mill effluent, deposition from combustion source, and effluent from magnesium production (Zitko 1992).

Table 5-11. Levels of Chlorodibenzofurans (CDFs) in Fish and Other Aquatic Organisms

Species	Sampling area	CDF	Concentration (ppt [wet weight])	Reference
Striped bass (*Morone saxatilis*), meat	Newark Bay and New York Bight	2,3,7,8-TetraCDF	68.7	Rappe et al. 1991b
		Total tetraCDF	92.5	
		1,2,3,7,8-/1,2,3,4,8-PentaCDF	7.1	
		2,3,4,7,8-PentaCDF	30.3	
		Total pentaCDF	58.5	
		1,2,3,4,7,8-/1,2,3,4,7,9-HexaCDF	1.1	
		1,2,3,6,7,8-HexaCDF	0.4	
		1,2,3,7,8,9-HexaCDF	<0.1	
		2,3,4,6,7,8-HexaCDF	<2.6	
		Total hexaCDF	3.2	
		1,2,3,4,6,7,8-HeptaCDF	1.6	
		1,2,3,4,7,8,9-HeptaCDF	<0.4	
		OctaCDF	<3.0	

Table 5-11. Levels of Chlorodibenzofurans (CDFs) in Fish and Other Aquatic Organisms

Species	Sampling area	CDF	Concentration (ppt [wet weight])	Reference
Blue crab (*Callinectes sapidus*), meat	Newark Bay and New York Bight	2,3,7,8-TetraCDF	13.3	Rappe et al. 1991b
		Total tetraCDF	148.7	
		1,2,3,7,8-/1,2,3,4,8-PentaCDF	5.5	
		2,3,4,7,8-PentaCDF	7.3	
		Total pentaCDF	91.9	
		1,2,3,4,7,8-/1,2,3,4,7,9-HexaCDF	2.6	
		1,2,3,6,7,8-HexaCDF	0.6	
		1,2,3,7,8,9-HexaCDF	<0.2	
		2,3,4,6,7,8-HexaCDF	<2.3	
		Total hexaCDF	9.4	
		1,2,3,4,6,7,8-HeptaCDF	3.2	
		1,2,3,4,7,8,9-HeptaCDF	<0.9	
		Total Hepta CDF	3.2	
		OctaCDF	<7.1	
Blue crab (*C. sapidus*), hepatopancreas	Newark Bay and New York Bight	2,3,7,8-TetraCDF	628.3	Rappe et al. 1991b
		Total tetraCDF	7,049.3	
		1,2,3,7,8-/1,2,3,4,8-PentaCDF	185.7	
		2,3,4,7,8-PentaCDF	391.4	
		Total pentaCDF	4,219.1	
		1,2,3,4,7,8-/1,2,3,4,7,9-HexaCDF	261.0	
		1,2,3,6,7,8-HexaCDF	43.3	
		1,2,3,7,8,9-HexaCDF	<5.0	
		2,3,4,6,7,8-HexaCDF	9.8	
		Total hexaCDF	803.3	
		1,2,3,4,6,7,8-HeptaCDF	184.6	
		1,2,3,4,7,8,9-HeptaCDF	7.1	
		OctaCDF	<51	
Lobster (*Homarus americanus*), meat	Newark Bay and New York Bight	2,3,7,8-TetraCDF	<0.3	Rappe et al. 1991b
		Total tetraCDF	27.1	
		1,2,3,7,8-/1,2,3,4,8-PentaCDF	2.4	
		2,3,4,7,8-PentaCDF	1.8	
		Total pentaCDF	33.6	
		1,2,3,4,7,8-/1,2,3,4,7,9-HexaCDF	0.4	
		1,2,3,6,7,8-HexaCDF	<0.2	
		1,2,3,7,8,9-HexaCDF	<0.2	
		2,3,4,6,7,8-HexaCDF	<2.0	
		Total hexaCDF	7.8	
		1,2,3,4,6,7,8-HeptaCDF	<0.9	
		1,2,3,4,7,8,9-HeptaCDF	<0.9	
		OctaCDF	<7.7	

Table 5-11. Levels of Chlorodibenzofurans (CDFs) in Fish and Other Aquatic Organisms

Species	Sampling area	CDF	Concentration (ppt [wet weight])	Reference
Lobster (*H. americanus*), hepatopancreas	Newark Bay and New York Bight	2,3,7,8-TetraCDF Total tetraCDF 1,2,3,7,8-/1,2,3,4,8-PentaCDF 2,3,4,7,8-PentaCDF Total pentaCDF 1,2,3,4,7,8-/1,2,3,4,7,9-HexaCDF 1,2,3,6,7,8-HexaCDF 1,2,3,7,8,9-HexaCDF 2,3,4,6,7,8-HexaCDF Total hexaCDF 1,2,3,4,6,7,8-HeptaCDF 1,2,3,4,7,8,9-HeptaCDF OctaCDF	365.7 1,568.6 79.5 179.2 1,008.4 10.7 <6.0 <3.0 7.0 172.1 <3.8 <3.8 <29.2	Rappe et al. 1991b
Lobster (*H. americanus*), digestive gland	Mipamichi Bay and Limestone Point, New Brunswick; Sydney Harbor and Port Morien, Nova Scotia	Total tetraCDF Total pentaCDF Total hexaCDF Total heptaCDF OctaCDF	189.8 52.2 37.9 <9.1 (2–10)[a]	Clement et al. 1987b
Carp (*Cyprinus carpio*); Coho salmon (*Oncorhynchus kitutch*); lake trout (*Salvelimus namayeush*); bloater (*Copegonus hoyi*); brown trout (*Salmo trutta*); walleye trout (*Stizostedion vitreum vitreum*), composite	Lake Ontario	Total pentaCDFs Total tetraCDFs	1,015 327	Stalling et al. 1985

Table 5-11. Levels of Chlorodibenzofurans (CDFs) in Fish and Other Aquatic Organisms

Species	Sampling area	CDF	Concentration (ppt [wet weight])	Reference
Lake trout (*S. namaycush*); walleye trout (*S. vitreum vitreum*), composite	Lake St. Clair	2,3,7,8-TetraCDF 1,2,3,7,8-PentaCDF 2,3,4,7,8-PentaCDF 1,2,3,4,7,8-HexaCDF 1,2,3,6,7,8-HexaCDF 1,2,3,7,8,9-HexaCDF 2,3,4,6,7,8-HexaCDF 1,2,3,4,6,7,8-HeptaCDF 1,2,3,4,7,8,9-HeptaCDF OctaCDF	24.8 3.7 5.4 0.5 0.5 <0.05 0.9 0.5 <0.2 0.8	Zacharewski et al. 1989
Lake trout (*S. namaycush*); walleye trout (*S. vitreum vitreum*), composite	Lake Michigan	2,3,7,8-TetraCDF 1,2,3,7,8-PentaCDF 2,3,4,7,8-PentaCDF 1,2,3,4,7,8-HexaCDF 1,2,3,6,7,8-HexaCDF 1,2,3,7,8,9-HexaCDF 2,3,4,6,7,8-HexaCDF 1,2,3,4,6,7,8-HeptaCDF 1,2,3,4,7,8,9-HeptaCDF OctaCDF	34.8 4.9 10.2 1.4 1.1 <0.05 1.3 0.9 <0.2 <0.2	Zacharewski et al. 1989
Lake trout (*S. namaycush*); walleye trout (*S. vitreum vitreum*), composite	Lake Ontario	2,3,7,8-TetraCDF 1,2,3,7,8-PentaCDF 2,3,4,7,8-PentaCDF 1,2,3,4,7,8-HexaCDF 1,2,3,6,7,8-HexaCDF 1,2,3,7,8,9-HexaCDF 2,3,4,6,7,8-HexaCDF 1,2,3,4,6,7,8-HeptaCDF 1,2,3,4,7,8,9-HeptaCDF OctaCDF	20.6 4.7 20.2 12.7 1.9 <0.1 1.2 0.9 <0.1 <0.9	Zacharewski et al. 1989
Lake trout (*S. namaycush*); walleye trout (*S. vitreum vitreum*), composite	Lake Huron	2,3,7,8-TetraCDF 1,2,3,7,8-PentaCDF 2,3,4,7,8-PentaCDF 1,2,3,4,7,8-HexaCDF 1,2,3,6,7,8-HexaCDF 1,2,3,7,8,9-HexaCDF 2,3,4,6,7,8-HexaCDF 1,2,3,4,6,7,8-HeptaCDF 1,2,3,4,7,8,9-HeptaCDF OctaCDF	22.8 6.2 12.8 1.6 1.2 <0.07 1.4 0.5 <0.1 <0.3	Zacharewski et al. 1989

Table 5-11. Levels of Chlorodibenzofurans (CDFs) in Fish and Other Aquatic Organisms

Species	Sampling area	CDF	Concentration (ppt [wet weight])	Reference
Lake trout (*S. namaycush*); walleye trout (*S. vitreum vitreum*), composite	Lake Erie	2,3,7,8-TetraCDF 1,2,3,7,8-PentaCDF 2,3,4,7,8-PentaCDF 1,2,3,4,7,8-HexaCDF 1,2,3,6,7,8-HexaCDF 1,2,3,7,8,9-HexaCDF 2,3,4,6,7,8-HexaCDF 1,2,3,4,6,7,8-HeptaCDF 1,2,3,4,7,8,9-HeptaCDF OctaCDF	11.3 1.4 2.7 0.2 0.3 <0.1 0.5 0.6 <0.2 <1.1	Zacharewski et al. 1989
Lake trout (*S. namaycush*); walleye trout (*S. vitreum vitreum*), composite	Lake Superior	2,3,7,8-TetraCDF 1,2,3,7,8-PentaCDF 2,3,4,7,8-PentaCDF 1,2,3,4,7,8-HexaCDF 1,2,3,6,7,8-HexaCDF 1,2,3,7,8,9-HexaCDF 2,3,4,6,7,8-HexaCDF 1,2,3,4,6,7,8-HeptaCDF 1,2,3,4,7,8,9-HeptaCDF OctaCDF	15.7 1.7 2.8 0.5 0.3 <0.06 0.4 0.4 <0.2 <0.8	Zacharewski et al. 1989
Sperm whales	Mediterranean Ocean	ΣCDFs	23.9–35.9	Bartalini et al. 2019
Walleye	Lake Erie	2,3,7,8-TetraCDF	9.52 (average)	Pagano et al. 2018
Walleye	Lake Erie	2,3,7,8-TetraCDF	3.24 (average)	Pagano et al. 2018
Lake trout	Lake Erie	2,3,7,8-TetraCDF	10.0 (average)	Pagano et al. 2018
Lake trout	Lake Huron	2,3,7,8-TetraCDF	26.86 (average)	Pagano et al. 2018
Lake trout	Lake Michigan	2,3,7,8-TetraCDF	16.10 (average)	Pagano et al. 2018
Lake trout	Lake Ontario	2,3,7,8-TetraCDF	17.84 (average)	Pagano et al. 2018
Lake trout	Lake Superior	2,3,7,8-TetraCDF	12.58 (average)	Pagano et al. 2018
Lake trout	Lake Superior	2,3,7,8-TetraCDF	7.46 (average)	Pagano et al. 2018

[a]Detection limit.

CDF levels have been measured in a multitude of environmental samples, including cork and wall paper (Frommberger 1991); foods of animal and vegetable origin (Furst et al. 1990; Glidden et al. 1990; Ryan et al. 1985b; Schecter et al. 1989b); commercial detergents and related products (Rappe et al. 1990b); coffee filters (Fricker and Hardy 1990; LeBel et al. 1992; Wiberg et al. 1989); several consumers products, including diapers, shopping bags, cigarette paper, tampons, and cotton (LeBel et al. 1992; Wiberg et al.

1989); paper products (LeBel et al. 1992; Keenan and Sullivan 1989); latex nipples (Gorski 1981); pine needles (Safe et al. 1992); marine mammals (Norstrom et al. 1990); and eggs of Great Blue Herons (Elliott et al. 1989). Comparison of data for bulk milk and milk in cartons indicates that 2,3,7,8-tetraCDF migrates in small amounts from some bleached paper cartons to bulk milk (Glidden et al. 1990; Ryan et al. 1992). The transfer of CDFs from cardboard and plastic-coated bleached paperboard milk cartons to bulk milk has been observed by other investigators (Beck et al. 1990b; Ryan et al. 1992). The mean concentrations of tetraCDF in bond paper composite, paper towel composite, and composite diaper pulp were 265, 33, and 8 ppt, respectively (Keenan and Sullivan 1989). The concentrations of 2,3,7,8-tetraCDF in bleached coffee filters, shopping bags, and tampons were 22, 7.6, and 0.9 ppt, respectively (Wieberg et al. 1989). On the other hand, no CDFs (detection limit ≤1 ppt) were detected in commercially available coffee filters in the United States (Fricker and Hardy 1990).

The percent migration of 2,3,7,8-tetraCDF from commercial articles of food contact products (e.g., milk packaged in cartons, coffee filters, paper cups and plates, popcorn bags) to foods may range from 0.1 to 35% under normal use conditions (Cramer et al. 1991). Therefore, the concentration of CDFs in packaged whole milk depends on the packaging material. Usually, commercial milk packaged in glass contains less CDFs than milk packaged in cartons (Rappe et al. 1990c). The mean concentration of 2,3,7,8-tetraCDF in whole milk packaged in cartons from California was 0.45 pg/g wet weight (Hayward et al. 1991). All other 2,3,7,8-substituted CDFs were either not detected or detected at very low levels (Hayward et al. 1991). Commercial milk from Sweden contained significant levels of other 2,3,7,8-substituted CDFs (Rappe et al. 1990c). The intake of CDDs/CDFs from all bleached paper food-contact articles was estimated to be 8.8 pg toxic equivalent/person/day (Cramer et al. 1991). However, with the reduction of CDD/CDF levels in paper pulp available at the present time, the exposure may be considerably less than this estimate (Cramer et al. 1991).

The levels of CDFs in the tissues of aquatic and terrestrial birds and in dolphins from contaminated areas are also available (Ankley et al. 1993; Jarman et al. 1993; Jones et al. 1993; Kuehl et al. 1991). Generally, CDDs/CDFs contribute a small portion of the total TCDD-equivalent toxicity in aquatic birds, while most of the TCDD-equivalent toxicity is contributed by non-ortho-substituted PCBs. In terrestrial birds, the contribution of CDDs/CDFs towards the total TCDD-equivalent toxicity is greater than in aquatic birds (Jones et al. 1993).

5.6 GENERAL POPULATION EXPOSURE

The general population is primarily exposed to CDFs by ingestion of foods containing these substances. Exposure may also occur through inhalation of air, ingestion of drinking water, and use of certain consumer products. Since the concentrations of CDFs in ambient air and drinking water are low (see Section 5.5), the intake of CDFs by inhalation and ingestion of drinking water would be low. It has been shown that inhalation exposure was not a major pathway of human exposure to CDFs (Travis and Hattermer-Frey 1989). The estimate that inhalation exposure contributes 2% of the total average human intake of CDDs/CDFs (Hattermer-Frey and Travis 1989) has been questioned as too low by other investigators (Goldfarb and Harrad 1991). The concentrations of CDD/CDF in foods consumed by a typical German were determined, and the intake of total CDD/CDF from food expressed as TEQ to 2,3,7,8-TCDD was estimated to be 1.2 pg TEQ/kg body weight/day (international dioxin toxic equivalent) (Fürst et al. 1990). The estimated intake of CDD/CDF from typical Canadian food was 1.5 pg TEQ/kg body weight/day (Birmingham et al. 1989a). From detailed determinations of the levels of TCDD/TCDF in air, water, soil, food, and consumer products in Canada, the estimated intakes of CDD/CDF were 0.07 pg TEQ/kg body weight/day from air, 0.002 pg TEQ/kg body weight/day from water, 0.02 pg TEQ/kg body weight/day from ingestion of soil, 2.328 pg TEQ/kg body weight/day from food, and 0.005 pg TEQ/kg body weight/day from consumer products (Birmingham et al. 1989b). Therefore, based on toxic equivalency, inhalation constitutes 2.9%, ingestion of drinking water constitutes 0.l%, ingestion of soil constitutes 0.8%, ingestion of food constitutes 96% and consumer products constitutes the residual 0.2% of the estimated total daily intake of TCDDs/TCDFs. The estimated daily intakes of 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF in the United States are 0.05 and 0.068 ng, respectively (Graham et al. 1986), but data for the daily intake of total CDFs and all of the 2,3,7,8-substituted CDFs from the different routes of exposure in the United States were not located. However, data for the daily intake of the combination of CDDs and CDFs from different exposure routes in Canada are available. The total average daily intake of CDDs/CDFs in the industrialized countries is estimated at 1.9 pg TEQ/kg body weight/day (Fishbein et al. 1992).

The levels of CDFs as reported in the Fourth National Report on Human Exposure to Environmental Chemicals NHANES in blood serum levels in 1999–2000, 2001–2002, and 2003–2004 are shown in Table 5-12 (CDC 2021). After 2003–2004, CDF levels were measured in pooled samples. Pooled samples are used when larger sample volumes are needed to improve the sensitivity of the measurements and to reduce the number of samples being analyzed, balancing the cost of the analysis against a low frequency of detectable results. The weighted arithmetic means for age groups, races, and sexes for 1999-

2004 surveys are presented in Table 5-13. Serum levels are presented as pg/g of total lipid or ppt on a lipid-weight basis. These compounds are lipophilic and concentrate in the body's lipids, including the lipid in serum. Serum levels reported per gram of total lipid reflect the amount of these compounds stored in body fat.

Table 5-12. Chlorodibenzofuran (CDF) Levels (pg/g lipid) in the U.S. Population 1999–2004

Congener	1999–2000		2001–2002		2003–2004	
	Geometric Mean	90th percentile	Geometric Mean	90th percentile	Geometric Mean	90th percentile
1,2,3,4,6,7,8,-HeptaCDF[a]	*[b]	14.7	9.64	21.3	*	14.6
1,2,3,4,7,8,9-HeptaCDF[c]	No data		*	<LOD	*	<LOD
1,2,3,4,7,8-HexaCDF[d]	*	<LOD	*	12.1	*	7.50
1,2,3,6,7,8-HexaCDF[e]	*	<LOD	*	10.4	*	14.0
1,2,3,7,8,9-HexaCDF[f]	*	<LOD	*	<LOD	*	<LOD
2,3,4,6,7,8-HexaCDF[g]	*	<LOD	*	<LOD	*	<LOD
OctaCDF[h]	*	<LOD	*	<LOD	*	<LOD
1,2,3,7,8-PentaCDF[i]	*	<LOD	*	<LOD	*	<LOD
2,3,4,7,8-PentaCDF[j]	*	<LOD	*	14.3	*	9.90
2,3,7,8-TetraCDF[k]	*	<LOD	*	<LOD	*	<LOD

[a]Asterisk indicates that a geometric mean was not calculated because the proportion of results below the LOD was too high to provide a valid result.
[b]LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 13.5, 7.0, and 8.6 pg/g lipid, respectively.
[c]LODs for survey years 2001–2002 and 2003–2004 were 7.0 and 8.6 pg/g lipid, respectively.
[d]LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 12.7, 6.5, and 7.4 pg/g lipid, respectively.
[e]LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 12.6, 6.1, and 7.9 pg/g lipid, respectively.
[f]LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 12.7, 6.0, and 8.3 pg/g lipid, respectively.
[g]LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 12.9, 5.8, and 8.2 pg/g lipid, respectively.
[h]LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 35.6, 21.0, and 12.0 pg/g lipid, respectively.
[i]LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 13.2, 5.8, and 7.1 pg/g lipid, respectively.
[j]LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 12.7, 5.5, and 6.8 pg/g lipid, respectively.
[k]LODs for survey years 1999–2000, 2001–2002, and 2003–2004 were 11.9, 5.2, and 6.0 pg/g lipid, respectively.

LOD = limit of detection

Source: CDC 2021

Table 5-13. Chlorodibenzofuran (CDF) Levels (pg/g lipid) in the U.S. Population 2005-2010

	2005–2006				2007–2008				2009–2010			
	Age (years)											
Congener	12–19	20–39	40–59	60+	12–19	20–39	40-59	60+	12–19	20–39	40–59	60+
1,2,3,4,6,7,8,-HeptaCDF[a]												
Non-Hispanic Whites												
Males	12.5	7.09	8.33	8.16	12.0	8.07	7.42	7.24	7.93	6.63	7.00	6.32
Females	7.63	6.94	6.85	7.74	8.74	8.22	7.00	8.12	7.84	6.26	4.96	6.30
Non-Hispanic Blacks												
Males	10.8	8.24	7.85	10.6	10.2	7.61	7.10	7.78	7.62	5.58	6.14	5.43
Females	8.80	6.20	6.35	10.5	8.73	7.86	9.30	8.95	7.11	5.24	5.09	7.45
Mexican Americans												
Males	9.25	6.57	7.45	7.18	8.38	8.14	6.77	6.33	8.90	7.22	5.63	7.47
Females	5.61	6.00	8.74	6.28	8.97	7.42	6.36	6.66	5.49	6.11	6.64	8.50
All Hispanics												
Males			No data				No data		9.87	7.48	5.43	7.24
Females			No data				No data		5.81	5.76	6.65	7.04
1,2,3,4,7,8,9-HeptaCDF[b]												
Non-Hispanic Whites												
Males	*[c]	*	*	*	*	*	*	*	*	*	*	*
Females	*	*	*	*	*	*	*	*	*	*	*	*
Non-Hispanic Blacks												
Males	*	*	*	*	*	*	*	*	*	*	*	*
Females	*	*	*	*	*	*	*	*	*	*	*	*
Mexican Americans												
Males	*	*	*	*	*	*	*	*	*	*	*	*
Females	*	*	*	*	*	*	*	*	*	*	*	*
All Hispanics												
Males			No data				No data		*	*	*	*
Females			No data				No data		*	*	*	*

Table 5-13. Chlorodibenzofuran (CDF) Levels (pg/g lipid) in the U.S. Population 2005-2010

	2005–2006				2007–2008				2009–2010			
	Age (years)											
Congener	12–19	20–39	40–59	60+	12–19	20–39	40-59	60+	12–19	20–39	40–59	60+
1,2,3,4,7,8-HexaCDF[d]												
Non-Hispanic Whites												
Males	2.18	2.51	4.55	5.40	2.58	3.13	3.78	4.80	2.03	2.50	4.11	4.31
Females	1.71	2.36	3.58	5.54	1.76	2.29	3.24	5.29	1.61	2.09	2.77	4.06
Non-Hispanic Blacks												
Males	1.79	2.61	3.33	5.35	1.87	2.68	3.69	4.49	1.45	1.59	2.52	3.36
Females	1.25	2.14	3.37	8.98	1.53	2.17	3.61	6.68	1.46	1.76	2.94	6.00
Mexican Americans												
Males	1.67	2.29	3.28	4.09	1.30	2.70	2.97	3.52	1.74	2.52	2.94	5.04
Females	1.30	1.83	3.15	4.45	*	2.06	2.71	4.69	1.10	1.60	2.74	4.68
All Hispanics												
Males		No data				No data			1.73	2.28	2.88	4.30
Females		No data				No data			1.19	1.65	2.75	4.35
1,2,3,6,7,8-HexaCDF[e]												
Non-Hispanic Whites												
Males	2.46	2.68	4.91	5.44	3.09	2.98	3.97	4.82	2.21	2.71	4.62	4.41
Females	1.91	2.43	3.68	5.51	1.71	2.44	3.30	5.04	1.70	2.30	3.08	4.58
Non-Hispanic Blacks												
Males	1.81	2.28	3.00	5.27	2.04	2.32	3.42	4.38	1.62	1.66	2.68	3.73
Females	1.26	2.02	2.97	7.44	1.19	2.21	3.17	5.96	1.57	1.80	2.93	5.43
Mexican Americans												
Males	1.68	2.25	3.18	4.31	1.80	2.09	3.00	4.01	1.99	2.49	2.95	4.80
Females	1.42	1.87	2.88	4.10	*	2.13	2.82	4.74	1.47	1.76	2.88	4.61
All Hispanics												
Males		No data				No data			1.97	2.25	2.93	4.19
Females		No data				No data			1.48	1.78	2.91	4.27

Table 5-13. Chlorodibenzofuran (CDF) Levels (pg/g lipid) in the U.S. Population 2005-2010

	2005–2006				2007–2008				2009–2010			
	Age (years)											
Congener	12–19	20–39	40–59	60+	12–19	20–39	40-59	60+	12–19	20–39	40–59	60+
1,2,3,7,8,9-HexaCDF[f]												
Non-Hispanic Whites												
Males	*[c]	*	*	*	*	*	*	*	*	*	*	*
Females	*	*	*	*	*	*	*	*	*	*	*	*
Non-Hispanic Blacks												
Males	*	*	*	*	*	*	*	*	*	*	*	*
Females	*	*	*	*	*	*	*	*	*	*	*	*
Mexican Americans												
Males	*	*	*	*	*	*	*	*	*	*	*	*
Females	*	*	*	*	*	*	*	*	*	*	*	*
All Hispanics												
Males			No data				No data		*	*	*	*
Females			No data				No data		*	*	*	*
2,3,4,6,7,8-HexaCDF[g]												
Non-Hispanic Whites												
Males	0.555	0.882	1.40	1.31	*	0.782	1.08	1.09	0.743	0.960	1.38	1.19
Females	*	0.714	1.00	1.18	*	*	*	0.803	0.685	0.910	1.00	1.01
Non-Hispanic Blacks												
Males	0.418	1.23	0.794	0.969	*	*	0.6950	0.699	0.404	0.648	0.677	0.750
Females	*	0.528	0.773	1.11	*	*	*	*	0.540	0.601	0.821	0.955
Mexican Americans												
Males	0.481	0.825	1.15	1.16	*	*	*	*	0.836	1.13	1.08	1.52
Females	*	0.784	1.09	0.926	*	*	*	*	0.438	0.733	1.13	1.27
All Hispanics												
Males			No data				No data		0.760	0.971	1.12	1.45
Females			No data				No data		0.437	0.710	1.07	1.12

Table 5-13. Chlorodibenzofuran (CDF) Levels (pg/g lipid) in the U.S. Population 2005-2010

	2005–2006				2007–2008				2009–2010			
	Age (years)											
Congener	12–19	20–39	40–59	60+	12–19	20–39	40-59	60+	12–19	20–39	40–59	60+
OctaCDF[h]												
Non-Hispanic Whites												
Males	*	1.80	1.44	*	3.27	2.48	2.07	2.08	*	*	*	*
Females	1.83	*	1.55	1.95	2.92	1.96	2.17	2.14	*	*	*	*
Non-Hispanic Blacks												
Males	*	*	2.25	2.72	3.08	4.10	1.90	2.15	*	*	*	*
Females	2.95	3.42	3.09	3.28	2.11	2.86	2.93	2.37	*	*	*	*
Mexican Americans												
Males	*	*	*	*	2.65	2.90	1.88	1.77	*	*	*	*
Females	*	*	2.06	*	3.11	3.04	2.78	2.63	*	*	*	*
All Hispanics												
Males			No data				No data		*	*	*	*
Females			No data				No data		*	*	*	*
1,2,3,7,8-PentaCDF[i]												
Non-Hispanic Whites												
Males	*[c]	*	*	*	*	*	*	*	*	*	*	*
Females	*	*	*	*	*	*	*	*	*	*	*	*
Non-Hispanic Blacks												
Males	*	*	*	*	*	*	*	*	*	*	*	*
Females	*	*	*	*	*	*	*	*	*	*	*	*
Mexican Americans												
Males	*	*	*	*	*	*	*	*	*	*	*	*
Females	*	*	*	*	*	*	*	*	*	*	*	*
All Hispanics												
Males			No data				No data		*	*	*	*
Females			No data				No data		*	*	*	*

Table 5-13. Chlorodibenzofuran (CDF) Levels (pg/g lipid) in the U.S. Population 2005-2010

	2005–2006				2007–2008				2009–2010			
	Age (years)											
Congener	12–19	20–39	40–59	60+	12–19	20–39	40-59	60+	12–19	20–39	40–59	60+
2,3,4,7,8-PentaCDF[j]												
Non-Hispanic Whites												
Males	2.26	3.45	5.82	8.03	3.20	3.76	5.40	7.32	2.51	3.31	6.16	7.33
Females	1.79	2.70	4.56	8.49	1.97	2.99	4.59	7.82	1.77	2.46	4.22	8.19
Non-Hispanic Blacks												
Males	1.84	3.48	3.86	7.19	2.01	2.61	4.78	6.78	1.35	2.13	3.98	5.62
Females	1.19	2.13	3.98	12.7	1.41	2.09	1.58	9.57	1.39	1.70	4.13	9.52
Mexican Americans												
Males	1.67	2.65	3.82	5.90	2.36	3.03	4.45	5.61	2.01	2.82	3.92	8.07
Females	1.00	2.05	3.51	6.10	1.37	2.10	3.79	7.29	*	1.92	3.61	7.10
All Hispanics												
Males			No data				No data		1.96	2.54	4.17	7.10
Females			No data				No data		*	1.96	3.62	6.83
2,3,7,8-TetraCDF[k]												
Non-Hispanic Whites												
Males	*[c]	*	*	*	*	*	0.502	*	*	*	*	*
Females	*	*	*	*	*	*	*	*	*	*	*	*
Non-Hispanic Blacks												
Males	*	*	*	*	*	*	*	*	*	*	*	*
Females	*	*	*	*	*	*	*	*	*	*	*	*
Mexican Americans												
Males	*	*	*	*	*	*	*	*	*	*	*	*
Females	*	*	*	*	*	*	*	*	*	*	*	*

Table 5-13. Chlorodibenzofuran (CDF) Levels (pg/g lipid) in the U.S. Population 2005-2010

	2005–2006				2007–2008				2009–2010			
	Age (years)											
Congener	12–19	20–39	40–59	60+	12–19	20–39	40-59	60+	12–19	20–39	40–59	60+
All Hispanics												
Males	No data				No data				*	*	*	*
Females	No data				No data				*	*	*	*

[a]LODs for survey years 2005–2006, 2007–2008, and 2009–2010 were 0.23, 0.05, and 2.69 pg/g lipid, respectively.
[b]LODs for survey years 2005–2006, 2007–2008, and 2009–2010 were 0.23, 0.33, and 0.49 pg/g lipid, respectively.
[c]Asterisk indicates that a weighted arithmetic mean was not calculated because the proportion of results below the LOD was too high to provide a valid result.
[d]LODs for survey years 2005–2006, 2007–2008, and 2009–2010 were 0.27, 0.39, and 0.78 pg/g lipid, respectively.
[e]LODs for survey years 2005–2006, 2007–2008, and 2009–2010 were 0.1, 0.14, and 0.27 pg/g lipid, respectively.
[f]LODs for survey years 2005–2006, 2007–2008, and 2009–2010 were 0.23, 0.35, and 0.52 pg/g lipid, respectively.
[g]LODs for survey years 2005–2006, 2007–2008, and 2009–2010 were 0.13, 0.2, and 0.3 pg/g lipid, respectively.
[h]LODs for survey years 2005–2006, 2007–2008, and 2009–2010 were 1.17, 1.14, and 3.68 pg/g lipid, respectively.
[i]LODs for survey years 2005–2006, 2007–2008, and 2009–2010 were 0.47, 0.81, and 1.2 pg/g lipid, respectively.
[j]LODs for survey years 2005–2006, 2007–2008, and 2009–2010 were 0.39, 0.38, and 1.3 pg/g lipid, respectively.
[k]LODs for survey years 2005–2006, 2007–2008, and 2009–2010 were 0.3, 0.45, and 0.68 pg/g lipid, respectively.

Source: CDC 2021

Lakind et al. (2009) analyzed data from three NHANES sampling periods spanning 1999–2004 to assess whether there are discernable temporal trends in the United States for exposure to CDFs and CDDs. The authors reported serum CDD/CDF data from 1999 to 2004 suggest that levels of these compounds in the serum of the U.S. population are declining as controls on the emission of these substances have increased. The authors concluded that PCDD/PCDF levels decreased by 56% for the 12–19-year-old group and 38% for the 20–39-year-old group, with a slight nonsignificant decrease for the 40–59-year-old group and a slight significant increase for adults ≥60 years old.

Bloom et al. (2006) analyzed serum levels of CDFs among licensed anglers between 18 and 40 years of age, residing in 16 New York counties proximally to Lake Erie and Lake Ontario. The detection frequency of the most common CDF congeners ranged from 42 to 100% in the serum of the study participants with the exception of 1,2,3,7,8,9-hexaCDF, which was not detected in the serum of any of the study participants.

Occupational exposure to CDFs may occur. For example, the level of CDFs in the blood of workers in the saw mill industry (exposure to 2,3,4,6-tetrachlorophenolate), textile industry (PCP exposure during fabric impregnation), and leather industry (PCP exposure during tanning) were measured, and the pattern of CDFs in the blood of exposed workers correlated with the CDFs in the exposed compounds (Rappe and Buser 1981). The intake from dermal exposure to CDD/CDF for workers in pulp mill (exposing hands in wet pulp) can be ≤7 pg TEQ/day (Kelada 1990). The concentrations of CDFs in adipose tissues of workers of a chemical plant (producing chlorophenols and 2,4,5-trichlorophenol among other chemicals) was much higher than those of a control population (Beck et al. 1989). Small, but significantly ($p<0.05$) higher, levels of 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF were found in the lipid-adjusted serum of workers in a pesticide plant (2,4,5-trichlorophenol or its derivatives) compared to the levels in a control group (Piacitelli et al. 1992). Occupational exposure to CDFs may also occur in factories manufacturing and repairing transformers and capacitors, in factories with heat exchange systems containing PCBs, in factories using casting waxes containing PCBs, or in industrial incinerators where materials containing chlorinated phenols, PCBs, and PCB ethers are incinerated (Rappe et al. 1979). The concentrations of CDDs/CDFs expressed as 2,3,7,8-TCDD TEQ in air of a municipal incinerator and an electrical transformer metal reclamation plant were significantly higher than ambient levels for these compounds (Crandall et al. 1992). However, no significant risk of exposure to tetraCDFs was found in modem resource recovery plants in Bristol, Connecticut, and Hillsborough County, Florida (Hahn et al. 1989).

Numerous data are available regarding the levels of CDFs in body tissue and fluids of exposed and background (no obvious source of exposure) populations (Nagayama et al. 1977; Ryan 1986; Schecter et al. 1987; Tiernan et al. 1984; Young 1984). CDFs are lipophilic and tend to concentrate in fatty tissues. A positive correlation between 2,3,4,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, and 2,3,4,6,7,8-hexaCDF in adipose tissue and age of donor (higher concentrations at older age) was found (LeBel et al. 1990). A similar correlation between 1,2,3,4,7,8-/1,2,3,6,7,8-hexaCDF and age of donor was also reported among the urban population in California (CARB 1989). No significant correlation between either the level of 2,3,7,8-tetraCDF, 1,2,3,4,6,7,8-heptaCDF, and octaCDF in adipose tissue and age of donor or between any CDFs and sex was discernable (Le Be1 et al. 1990). The latter findings differ from the case of 2,3,7,8-TCDD where higher concentrations of 2,3,7,8-TCDD were detected in female donors than in male donors and a positive correlation between 2,3,7,8-TCDD levels and age of donors was found (Patterson et al. 1986). The average levels of 2,3,7,8-substituted CDFs in human fat of exposed and background populations of different countries have been reviewed (Jensen 1987). Data for the background levels of 2,3,7,8-substituted CDFs in human adipose tissues from different countries are given in Table 5-14. A comparative study of CDF content in liver and adipose tissue of control humans (Germany) showed that on a fat basis, the concentrations of CDFs were higher in the liver than in adipose tissue (Beck et al. 1990b; Thoma et al. 1990).

Table 5-14. Levels of Chlorodibenzofurans (CDFs) in Human Adipose Tissue

	Sample source and mean concentrations (ppt on fat basis)				
Congener	Japan[a]	Sweden[a]	Germany[a]	Canada[b]	United States[c]
2,3,7,8-TetraCDF	9	3.9	0.9	3.3	9.1[d]
2,3,4,7,8-PentaCDF	25	54	44	33.3	40[e]
1,2,3,4,7,8-HexaCDF	15	6	10	37[f]	9.
1,2,3,6,7,8-HexaCDF	14	5	6.7	37[f]	5.4
2,3,4,6,7,8-HexaCDF	8	2	3.8	5.2	1.8
1,2,3,4,6,7,8-HeptaCDF	No data	11	19.5	37.1	21[e]
OctaCDF	No data	4	<1	12	60[d]

[a]Rappe et al. 1987.
[b]LeBel et al. 1990.
[c]Derived from Rappe 1989, unless otherwise stated.
[d]Stanley et al. 1986.
[e]EPA 1989a.
[f]These isomers were not separated.

Several studies indicate that the levels of CDFs in the adipose tissue of exposed populations exceed the levels detected in background or control populations. For example, adipose tissue levels of CDFs in an

exposed patient of the Binghamton State Office Building fire (Schecter and Ryan 1989; Schecter et al. 1985a, 1985b, 1986), Yusho victims in Japan (Miyata et al. 1989; Ryan et al. 1987a), and three patients with fatal PCP poisoning (Ryan et al. 1987b) are all higher than control populations. However, no conclusive evidence of higher CDF exposure was found in seven people exposed during the Missouri dioxin episode and in Vietnam veterans (Kang et al. 1991; Needham et al. 1987). Certain municipal incinerator workers, such as those engaged in ash cleaning are exposed to higher levels of CDFs. The whole blood level of total CDFs in pooled blood of 56 such workers was 102.8 ppt (on lipid basis) compared to 47.0 ppt in pooled blood of 14 control subjects (Schecter et al. 1991a). The concentrations of 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,7,8,9-hexaCDF, 2,3,4,6,7,8-hexaCDF, 1,2,3,4,7,8,9-heptaCDF, and octaCDF were also higher in the pooled blood of workers compared to pooled blood of control subjects. The estimated BCF for 2,3,7,8-tetraCDF in human fat (on lipid basis) was 591 and was higher than other chlorinated aromatics including PCBs, octachlorostyrene, OCDD, and octaCDF (Geyer et al. 1987).

Data are available on the levels of CDFs in human milk from different countries (Dewailly et al. 1991; Schecter and Gasiewicz 1987a, 1987b; Schecter et al. 1989c). In general, CDF levels seem to be lower in the less industrialized countries than in more industrialized countries. Certain differences in specific isomers may exist in different countries, reflecting sources of contamination (Schecter et al. 1989d). The levels of CDFs in human milk derived from different countries are shown in Table 5-15. Levels of CDFs in human milk from other countries including South and North Vietnam and the former Soviet Union are also available (Schecter et al. 1989c, 1990c). From these data, it appears that the most prevalent congener in human milk is 2,3,4,7,8-pentaCDF, followed by 1,2,3,4,7,8-hexaCDF. In one study, no correlation was found between consumption of contaminated fish and accumulation of CDFs in the milk from nursing mothers (Hayward et al. 1989). During the breastfeeding period, the level of CDFs in milk lipid is highest in the first week and slowly decreases thereafter (Beck et al. 1992; Fürst et al. 1989). The level of CDFs in breast milk is highest for women having their first child and distinctly lower for women having their second and third child (Beck et al. 1992).

Table 5-15. Levels of Chlorodibenzofurans (CDFs) in Human Milk

	Sample source and mean concentrations (ppt on fat basis)			
Congener	Sweden[a]	West Germany[b]	United States[c]	Japan[d]
2,3,7,8-TetraCDF	4.2	1.7	2.85	2.9
1,2,3, 7,8-PentaCDF	<1.0	0.5	0.45	1.0
2,3,4,7,8-PentaCDF	21.3	26.7	7.3	23.0

Table 5-15. Levels of Chlorodibenzofurans (CDFs) in Human Milk

	Sample source and mean concentrations (ppt on fat basis)			
Congener	Sweden[a]	West Germany[b]	United States[c]	Japan[d]
1,2,3,4,7,8-HexaCDF	4.7	7.8	5.55	3.9
1,2,3,6,7,8-HexaCDF	3	6.5	3.2	2.5
2,3,4,6,7,8-HexaCDF	1.4	3.4	1.85	1.9
1,2,3,4,6,7,8-HeptaCDF	7.4	5.5	4.05	3.3
OctaCDF	3.2	1.4	4.1	<2.0

[a]Rappe et al. 1987.
[b]Fürst et al. 1992.
[c]Schecter et al. 1991b.
[d]Rappe 1992.

The levels of CDFs in human whole blood from various countries are listed in Table 5-16. Plasma levels of CDFs in people from different countries have been measured; the individual congener concentrations on a fat basis in control populations (not exposed to obvious sources of CDFs) vary from a minimum of <0.1 ppt for 2,3,7,8-tetraCDF to a maximum of 80 ppt for 2,3,4,7,8-pentaCDF (Chang et al. 1990; Nygren et al. 1988; Rappe 1991; Schecter 1991). The highest 2,3,4,7,8-pentaCDF concentration was found in a high fish-consuming population around the Baltic Sea (Svensson et al. 1991). The most prevalent congener in human plasma lipids in the United States was 1,2,3,4,6,7,8-heptaCDF, followed by 1,2,3,7,8- and 2,3,4,7,8-pentaCDF. This pattern was reversed in the plasma lipids of Swedish people, where 2,3,4,7,8-pentaCDF was the prevalent congener followed by 1,2,3,4,6,7,8-heptaCDF (Chang et al. 1990). A similar pattern of high 2,3,4,7,8-pentaCDF level in blood was observed in human blood from Germany (Schecter et al. 1991c). Using a multivariate analysis, the concentration of CDFs in the plasma of exposed Vietnam veterans from the United States were determined to be slightly higher than matched controls (Nygren et al. 1988). It was also determined that higher chlorinated CDFs do not appear to partition according to the lipid content of whole blood. As the degree of chlorination increases, the percent associated with the protein fraction also increases. Therefore, it was concluded that partitioning of higher chlorinated CDFs is not dependent on lipid content, but on specific binding to the protein fraction of serum and whole blood (Patterson et al. 1989; Schecter et al. 1991c).

Table 5-16. Mean Levels of Chlorodibenzofurans (CDFs) in Human Whole Blood (ppt lipid) from Various Countries

	Germany		United States	Vietnam		
Congener	N=85	SD	N=100[a]	Ho Chi Minh City N=50[a]	Dong Nai N=33[a]	Hanoi N=32[a]
2,3,7,8-TetraCDF	2.5	1.8	3.1	4.6	3.9	26
1,2,3,7,8-PentaCDF	ND		2.8	3.2	2.9	<1.1
2,3,4,7,8-PentaCDF	36.8	18.8	13.0	21	22	8.6
Total pentaCDF	36.8		15.8	24.2	24.	9.2
1,2,3,4,7,8-HexaCDF	17.5[b]		15.0	14.0	27.0	6.5
1,2,3,6,7,8-HexaCDF	13.7[b]		14.0	11.0	27.0	6.4
1,2,3,7,8,9-hexaCDF	ND[b]		ND (1.2)[c]	ND (1.4)[c]	ND (1.2)[c]	ND (1.1)[c]
2,3,4,6,7,8-hexaCDF	ND[b]		3.6	3.3	5	1.8
Total hexaCDF	32.1[b]	20.8	32.6	28.3	59	14.7
1,2,3,4,6,7,8-HeptaCDF	23.8[b]		36.0	22	31	12
1,2,3,4,7,8,9-HeptaCDF	ND[b]		ND (1.8)[c]	2.6	2.7	<1.2
Total heptaCDF	24.1[b]	12.0	3	24.6	33.7	12.6
OctaCDR	5.5	3.5	4.2	ND (5.5)[c]	11.0	<3.0

[a]These samples were pooled into one.
[b]These values are derived from Papke et al. 1989.
[c]The values in the parenthesis are the detection limits.

ND = not detected; SD = standard deviation

Source: Schecter 1991

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in industries that manufacture or use chemicals contaminated with CDFs are one segment of the population at high risk for CDF exposure (see Section 5.6). Persons working in the hazardous waste industry or first responders to incidents where CDFs may have been released (e.g., WTC first responders) will be exposed to higher levels than the general population. Although production of PCBs ceased in the United States over 40 years ago, the use of PCBs is still authorized in transformers and other electrical equipment and accidents involving PCB capacitors and transformers may entail high exposures to CDFs.

Among the general population, especially in more industrial countries, higher exposures to CDFs may occur among populations that consume high amounts of fatty fish contaminated with high levels of CDFs (Bloom et al. 2006; Svensson et al. 1991). Several 2,3,7,8-substituted CDFs are present in human milk at concentrations much higher than those in cow milk (Vainio et al. 1989). Therefore, consumption of human milk containing high levels of CDFs may pose a risk to infants consuming breast milk (Schecter

and Gasiewicz 1987a, 1987b). Because of the relatively short period of intake and the accepted benefits of breastfeeding, the World Health Organization did not recommend limitations on breastfeeding (Vainio et al. 1989). Another population group that may be exposed to higher concentrations of CDFs includes people who live adjacent to uncontrolled landfill sites with soils containing high concentrations of CDFs. Attic dust and blood levels of dioxin-like compounds were analyzed for in a community nearby a wood treatment facility in southern Alabama (Hensley et al. 2007). It was determined that concentrations of CDDs/CDFs measured in the blood samples of exposed community members exceeded the 1999-2002 NHANES 90th percentile for total dioxin TEQ levels found in the general U.S. adult population.

Nadal et al. (2019) analyzed the temporal trends of total CDDs/CDFs in the plasma of residents living in the vicinity of a hazardous waste incinerator that was constructed in 1998 in Catalonia, Spain. Over a 2-decade period (1998–2018), they reported between a 59 and 80% decrease in plasma CDD/CDF levels for these residents depending upon age and gender. They concluded that these decreases were due to reduced dietary intakes of these substances and that the incinerator did not create measurable risk to the health of the population living in the vicinity of the facility.

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of CDFs is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of CDFs.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

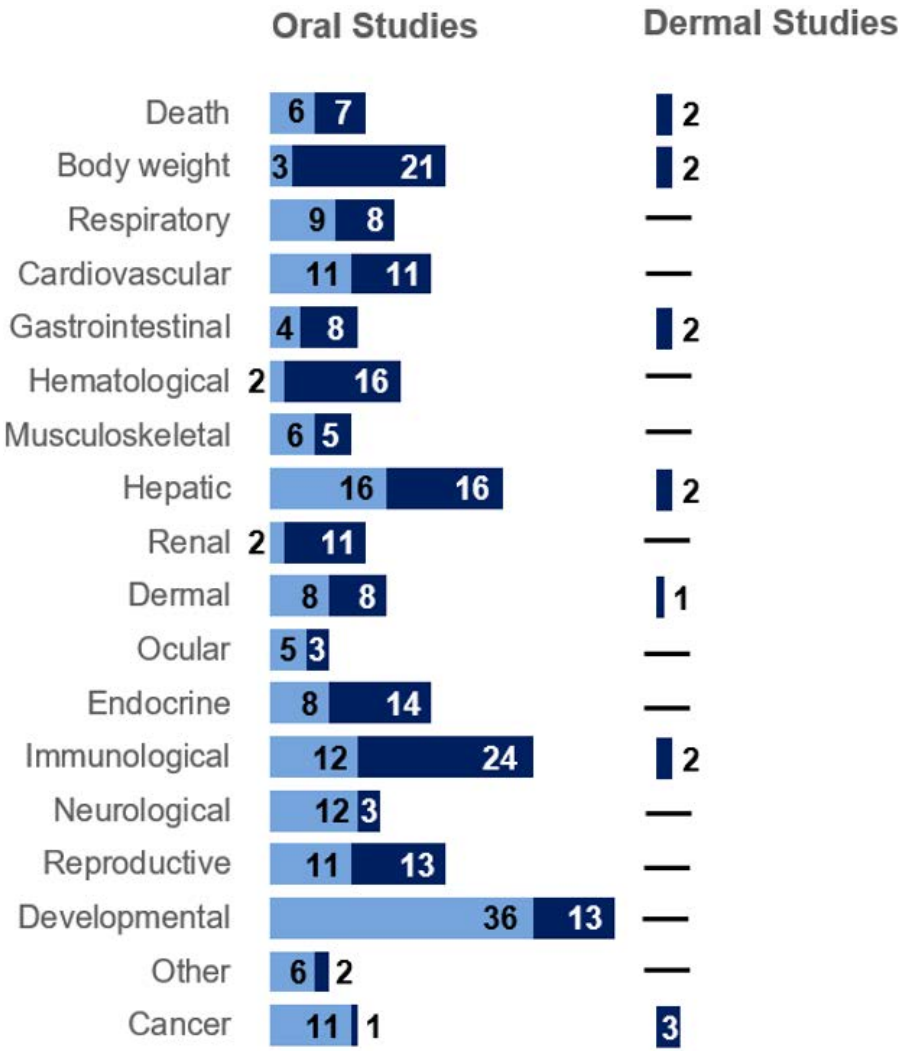
6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to CDFs that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of CDFs. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

As illustrated in Figure 6-1, most of the data on the toxicity of CDFs come from oral exposure studies in humans and animals. Most of the epidemiological studies are of populations exposed to contaminated rice oil for 9–10 months (Yusho and Yu-Cheng incidents); it is assumed that the exposure was intermediate-duration oral exposure; oral exposure is also the presumed route of environmental exposures. The most commonly examined endpoints in the epidemiological studies are developmental, hepatic, immunological, and neurological. The majority of laboratory animal studies involved oral exposure to a single CDF congener, and more than half of the studies are acute-duration exposures. The frequently examined endpoints were immunological, hepatic, and body weight. The majority of the animal studies involved exposure to 2,3,4,7,8-pentaCDF or 2,3,7,8-tetraCDF (75% of studies), with one to four studies evaluating 1,2,3,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,4,8-pentaCDF, 1,2,3,6,7,8-hexaCDF, 1,2,3,4,6,7,8-heptaCDF, and octaCDF. A small number of studies examined

Figure 6-1. Summary of Existing Health Effects Studies on Chlorodibenzofurans (CDFs) By Route and Endpoint*

Potential hepatic, immunological, and developmental effects were the most studied endpoints
The majority of the studies examined oral exposure in **humans** (versus **animals**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect; some studies examined multiple endpoints.

exposure to mixed CDF congeners. No inhalation exposure epidemiological or toxicological studies were identified and a small number of animal studies examined dermal toxicity.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. Inhalation studies were not identified for any CDF congener, and studies are needed to identify critical targets of toxicity. A number of studies have evaluated the acute-duration oral toxicity of CDFs; however, the database was only considered adequate to derive a provisional acute oral MRL for 2,3,4,7,8-pentaCDF. Several studies evaluated 2,3,7,8-tetraCDF and reported adverse outcomes but there was uncertainty as to whether the most sensitive target was identified, particularly since several of the studies did not evaluate the animals until 30–60 days post-exposure. Additional studies evaluating a wide range of potential endpoints including the liver, thyroid, and thymus are needed to identify the most sensitive target and evaluate dose-response relationships. Available studies on 1,2,3,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,4,6,7,8-heptaCDF, and octaCDF examined a limited number of endpoints and were not considered adequate for identifying the critical effect for these congeners or did not report adverse effects at the highest dose tested. No acute-duration oral studies were identified for 1,2,3,4,8-pentaCDF or 1,2,3,6,7,8-hexaCDF. Studies for these congeners are needed to identify critical targets and establish dose-response relationships.

Intermediate-Duration MRLs. No inhalation studies were identified for any CDF congener, and studies are needed to identify critical targets of toxicity. The databases were considered adequate for derivation of provisional intermediate-duration oral MRLs for 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, and 1,2,3,6,7,8-hexaCDF. For 1,2,3,7,8-pentaCDF and 1,2,3,6,7,8-hexaCDF, only one study was identified; additional studies on these congeners would provide support for their respective MRLs.

A small number of studies have evaluated the intermediate toxicity of 2,3,7,8-tetraCDF and identified several targets of toxicity; however, the doses tested were also associated with increased deaths (McNulty et al. 1981) precluding using these studies for MRL derivation. Additional studies examining effects at

nonlethal doses are needed. No intermediate-duration oral studies were identified for 1,2,3,4,7,8-hexaCDF, 1,2,3,4,6,7,8-heptaCDF, or octaCDF. An intermediate-duration study was identified for 1,2,3,4,8-pentaCDF; however, no adverse effects were observed at the highest dose tested. Intermediate-duration oral studies for these four congeners are necessary to support derivation of MRLs. These studies should evaluate a range of potential endpoints including the liver, thymus, and thyroid.

Chronic-Duration MRLs. No chronic-duration inhalation studies were identified for CDFs, studies are needed for MRL derivation. No epidemiological studies were identified that could be used to derive chronic-duration oral MRLs and the laboratory animal database is limited to a single chronic oral study for 2,3,4,7,8-pentaCDF. This study was considered adequate for derivation of a provisional chronic-duration oral MRL for 2,3,4,7,8-pentaCDF. Chronic oral studies are needed for other congeners.

Health Effects.

Endocrine. Acute and intermediate oral studies have examined the potential of several congeners to induce decreases in serum T4 levels; increases in serum T3 were also reported in an intermediate 2,3,4,7,8-pentaCDF study. The alterations in serum T4 and T3 levels were not associated with histological alterations in the thyroid, and there were some indications that these alterations were secondary to hepatic changes rather than a direct impact on the thyroid. Studies are needed to further define the mechanisms of action.

Immunotoxicity. Clinical observations of increased susceptibility to respiratory and dermal infections and various changes in immune parameters in Yusho and Yu-Cheng victims provide limited information on immunological effects of CDFs in humans. Acute- and intermediate-duration oral exposure to CDFs induces decreased organ weight and atrophy in the thymus. The induction of thymic toxicity at doses as low or lower than those known to cause other adverse effects in acute- and intermediate-duration studies indicates that the immune system may be one of the most sensitive targets for CDFs. There is suggestive evidence of CDF-induced impaired functional immune response in guinea pigs, but an immunocompetence test in mice was inconclusive. Additional studies would be necessary to determine if the immune system is a critical target of CDFs. Decreased thymus weights with atrophy also occurred in mice dermally treated with CDFs in an intermediate-duration study, indicating that immunological effects of CDFs are unlikely to be route specific (Hebert et al. 1990).

Reproductive. Irregular menstrual cycles, abnormal basal body temperature patterns, and decreased urinary excretion of estrogens and pregnanediol were observed in female Yu-Cheng patients (Kusuda 1971). Although possibly suggestive of corpus luteum insufficiency and retarded follicular maturation, studies of fertility, fecundity, and rates of spontaneous abortion in Yu-Cheng and/or Yusho would provide more definite information on reproductive toxicity of CDFs. Some intermediate-duration oral studies showed no histological alterations in the ovaries, uterus, or testes of rats treated with various CDFs, although there is some evidence from other oral studies that the testes are a target (Moore et al. 1979; Oishi et al. 1978), and uterine effects have been reported after chronic duration oral exposure to 2,3,4,7,8-pentaCDF (NTP 2006). Although pathological examinations performed as part of 90-day oral toxicity studies would be useful for identifying and corroborating susceptibility of the reproductive system and determining sensitive species, studies assessing effects of CDFs on reproductive function in males and females would be more informative.

Developmental. Various toxic effects were observed in children born to mothers exposed during the Yusho and Yu-Cheng incidents, including dermal lesions, decreased birth weights, neurobehavioral deficits, and some perinatal deaths (Funatsu et al. 1971; Gladen et al. 1990; Hsu et al. 1985; Lan et al. 1987; Rogan et al. 1988; Taki et al. 1969; Yamaguchi et al. 1971; Yu et al. 1991). Although no exposure-related congenital malformations were reported in these children, oral studies in mice and rats have documented induction of hydronephrosis and/or cleft palate by 2,3,7,8-substituted tetra-, penta-, and hexaCDF congeners (Birnbaum et al. 1987a; Couture et al. 1989; Madsen and Larsen 1989; Weber et al. 1984, 1985). Tissues other than kidney and palate were examined only in the rat studies, which provide some evidence indicating that rats are more susceptible to CDFs than mice and that neonatal thymic toxicity is a more sensitive developmental endpoint than fetal mortality or cleft palate in rats (Couture et al. 1989; Madsen and Larsen 1989). There is also evidence suggesting that the developing reproductive system is a sensitive target in male and female offspring (Salisbury and Marcinkiewicz 2002; Taura et al. 2014). Additional studies could potentially verify that reproductive system and thymic toxicity are the most sensitive endpoints and that the rat is the most sensitive species for developmental effects. Immunological evaluations of offspring would be valuable to determine the importance of thymic changes, and neurobehavioral evaluations in monkey offspring would be particularly relevant, due to the deficits observed in children of Yu-Cheng mothers. Since nursing can significantly contribute to offspring body burden and CDFs are retained in adipose long after

external exposure has been discontinued, follow-up evaluations of highly exposed populations sensitive developmental endpoints is desirable.

Cancer. There are limited data on the carcinogenicity of CDF congeners in animals. The oral carcinogenicity database is limited to a chronic-duration study of 2,3,4,7,8-pentaCDF in female rats (NTP 2006). The remainder of the database consists of dermal tumor promotion studies on 2,3,7,8-tetraCDF, 2,3,4,7,8-pentaCDF, and 1,2,3,4,7,8-hexaCDF. Additional carcinogenicity studies are needed to assess the carcinogenic potential of CDFs.

Epidemiology and Human Dosimetry Studies. Studies of the Yusho and Yu-Cheng populations provide a wealth of information on health effects attributable to CDFs, and these populations are the best available population for assessing the effects of CDFs in humans. Additional studies could possibly provide information on dose-response for sensitive effects and discern which effects represent delayed and/or irreversible toxicity. Follow-up studies would also be useful for more adequately assessing risk of cancer. Municipal incineration workers (Schecter et al. 1991a) and certain other worker populations may be exposed to CDFs by inhalation and/or dermal contact. However, co-exposure to CDDs and other chemicals is more of an issue in these populations than in the Yusho and Yu-Cheng cohorts.

Biomarkers of Exposure and Effect.

Exposure. Due to their lipophilicity, CDFs are stored in highest concentrations, on whole weight basis, in adipose tissue, are frequently measured in blood and human milk, and have been found at lower concentrations in all other tissues examined to date. Several studies indicate that serum and adipose levels of CDFs are biomarkers of exposure feasible for estimating body burden or exposure. Further studies on the predictive value of CDF levels in human serum, adipose, and milk could provide valuable information that could lead to early detection of exposure. Several studies evaluating whether hair levels could be used as a biomarker of exposure suggest that the levels in hair are reflective of body burden and environmental levels. Additional studies are needed to evaluate whether hair levels accurately reflect body burden.

Effect. An association between CDF body burden and chloracne has been calculated using data from Yu-Cheng victims (Ryan et al. 1990). Additional studies could evaluate the feasibility of using body burden as a biomarker for predicting other effects of CDFs. Chloracne and many other effects of CDFs, however, are common to other chloroaromatics that use an Ah receptor-mediated mechanism. There are

no specific clinical or biochemical biomarkers of effect for CDFs, although some (e.g., changes in lipid and porphyrin metabolism) may be limited to chloroaromatics using a common mechanism. Further studies to identify specific biomarkers of effect for PCBs would facilitate medical surveillance leading to early detection and prevention of potentially adverse health effects from exposure.

Absorption, Distribution, Metabolism, and Excretion. There are no quantitative data regarding absorption in humans by the inhalation, oral, or dermal routes, but data from accidentally exposed individuals suggest that exposure by any of these routes, or a combination of them, may lead to considerable accumulation of CDFs in tissues (Chen et al. 1985a; Masuda et al. 1985; Schecter and Ryan 1989). The animal data indicate that CDFs (mostly tetra- and pentaCDFs) are efficiently absorbed by the oral route (Birnbaum et al. 1980; Brewster and Birnbaum 1987; Van den Berg et al. 1989). Inhalation absorption data are not available. Dermal absorption data were limited to one study in rats that showed relatively low absorption for two pentaCDFs, compared with oral rates (Brewster et al. 1989). No studies were located in which a range of doses of different CDF congeners were administered by the inhalation, oral, and dermal routes, and for various exposure periods.

As with absorption, distribution data in humans are limited to qualitative information derived from cases of accidental ingestion of food contaminated with CDFs (Chen et al. 1985a; Masuda et al. 1985), cases of occupational exposure through inhalation or dermal contact with CDFs (Schecter and Ryan 1989), and autopsy reports from the general population (Ryan et al. 1985a; Schecter et al. 1989a). These data suggest that CDFs distribute preferentially to tissues with high fat content regardless of the route of exposure. Data derived from oral and dermal administration of single CDF congeners to animals indicate that CDFs distribute first to the liver and are subsequently translocated to adipose tissue for storage (Birnbaum et al. 1980; Brewster and Birnbaum 1987; Brewster et al. 1989; Decad et al. 1981a).

Data regarding biotransformation of CDFs in humans are limited to individuals who accidentally consumed food contaminated with CDFs (Chen et al. 1985a; Masuda et al. 1985). The use of human cell systems in culture might be considered a useful addition to whole animal studies for studying the metabolic fate of CDFs. The metabolism of some CDF congeners after acute oral administration to rats has been studied (Poiger et al. 1989). Although information regarding metabolism following inhalation or dermal exposure is lacking, there is no reason to believe that the metabolism would differ from that of the oral route.

Studies regarding urinary or fecal excretion of CDFs in humans were not located; however, elimination of CDFs through maternal milk is well documented (Van den Berg et al. 1986). Fecal excretion is the main route of elimination of CDFs in animals after acute oral exposure (Birnbaum et al. 1980; Brewster and Birnbaum 1987; Decad et al. 1981a; Weber and Birnbaum 1985). Excretion data following dermal exposure support the oral data, but the information is derived from a single study (Brewster et al. 1989).

Comparative Toxicokinetics. The existing evidence suggests that qualitative differences in the toxicokinetic disposition of CDFs exist among humans and among animal species. However, these differences appear to be highly dependent on the specific congener studied. In general, all species absorb CDFs efficiently and accumulate CDFs in tissues rich in fat. Once absorbed, CDFs distribute in a similar manner in all examined animal species (high initial concentration in blood, liver, and muscle, followed by gradual increase in CDF concentration in adipose tissue) (Birnbaum et al. 1980; Brewster and Birnbaum 1987; Decad et al. 1981a; Weber and Birnbaum 1985). Identification of metabolites in humans and rats suggests that both species share some common biochemical reactions (Chen et al. 1985a; Poiger et al. 1989). Experimental data in animals indicate that fecal elimination is the main route of excretion (Birnbaum et al. 1980; Brewster and Birnbaum 1987; Decad et al. 1981a; Weber and Birnbaum 1985), but no human information was located in the existing literature. Analysis of the excreta of humans accidentally exposed to CDFs or living near hazardous waste sites would provide information regarding biotransformation and elimination kinetics in humans. In addition similar target organs have been identified across animal species. Monkeys seem to be one of the most sensitive species tested. Although the toxicological data in humans are limited, adverse cutaneous and ocular (e.g., Meibomian gland) reactions documented in humans (Kuratsune 1989) are also seen in monkeys (McNulty et al. 1981), suggesting that monkeys may represent a suitable animal model. Additional studies are needed to provide more definitive data for selecting animal models for CDF toxicity in humans.

Children's Susceptibility. There are limited information on children's susceptibility to CDF toxicity. Epidemiological and laboratory animal studies provide evidence that exposure can result in developmental effects. However, no studies were identified that examined the susceptibility of children. The assumption is that effects observed in adults would also occur in children, but there is no information to assess whether children would be more sensitive. Studies evaluating the toxicity of CDFs at various ages would provide useful information for evaluating the environmental risk.

Physical and Chemical Properties. The synthesis and purification of a specific CDF congener is a difficult task. The low water solubilities and vapor pressures contribute to the difficulty in determining

the basic physico-chemical properties of the CDFs. In addition, the toxicity of some CDF congeners requires extra care in their handling. Consequently, experimental data regarding the fundamental physical and chemical properties, such as melting point, boiling point, vapor pressure, and chemical reactivity for individual CDF congeners is not completely known (see Table 4-2). Determination of experimental data on water solubility, K_{ow}, Henry's law constant, and K_{oc}, particularly for the 2,3,7,8-substituted CDFs (because of higher toxicity) would be useful for predicting the environmental fates and transport of these compounds.

Production, Import/Export, Use, Release, and Disposal. CDFs are produced on a small scale for chemical and biological laboratory use. These compounds have no other known use. Therefore, further development of data on the production, import/export, and use of these compounds would not be useful. The release of CDFs in the environment is one of the most intensively studied subjects in the literature (see Section 5.3). The regulations governing the disposal of CDF-containing wastes are well defined (see Section 5.2.4). No data needs are identified.

Environmental Fate. The understanding of the environmental fate and transport of CDFs is generally understood (Atkinson 1991; Koester and Hites 1992). The lower chlorinated congeners are semi-volatile and degrade in the atmosphere relatively quickly, while the higher chlorinated congeners are less volatile but undergo atmospheric degradation slowly and are subject to long range transport. Like many other highly halogenated substances, higher chlorinated congeners are slow to degrade in the environment via microbial means (aerobic biodegradation) and tend to bioconcentrate. These substances tend to undergo reductive dehalogenation under anoxic conditions. The development of additional data regarding the biodegradability of these compounds in soil, water, and sediment is a data need.

Bioavailability from Environmental Media. Because of the strong adsorption of CDFs in soil, the bioavailability of these compounds from dermal contact with soil is expected to be low. Since CDFs are present predominantly in the particulate-sorbed state in both air and in water, the bioavailability of CDFs in these media, from inhalation exposure and ingestion of drinking water or soil, would be lower than the bioavailability of the compounds in the unadsorbed states (e.g., administered in solution or vapor form). Roberts et al. (2019) studied the expected bioaccessibility of CDFs from soils from a hazardous waste site. No data needs are identified.

Food Chain Bioaccumulation. CDFs are bioconcentrated in aquatic organisms and in marine and terrestrial animals. Predictive QSAR models for bioconcentration and bioaccumulation factors predict

that the higher chlorinated congeners are expected to bioaccumulate in aquatic organisms (Arnot et al. 2009). Additional data on the biotransfer ratio of CDFs from soils to different plants is a data need.

Exposure Levels in Environmental Media. Data on the levels of CDFs in air, water, soil, sediment, and vegetation are available (see Section 5.5). Exposure to the general population overwhelmingly comes from ingestion of food. Continued monitoring data are required in order to assess the temporal trends in CDFs in environmental media.

Reliable monitoring data for the levels of CDFs in contaminated media at hazardous waste sites are needed so that the information obtained on levels of CDFs in the environment can be used in combination with the body burden of CDFs to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. The levels of CDFs in tissues and body fluids of both exposed and control population groups in the United States have been studied. NHANES data suggest that serum levels of CDFs are declining in the United States (CDC 2021; Lakind et al. 2009). Continued monitoring of CDF levels in the U.S. population is important to understand the temporal exposure to these substances.

Exposures of Children. CDFs can be transferred from mother to fetus via the placenta, or to nursing infants via breast milk (Nakano et al. 2005). Continued monitoring of CDF levels in breast milk of lactating mothers, cord blood, and food items that are an important part of or unique to a toddler's (or young child's) diet (e.g., formula and other baby foods) is a data need.

6.3 ONGOING STUDIES

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2020) database.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding CDFs in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for CDFs.

Table 7-1. Regulations and Guidelines Applicable to Chlorodibenzofurans (CDFs)

Agency	Description	Information	Reference
	Air		
EPA	RfC	No data	IRIS 2020
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories	Not listed	EPA 2018a
	National primary drinking water regulations	Not listed	EPA 2009
	RfD	No data	IRIS 2020
WHO	Drinking water quality guidelines	Not listed	WHO 2017
FDA	Substances Added to Food	No data[a]	FDA 2020
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	No data	IRIS 2020
IARC	Carcinogenicity classification		
	2,3,4,7,8-PentaCDF	Group 1[b]	IARC 2012
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction	No data	OSHA 2019a, 2019b, 2019c
NIOSH	REL (up to 10-hour TWA)	No data[c]	NIOSH 2018
	Emergency Criteria		
EPA	AEGLs-air	Not listed	EPA 2018b
DOE	PACs-air		DOE 2018a
	2,3,7,8-TetraCDF and 2,3,4,7,8-pentaCDF		
	PAC-1[c]	4.30×10^{-4} mg/m^3	
	PAC-2[c]	0.0046 mg/m^3	
	PAC-3[c]	0.028 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Chlorodibenzofurans (CDFs)

Agency	Description	Information	Reference
	1,2,3,7,8-PentaCDF		
	PAC-1[c]	0.0043 mg/m^3	
	PAC-2[c]	0.046 mg/m^3	
	PAC-3[c]	0.28 mg/m^3	
	1,2,3,4,7,8-HexaCDF, 1,2,3,6,7,8-hexaCDF, 1,2,3,7,8,9-hexaCDF, 2,3,4,6,7,8-hexaCDF, 1,2,3,4,6,7,8-heptaCDF, and 1,2,3,4,7,8,9-heptaCDF		
	PAC-1[c]	0.0013 mg/m^3	
	PAC-2[c]	0.014 mg/m^3	
	PAC-3[c]	0.085 mg/m^3	
	1,2,3,4,6,7,8-HeptaCDF and 1,2,3,4,7,8,9-heptaCDF		
	PAC-1[c]	0.013 mg/m^3	
	PAC-2[c]	0.14 mg/m^3	
	PAC-3[c]	0.85 mg/m^3	
	1,2,3,4,6,7,8,9-OctaCDF		
	PAC-1[c]	0.43 mg/m^3	
	PAC-2[c]	4.7 mg/m^3	
	PAC-3[c]	28 mg/m^3	

[a]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited in food, delisted color additives, and some substances "no longer FEMA GRAS."
[b]Group 1: carcinogenic to humans.
[c]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. 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.

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 S102-1, 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. 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 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

Provisional 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 a provisional intermediate MRL for 1,2,3,7,8-pentaCDF;

provisional acute, intermediate and chronic oral MRLs for 2,3,4,7,8-pentaCDF; and a provisional intermediate MRL for 1,2,3,6,7,8-hexaCDF.

Table A-2. Provisional 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 the 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). 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: January 2022
Profile Status: Draft for Public Comment
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: January 2022
Profile Status: Draft for Public Comment
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: January 2022
Profile Status: Draft for Public Comment
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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for 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: January 2022
Profile Status: Draft for Public Comment
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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of an acute-duration oral MRL for 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: January 2022
Profile Status: Draft for Public Comment
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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for 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: January 2022
Profile Status: Draft for Public Comment
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: January 2022
Profile Status: Draft for Public Comment
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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
MRL: 0.007 µg/kg/day ($7x10^{-3}$ µg/kg/day) (provisional)
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: A provisional 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 1989a); 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

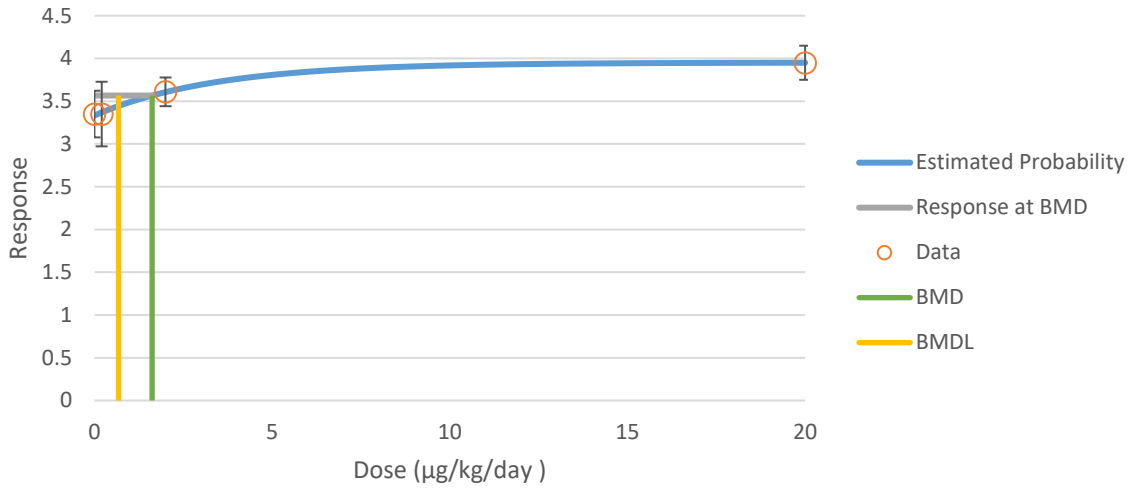


Table A-9. Results from BMD Analysis (Constant Variance) of Relative Liver Weight in Female Rats Exposed to 1,2,3,7,8-Pentachlorodibenzofuran in the Diet for 13 Weeks (Pluess et al. 1988a)

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[e]	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 sufficiently close (differed by <3-fold); therefore, the model with the lowest AIC was selected (Linear).

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

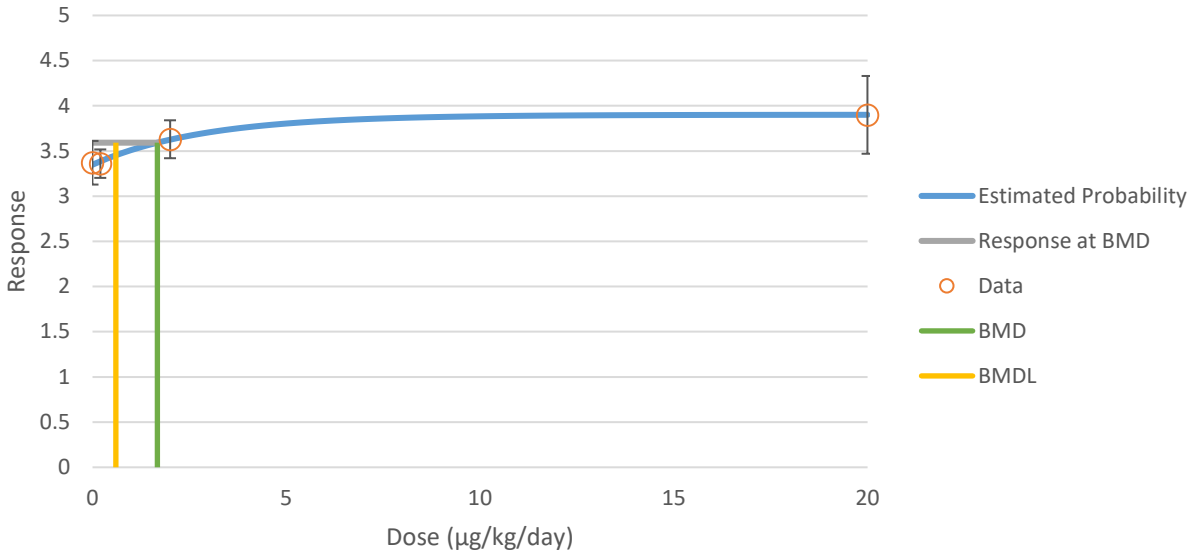


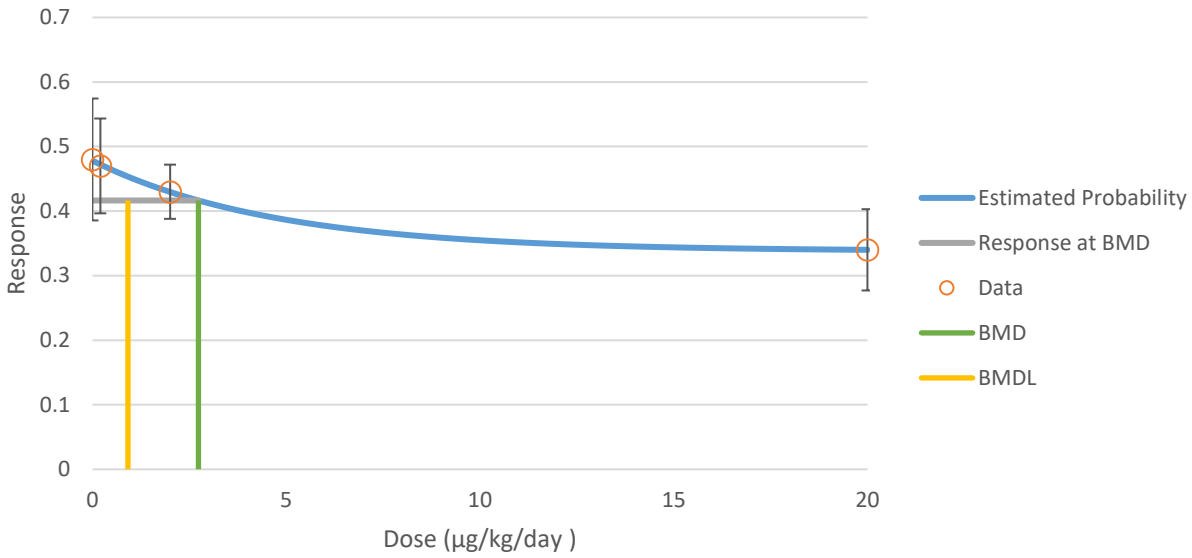
Table A-10. Results from BMD Analysis (Constant Variance) of Absolute Thymus Weight in Female Rats Exposed to 1,2,3,7,8-Pentachlorodibenzofuran in the Diet for 13 Weeks (Pluess et al. 1988a)

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

Provisional MRL = $BMDL_{1SD} \div UF$
0.68 μg/kg/day ÷ (10 x 10) = 0.007 μg/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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for 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: January 2022
Profile Status: Draft for Public Comment
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:	January 2022
Profile Status:	Draft for Public Comment
Route:	Oral
Duration:	Acute
MRL:	0.0005 µg/kg/day ($5x10^{-4}$ µg/kg/day) (provisional)
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: A provisional 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.

Provisional 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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
MRL: 0.000007 µg/kg/day (7 x 10^{-6} µg/kg/day) (provisional)
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: A provisional 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

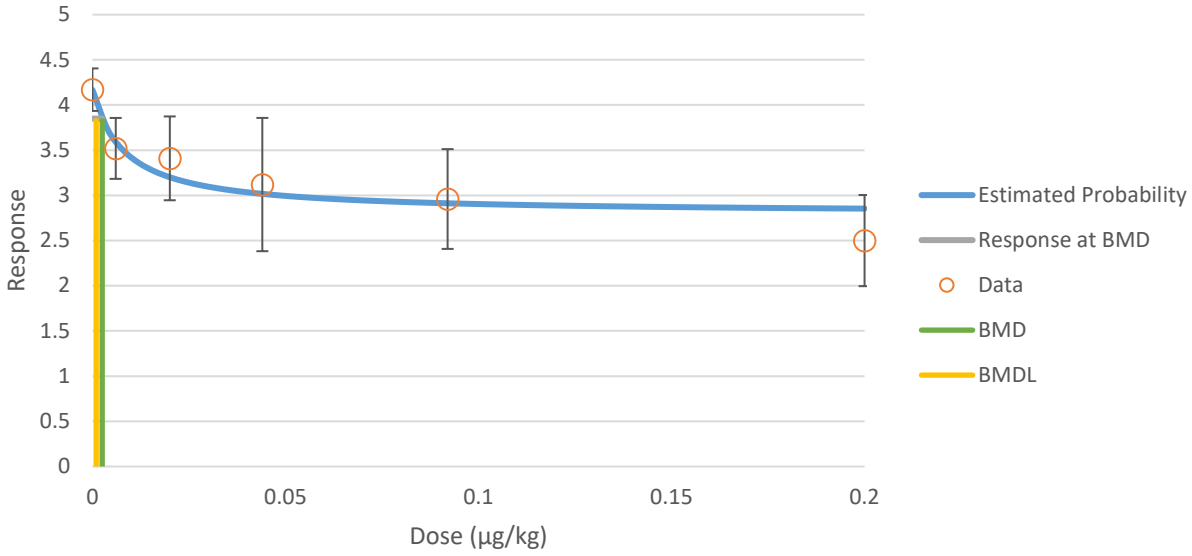


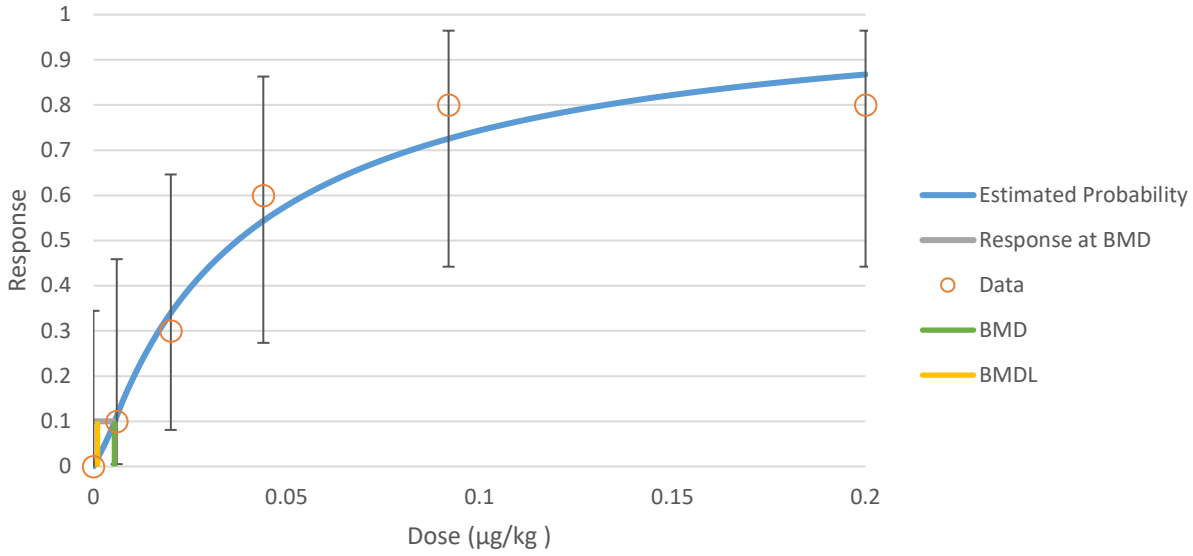
Table A-16. Results from BMD Analysis of Hepatocellular Hypertrophy Incidence in Female Rats Administered 2,3,4,7,8-Pentachlorodibenzofuran 5 Days/Week for 31 Weeks (NTP 2006)

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 ($7x10^{-3}$ 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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic
MRL: 0.000004 µg/kg/day (4 x 10^{-6} µg/kg/day) (provisional)
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 provisional 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 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 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: January 2022
Profile Status: Draft for Public Comment
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

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2,3,4,7,8-Hexachlorodibenzofuran
CAS Numbers: 70648-26-9
Date: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of an acute-duration oral MRL for 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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of an intermediate-duration oral MRL for 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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for 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: January 2022
Profile Status: Draft for Public Comment
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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of an acute-duration oral MRL for 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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
MRL: 0.005 µg/kg/day (provisional)
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: A provisional 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 starting 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

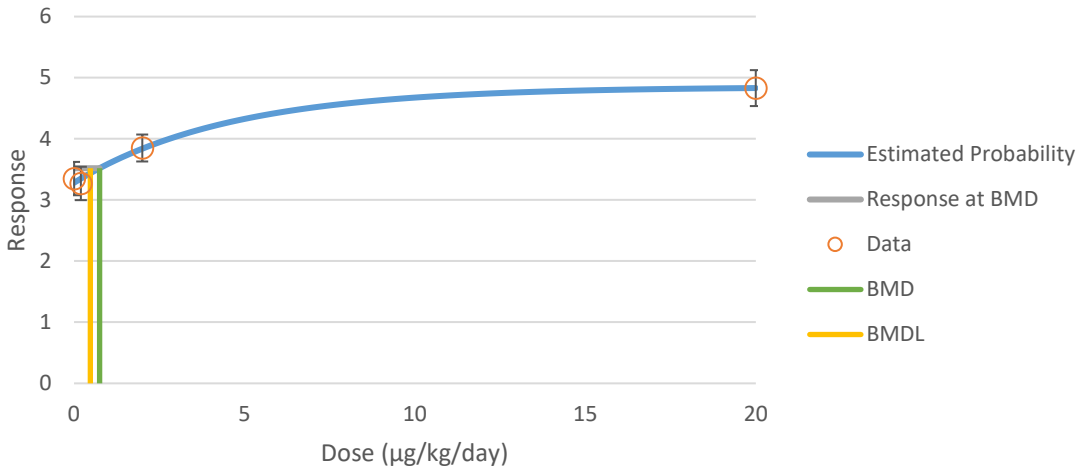


Table A-22. Results from BMD Analysis (Nonconstant Variance) of Absolute Thymus Weight in Female Rats Exposed to 1,2,3,6,7,8-Hexachlorodibenzofuran in the Diet for 13 Weeks (Pluess et al. 1988a)

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

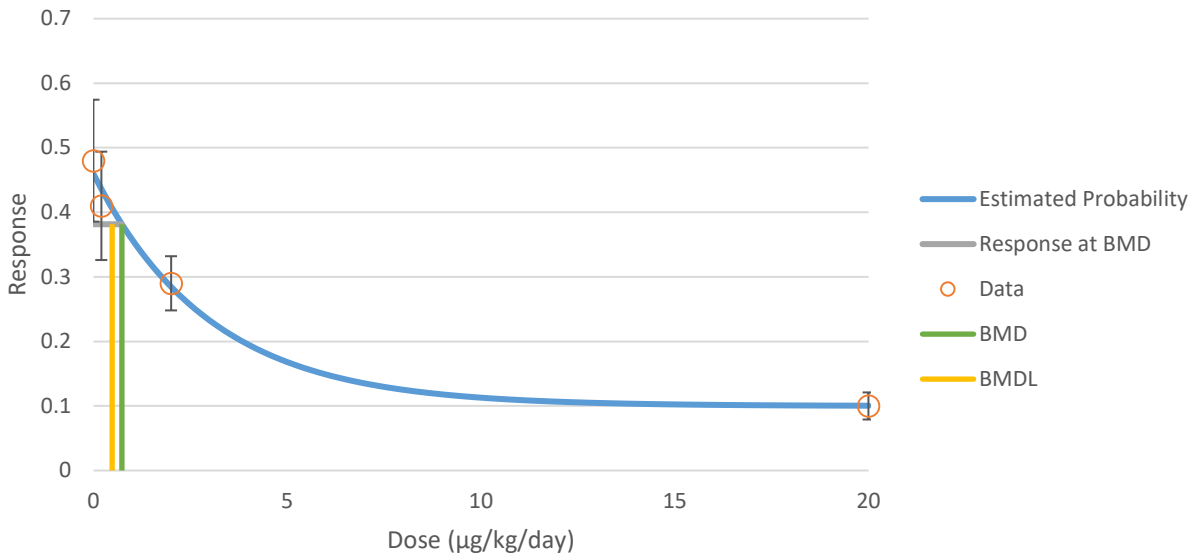


Table A-23 summarizes the potential candidate PODs for 1,2,3,6,7,8-hexaCDF. The lowest candidate POD was 0.48 µg/kg/day for increases in relative liver weight in males and decreases in absolute thymus weight in females; the $BMDL_{1SD}$ for these endpoints was selected as the POD.

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

Provisional 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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for 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: January 2022
Profile Status: Draft for Public Comment
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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of an acute-duration oral MRL for 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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of an intermediate-duration oral MRL for 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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for 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: January 2022
Profile Status: Draft for Public Comment
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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for the derivation of an acute-duration oral MRL for 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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for the derivation of an intermediate-duration oral MRL for 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 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: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for the derivation of a chronic-duration oral MRL for 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 was 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 1994 toxicological profile for CDFs; thus, the literature search was restricted to studies published between January 1992 and July 2019. The following main databases were searched in July 2019:

- PubMed
- National Library of Medicine's Toxline
- 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	
07/2019	(("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 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"[mh] AND cancer[sb]) OR ("Dibenzofurans, Polychlorinated/pharmacology"[majr])) AND (1992 : 3000[dp] OR 1992 : 3000[mhda] OR 1992 : 3000[edat] OR 1992 : 3000[crdat]) (("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 ("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 ("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 ("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,

Table B-2. Database Query Strings

Database search date	Query string
	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])) 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 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 "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"[mh] AND cancer[sb]) OR ("Benzofurans/pharmacology"[majr])) AND (1992 : 3000[dp] OR 1992 : 3000[mhda] OR 1992 : 3000[edat] OR 1992 : 3000[crdat])

Table B-2. Database Query Strings

Database search date	Query string
	(("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 "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

Table B-2. Database Query Strings

Database search date	Query string
	"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 "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

Table B-2. Database Query Strings

Database search date	Query string
	"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])) AND (("Dioxins/toxicity"[mh] OR "Dioxins/adverse effects"[mh] OR "Dioxins/poisoning"[mh] OR "Dioxins/pharmacokinetics"[mh]) OR ("Dioxins"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Dioxins"[mh] AND toxicokinetics[mh:noexp]) OR ("Dioxins/blood"[mh] OR "Dioxins/cerebrospinal fluid"[mh] OR "Dioxins/urine"[mh]) OR ("Dioxins"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Dioxins"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR

Table B-2. Database Query Strings

Database search date	Query string
	genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Dioxins/antagonists and inhibitors"[mh]) OR ("Dioxins/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Dioxins"[mh] AND cancer[sb]) OR ("Dioxins/pharmacology"[majr])) AND (1992 : 3000[dp] OR 1992 : 3000[mhda] OR 1992 : 3000[edat] OR 1992 : 3000[crdat]) ((((("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

Table B-2. Database Query Strings

Database search date	Query string
	"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 "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

Table B-2. Database Query Strings

Database search date	Query string
	"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]))) NOT medline[sb]) AND (1992 : 3000[dp] OR 1992 : 3000[mhda] OR 1992 : 3000[edat] OR 1992 : 3000[crdat]) ((((("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-

Table B-2. Database Query Strings

Database search date	Query string
	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 "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 ("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

Table B-2. Database Query Strings

Database search date	Query string
	"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 "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

Table B-2. Database Query Strings

Database search date	Query string
	"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]))) 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] OR cf[sh] OR ur[sh] OR "environmental exposure"[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

Table B-2. Database Query Strings

Database search date	Query string
	"Gene Expression Profiling"[mh])) OR cancer[sb] 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 (1992 : 3000[dp] OR 1992 : 3000[mhda] OR 1992 : 3000[edat] OR 1992 : 3000[crdat])
Toxline	
07/2019	(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]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 (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]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 ("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") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 ("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") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019

Table B-2. Database Query Strings

Database search date	Query string
	("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") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 ("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") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 ("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") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 ("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") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 ("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") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR

Table B-2. Database Query Strings

Database search date	Query string
	MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019
	("chlorinated dibenzo-furans" OR "dibenzofurans, chlorinated" OR "hepta chloro furans" OR "heptachlorofurans" OR "penta chloro furans" OR "polychlorinated dibenzo-furans") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019
	(("chlorinated" AND "dibenzofuran") OR ("polychlorinated" AND "dibenzofuran") OR (("monochlorinated" OR "dichlorinated" OR "trichlorinated" OR "tetrachlorinated" OR "pentachlorinated" OR "hexachlorinated" OR "heptachlorinated" OR "octachlorinated" OR "perchlorinated") AND "dibenzofuran") OR (("dipolychlorinated" OR "tripolychlorinated" OR "tetrapolychlorinated" OR "pentapolychlorinated" OR "hexapolychlorinated" OR "heptapolychlorinated" OR "octapolychlorinated" OR "perpolychlorinated" OR "polypolychlorinated") AND "dibenzofuran")) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019
	(("chlorinated" AND "dibenzofurans") OR ("polychlorinated" AND "dibenzofurans") OR (("monochlorinated" OR "dichlorinated" OR "trichlorinated" OR "tetrachlorinated" OR "pentachlorinated" OR "hexachlorinated" OR "heptachlorinated" OR "octachlorinated" OR "perchlorinated") AND "dibenzofurans") OR (("dipolychlorinated" OR "tripolychlorinated" OR "tetrapolychlorinated" OR "pentapolychlorinated" OR "hexapolychlorinated" OR "heptapolychlorinated" OR "octapolychlorinated" OR "perpolychlorinated" OR "polypolychlorinated") AND "dibenzofurans")) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019
	("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") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019
	("chlorodiphenylene oxide" OR "monochlorodiphenylene oxide" OR "dichlorodiphenylene oxide" OR "trichlorodiphenylene oxide" OR "tetrachlorodiphenylene oxide" OR "pentachlorodiphenylene oxide" OR "hexachlorodiphenylene oxide" OR

Table B-2. Database Query Strings

Database search date	Query string
	"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") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 ("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-") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 ("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-") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 ("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-") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 ("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-") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org]

Table B-2. Database Query Strings

Database search date	Query string
	OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019
	("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-") AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019
	(24478-72-6[rn] OR 24478-73-7[rn] OR 24478-74-8[rn] OR 25074-67-3[rn] OR 30402-14-3[rn] OR 30402-15-4[rn] OR 38998-75-3[rn] OR 39001-02-0[rn] OR 42934-53-2[rn] OR 43047-99-0[rn] OR 43048-00-6[rn] OR 51207-31-9[rn] OR 51230-49-0[rn] OR 5409-83-6[rn] OR 54589-71-8[rn] OR 55673-89-7[rn] OR 55684-94-1[rn] OR 55722-27-5[rn]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019
	(57117-31-4[rn] OR 57117-32-5[rn] OR 57117-33-6[rn] OR 57117-34-7[rn] OR 57117-35-8[rn] OR 57117-36-9[rn] OR 57117-37-0[rn] OR 57117-38-1[rn] OR 57117-39-2[rn] OR 57117-40-5[rn] OR 57117-41-6[rn] OR 57117-42-7[rn] OR 57117-43-8[rn] OR 57117-44-9[rn] OR 58802-14-5[rn] OR 58802-15-6[rn] OR 58802-16-7[rn] OR 58802-17-8[rn]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019
	(58802-18-9[rn] OR 58802-19-0[rn] OR 58802-20-3[rn] OR 58802-21-4[rn] OR 60390-27-4[rn] OR 60851-34-5[rn] OR 62615-08-1[rn] OR 64126-85-8[rn] OR 64126-86-9[rn] OR 64126-87-0[rn] OR 64560-13-0[rn] OR 64560-14-1[rn] OR 64560-15-2[rn] OR 64560-16-3[rn] OR 64560-17-4[rn] OR 66794-59-0[rn] OR 67481-22-5[rn] OR 67517-48-0[rn]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019
	(67562-39-4[rn] OR 67562-40-7[rn] OR 67652-39-5[rn] OR 69433-00-7[rn] OR 69698-57-3[rn] OR 69698-58-4[rn] OR 69698-59-5[rn] OR 69698-60-8[rn] OR 70648-13-4[rn] OR 70648-14-5[rn] OR 70648-15-6[rn] OR 70648-16-7[rn] OR 70648-18-9[rn] OR 70648-19-0[rn] OR 70648-20-3[rn] OR 70648-21-4[rn] OR 70648-22-5[rn] OR 70648-23-6[rn]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]

Table B-2. Database Query Strings

Database search date	Query string
	Year of Publication 1992 through 2019 (70648-24-7[rn] OR 70648-25-8[rn] OR 70648-26-9[rn] OR 70872-82-1[rn] OR 71998-72-6[rn] OR 71998-73-7[rn] OR 71998-74-8[rn] OR 71998-75-9[rn] OR 72918-21-9[rn] OR 74423-73-7[rn] OR 74918-40-4[rn] OR 74992-96-4[rn] OR 74992-97-5[rn] OR 74992-98-6[rn] OR 75198-38-8[rn] OR 75627-02-0[rn] OR 76621-12-0[rn] OR 79060-60-9[rn]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 (81638-37-1[rn] OR 82911-58-8[rn] OR 82911-59-9[rn] OR 82911-60-2[rn] OR 82911-61-3[rn] OR 83636-47-9[rn] OR 83690-98-6[rn] OR 83704-21-6[rn] OR 83704-22-7[rn] OR 83704-23-8[rn] OR 83704-24-9[rn] OR 83704-25-0[rn] OR 83704-26-1[rn] OR 83704-27-2[rn] OR 83704-28-3[rn] OR 83704-29-4[rn] OR 83704-30-7[rn] OR 83704-31-8[rn]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 (83704-32-9[rn] OR 83704-33-0[rn] OR 83704-34-1[rn] OR 83704-35-2[rn] OR 83704-36-3[rn] OR 83704-37-4[rn] OR 83704-38-5[rn] OR 83704-39-6[rn] OR 83704-40-9[rn] OR 83704-41-0[rn] OR 83704-42-1[rn] OR 83704-43-2[rn] OR 83704-44-3[rn] OR 83704-45-4[rn] OR 83704-46-5[rn] OR 83704-47-6[rn] OR 83704-48-7[rn] OR 83704-49-8[rn]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 (83704-50-1[rn] OR 83704-51-2[rn] OR 83704-52-3[rn] OR 83704-53-4[rn] OR 83704-54-5[rn] OR 83704-55-6[rn] OR 83710-07-0[rn] OR 83719-40-8[rn] OR 84761-86-4[rn] OR 89059-46-1[rn] OR 91538-83-9[rn] OR 91538-84-0[rn] OR 92341-04-3[rn] OR 92341-05-4[rn] OR 92341-06-5[rn] OR 92341-07-6[rn] OR 94538-00-8[rn] OR 94538-01-9[rn] OR 94538-02-0[rn] OR 94570-83-9[rn]) AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org] Year of Publication 1992 through 2019 (24478-72-6[rn] OR 24478-73-7[rn] OR 24478-74-8[rn] OR 25074-67-3[rn] OR 30402-14-3[rn] OR 30402-15-4[rn] OR 38998-75-3[rn] OR 39001-02-0[rn] OR 42934-53-2[rn] OR 43047-99-0[rn] OR 43048-00-6[rn] OR 51207-31-9[rn] OR 51230-49-0[rn] OR 5409-83-6[rn] OR 54589-71-8[rn] OR 55673-89-7[rn] OR 55684-94-1[rn] OR 55722-27-5[rn]) AND (TSCATS[org]) Year of Publication 1992 through 2019

Table B-2. Database Query Strings

Database search date	Query string
	(57117-31-4[rn] OR 57117-32-5[rn] OR 57117-33-6[rn] OR 57117-34-7[rn] OR 57117-35-8[rn] OR 57117-36-9[rn] OR 57117-37-0[rn] OR 57117-38-1[rn] OR 57117-39-2[rn] OR 57117-40-5[rn] OR 57117-41-6[rn] OR 57117-42-7[rn] OR 57117-43-8[rn] OR 57117-44-9[rn] OR 58802-14-5[rn] OR 58802-15-6[rn] OR 58802-16-7[rn] OR 58802-17-8[rn]) AND (TSCATS[org]) Year of Publication 1992 through 2019
	(58802-18-9[rn] OR 58802-19-0[rn] OR 58802-20-3[rn] OR 58802-21-4[rn] OR 60390-27-4[rn] OR 60851-34-5[rn] OR 62615-08-1[rn] OR 64126-85-8[rn] OR 64126-86-9[rn] OR 64126-87-0[rn] OR 64560-13-0[rn] OR 64560-14-1[rn] OR 64560-15-2[rn] OR 64560-16-3[rn] OR 64560-17-4[rn] OR 66794-59-0[rn] OR 67481-22-5[rn] OR 67517-48-0[rn]) AND (TSCATS[org]) Year of Publication 1992 through 2019
	(67562-39-4[rn] OR 67562-40-7[rn] OR 67652-39-5[rn] OR 69433-00-7[rn] OR 69698-57-3[rn] OR 69698-58-4[rn] OR 69698-59-5[rn] OR 69698-60-8[rn] OR 70648-13-4[rn] OR 70648-14-5[rn] OR 70648-15-6[rn] OR 70648-16-7[rn] OR 70648-18-9[rn] OR 70648-19-0[rn] OR 70648-20-3[rn] OR 70648-21-4[rn] OR 70648-22-5[rn] OR 70648-23-6[rn]) AND (TSCATS[org]) Year of Publication 1992 through 2019
	(70648-24-7[rn] OR 70648-25-8[rn] OR 70648-26-9[rn] OR 70872-82-1[rn] OR 71998-72-6[rn] OR 71998-73-7[rn] OR 71998-74-8[rn] OR 71998-75-9[rn] OR 72918-21-9[rn] OR 74423-73-7[rn] OR 74918-40-4[rn] OR 74992-96-4[rn] OR 74992-97-5[rn] OR 74992-98-6[rn] OR 75198-38-8[rn] OR 75627-02-0[rn] OR 76621-12-0[rn] OR 79060-60-9[rn]) AND (TSCATS[org]) Year of Publication 1992 through 2019
	(81638-37-1[rn] OR 82911-58-8[rn] OR 82911-59-9[rn] OR 82911-60-2[rn] OR 82911-61-3[rn] OR 83636-47-9[rn] OR 83690-98-6[rn] OR 83704-21-6[rn] OR 83704-22-7[rn] OR 83704-23-8[rn] OR 83704-24-9[rn] OR 83704-25-0[rn] OR 83704-26-1[rn] OR 83704-27-2[rn] OR 83704-28-3[rn] OR 83704-29-4[rn] OR 83704-30-7[rn] OR 83704-31-8[rn]) AND (TSCATS[org]) Year of Publication 1992 through 2019
	(83704-32-9[rn] OR 83704-33-0[rn] OR 83704-34-1[rn] OR 83704-35-2[rn] OR 83704-36-3[rn] OR 83704-37-4[rn] OR 83704-38-5[rn] OR 83704-39-6[rn] OR 83704-40-9[rn] OR 83704-41-0[rn] OR 83704-42-1[rn] OR 83704-43-2[rn] OR 83704-44-3[rn] OR 83704-45-4[rn] OR 83704-46-5[rn] OR 83704-47-6[rn] OR 83704-48-7[rn] OR 83704-49-8[rn]) AND (TSCATS[org]) Year of Publication 1992 through 2019
	(83704-50-1[rn] OR 83704-51-2[rn] OR 83704-52-3[rn] OR 83704-53-4[rn] OR 83704-54-5[rn] OR 83704-55-6[rn] OR 83710-07-0[rn] OR 83719-40-8[rn] OR 84761-86-4[rn] OR 89059-46-1[rn] OR 91538-83-9[rn] OR 91538-84-0[rn] OR 92341-04-3[rn] OR 92341-05-4[rn] OR 92341-06-5[rn] OR 92341-07-6[rn] OR 94538-00-8[rn] OR 94538-01-9[rn] OR 94538-02-0[rn] OR 94570-83-9[rn]) AND (TSCATS[org]) Year of Publication 1992 through 2019
Toxcenter	
07/2019	FILE 'TOXCENTER' ENTERED AT 17:35:48 ON 10 JUL 2019

Table B-2. Database Query Strings

Database search date	Query string
	CHARGED TO COST=EH038.02.01.LB.01

	L1 (8359)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 (879)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 (493)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 (8541)SEA FILE=TOXCENTER L1 OR L2 OR L3
	L5 (7817)SEA FILE=TOXCENTER 24478-72-6 OR 24478-73-7 OR 24478-74-8 OR 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
	L6 (5707)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
	L7 (4230)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
	L8 (4617)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
	L9 (4849)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
	L10 (265)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
	L11 (276)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

Table B-2. Database Query Strings

Database search date	Query string
	83704-47-6 OR 83704-48-7 OR 83704-49-8
	L12 (522)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
	L13 (8578)SEA FILE=TOXCENTER L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12
	L14 (8578)SEA FILE=TOXCENTER L4 OR L13
	L15 (8368)SEA FILE=TOXCENTER L14 NOT PATENT/DT
	L16 (8344)SEA FILE=TOXCENTER L15 NOT TSCATS/FS
	L17 (6869)SEA FILE=TOXCENTER L16 AND PY>1991
	L18 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L19 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L20 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L21 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L22 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L23 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L24 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L25 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L26 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L27 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L28 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L29 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L30 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L31 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L32 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L33 QUE (ENDOCRIN? AND DISRUPT?)
	L34 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L35 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L36 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)

Table B-2. Database Query Strings

Database search date	Query string
	L37 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L38 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L39 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L40 QUE (NEPHROTOX? OR HEPATOTOX?) L41 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) L42 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L43 QUE L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40 OR L41 OR L42 L44 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L45 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L46 QUE L43 OR L44 OR L45 L47 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L48 QUE L46 OR L47 L49 (2655)SEA FILE=TOXCENTER L17 AND L48 L50 2460 DUP REM L49 (195 DUPLICATES REMOVED) --------- D SCAN L50

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
07/2019	Compounds searched: 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	
07/2019	"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"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"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" "chlorodibenzofuran" "polychlorodibenzofuran" "monochlorodibenzofuran" "dichlorodibenzofuran" "heptachlorodibenzofuran" "octachlorodibenzofuran" "perchlorodibenzofuran" "trichlorodibenzofuran" "tetrachlorodibenzofuran" "pentachlorodibenzofuran" "hexachlorodibenzofuran"
NIH RePORTER	
04/2020	Text Search: dibenzofuran OR dibenzofurans (Advanced), Search in: Projects Admin IC: All, 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" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: "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" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: "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

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	dibenzofurans" OR "heptachloro dibenzofurans" OR "octachloro dibenzofurans" OR "perchloro dibenzofurans" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: "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), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: ("chlorinated" AND "dibenzofuran") OR ("polychlorinated" AND "dibenzofuran") (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: (("monochlorinated" OR "dichlorinated" OR "trichlorinated" OR "tetrachlorinated" OR "pentachlorinated" OR "hexachlorinated" OR "heptachlorinated" OR "octachlorinated" OR "perchlorinated") AND "dibenzofuran") (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: (("dipolychlorinated" OR "tripolychlorinated" OR "tetrapolychlorinated" OR "pentapolychlorinated" OR "hexapolychlorinated" OR "heptapolychlorinated" OR "octapolychlorinated" OR "perpolychlorinated" OR "polypolychlorinated") AND "dibenzofuran") (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: ("chlorinated" AND "dibenzofurans") OR ("polychlorinated" AND "dibenzofurans") (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: (("monochlorinated" OR "dichlorinated" OR "trichlorinated" OR "tetrachlorinated" OR "pentachlorinated" OR "hexachlorinated" OR "heptachlorinated" OR "octachlorinated" OR "perchlorinated") AND "dibenzofurans") (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: (("dipolychlorinated" OR "tripolychlorinated" OR "tetrapolychlorinated" OR "pentapolychlorinated" OR "hexapolychlorinated" OR "heptapolychlorinated" OR "octapolychlorinated" OR "perpolychlorinated" OR "polypolychlorinated") AND "dibenzofurans") (Advanced), Search in: Projects Admin IC: All, 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), Search in: Projects Admin IC: All, Fiscal Year: Active Projects

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	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 "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" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: "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 "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-" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: "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

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"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-" 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-" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2019 results were:

- Number of records identified from PubMed, Toxline, and TOXCENTER (after duplicate removal): 6,190
- Number of records identified from other strategies: 74
- Total number of records to undergo literature screening: 6,264

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.

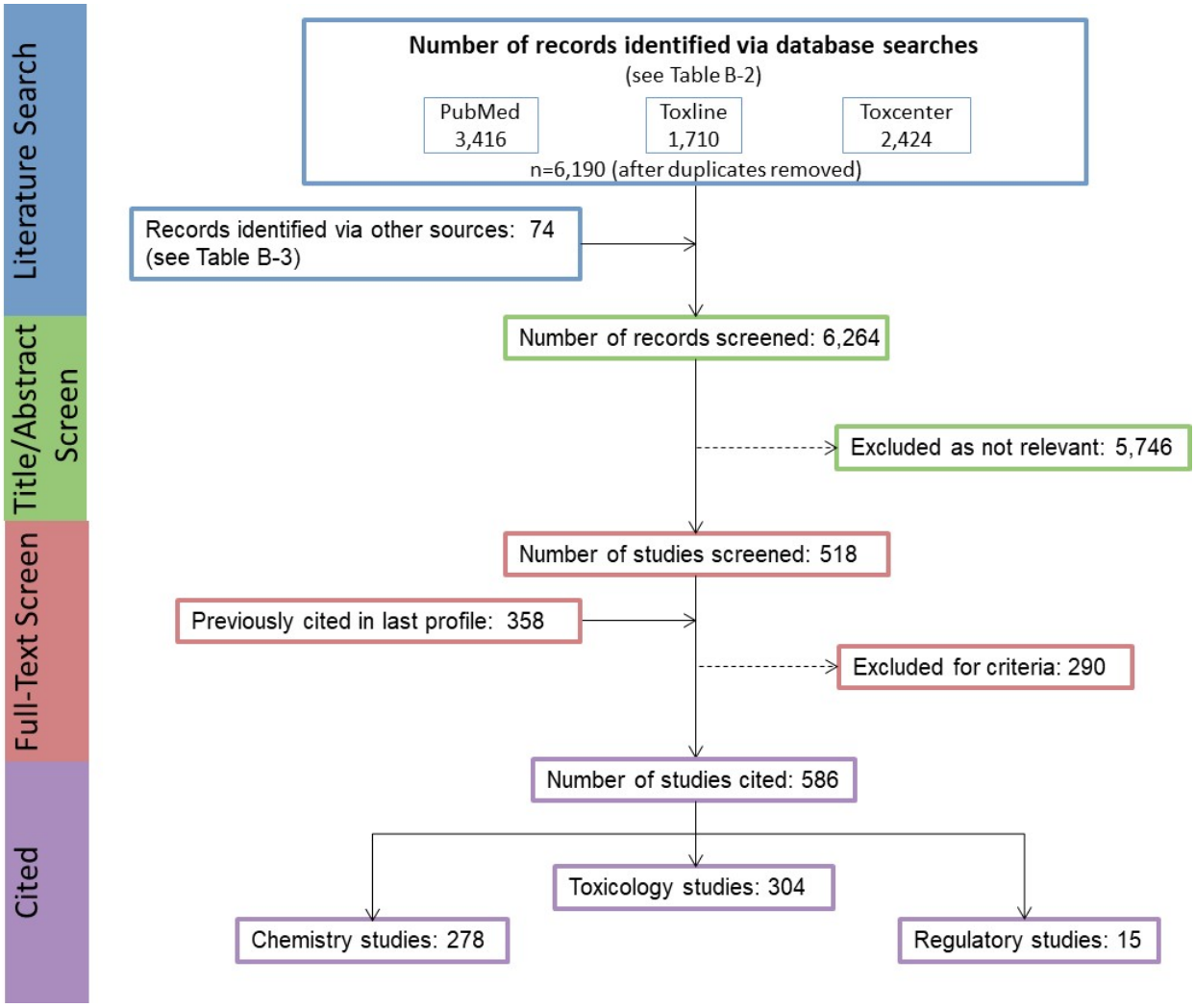
- Number of titles and abstracts screened: 6,264
- Number of studies considered relevant and moved to the next step: 518

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: 518
- Number of studies cited in the pre-public draft of the toxicological profile: 358
- Total number of studies cited in the profile: 586

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.

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

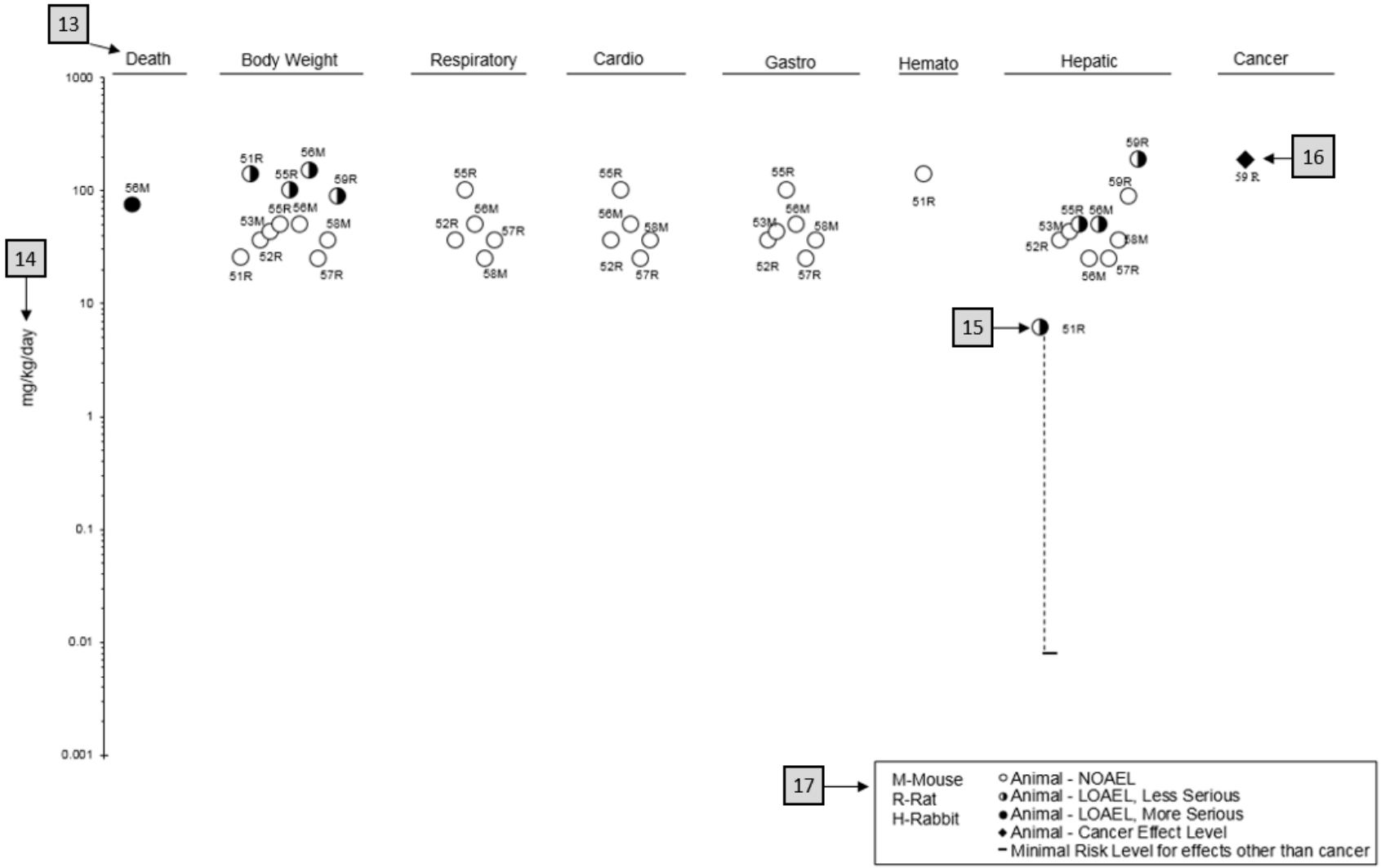
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 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).

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:

https://www.atsdr.cdc.gov/emes/health_professionals/index.html for more information on resources for clinicians.

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 aquatiic 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 level/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 equivqlent
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