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.

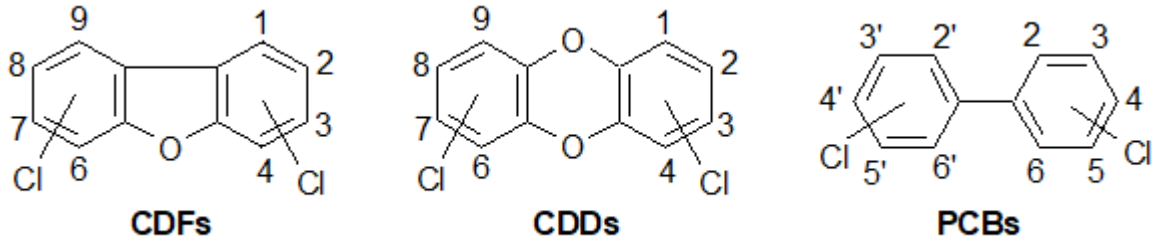
The higher chlorinated congeners of CDFs are particularly persistent in the environment and degrade slowly in air, water, and soil. They have been detected in remote areas far from their point of release and are subject to long-range transport. The higher chlorinated congeners are not highly volatile 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

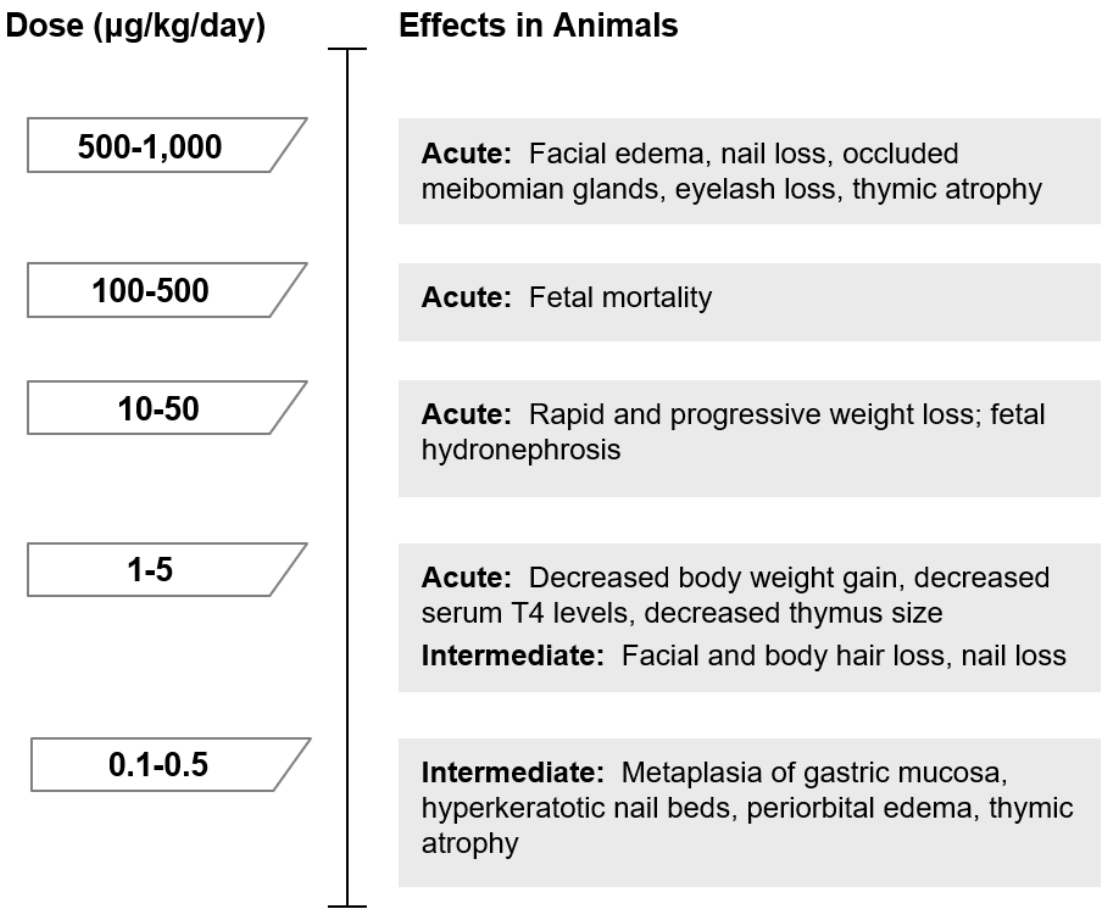


Figure 1-3. Health Effects Found in Animals Following Oral Exposure to 1,2,3,7,8-Pentachlorodibenzofuran

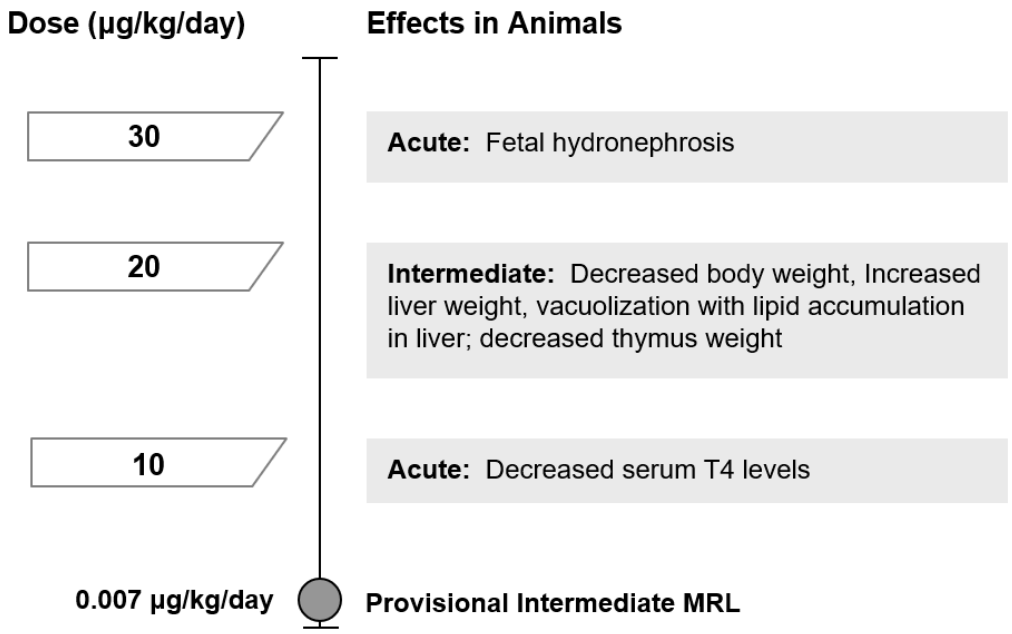


Figure 1-4. Health Effects Found in Animals Following Oral Exposure to 2,3,4,7,8-Pentachlorodibenzofuran

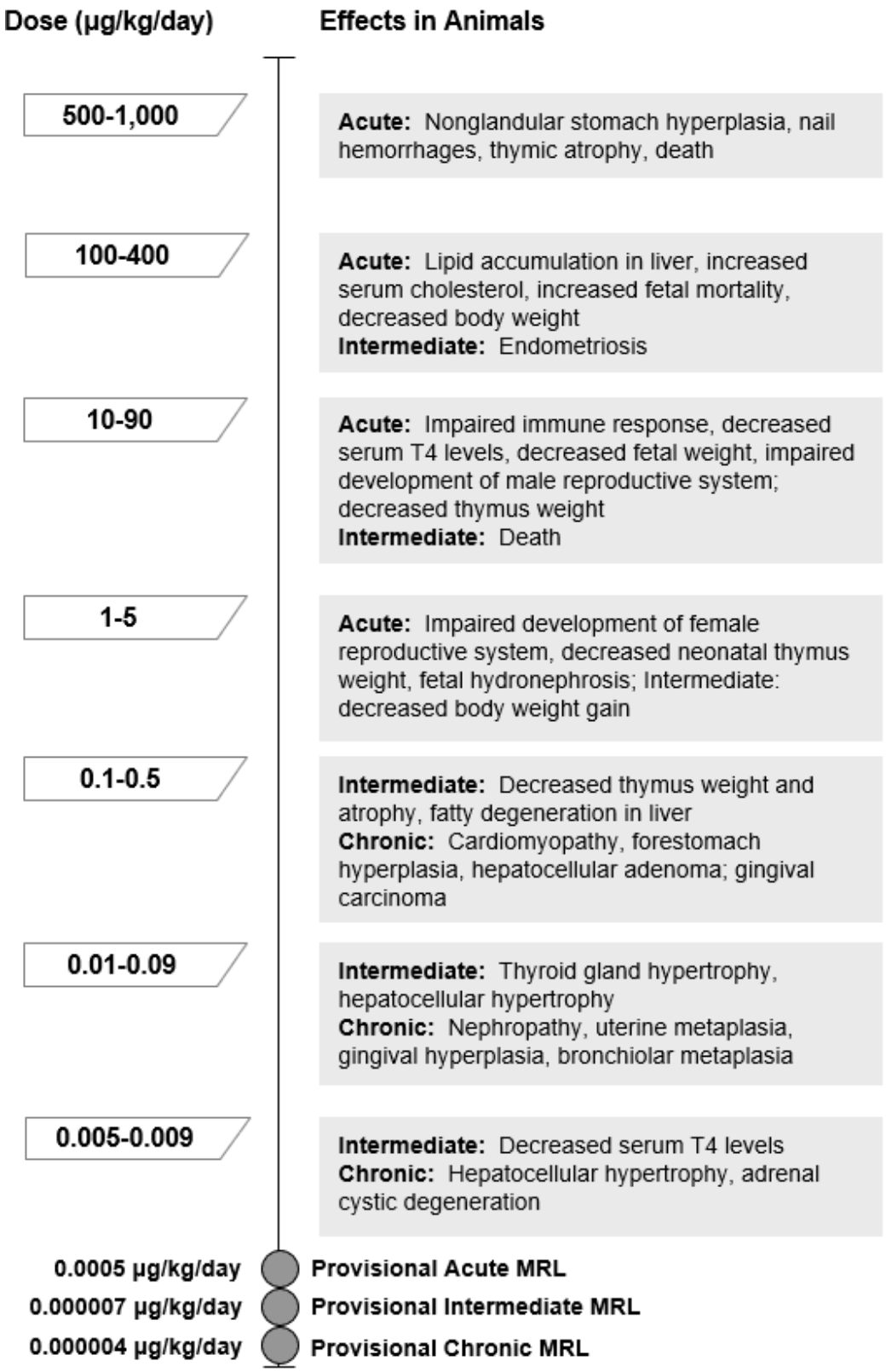
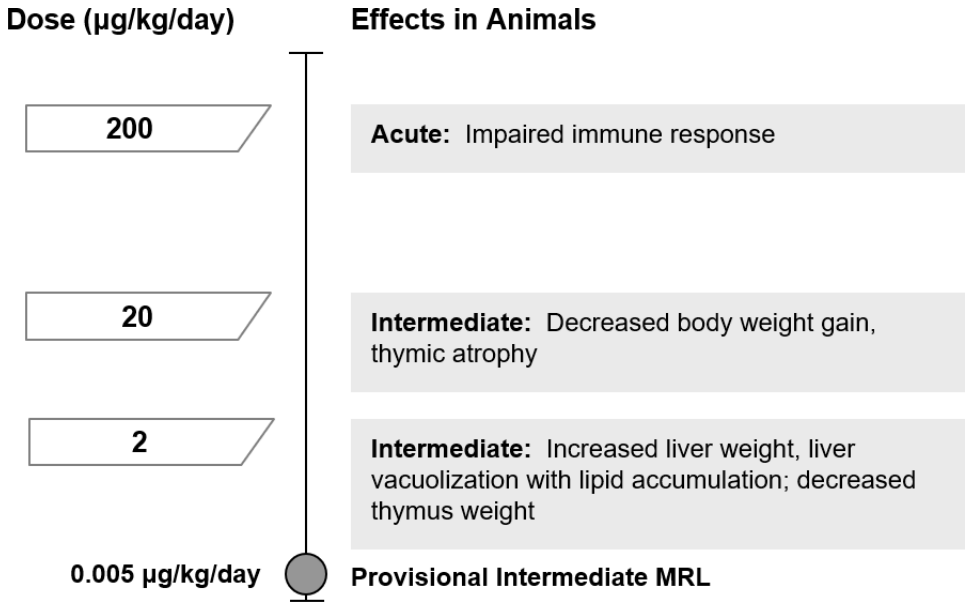


Figure 1-5. Health Effects Found in Animals Following Oral Exposure to 1,2,3,6,7,8-Hexachlorodibenzofuran



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.

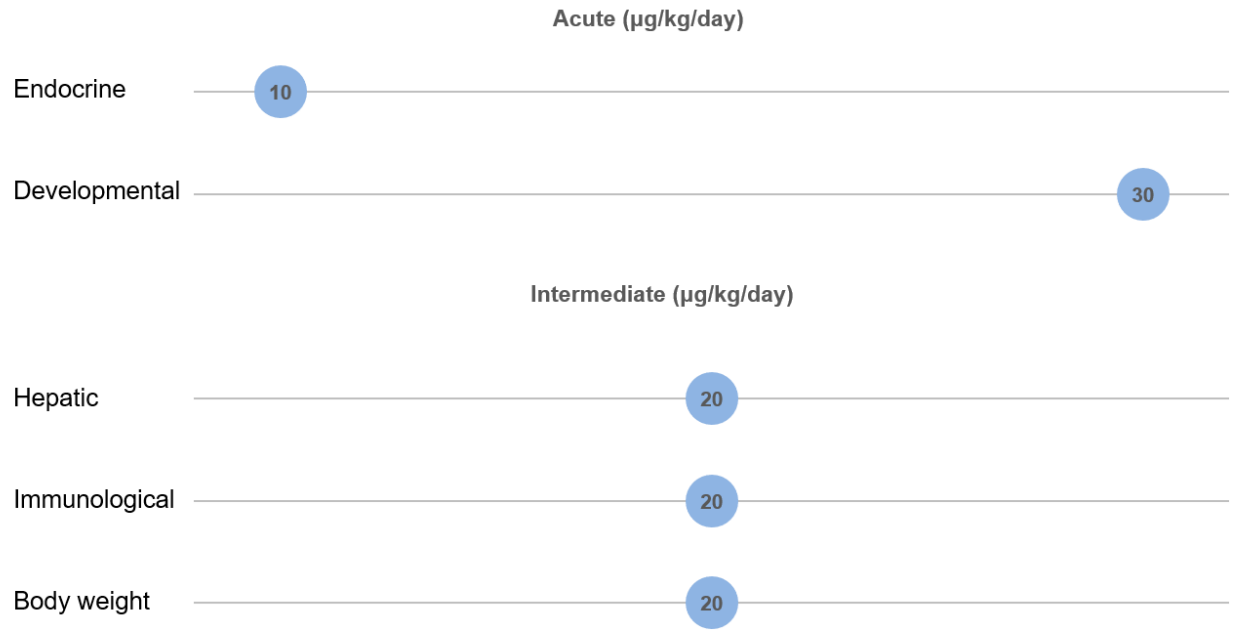


Figure 1-7. Summary of Sensitive Targets of 2,3,4,7,8-Pentachlorodibenzofuran – Oral

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.

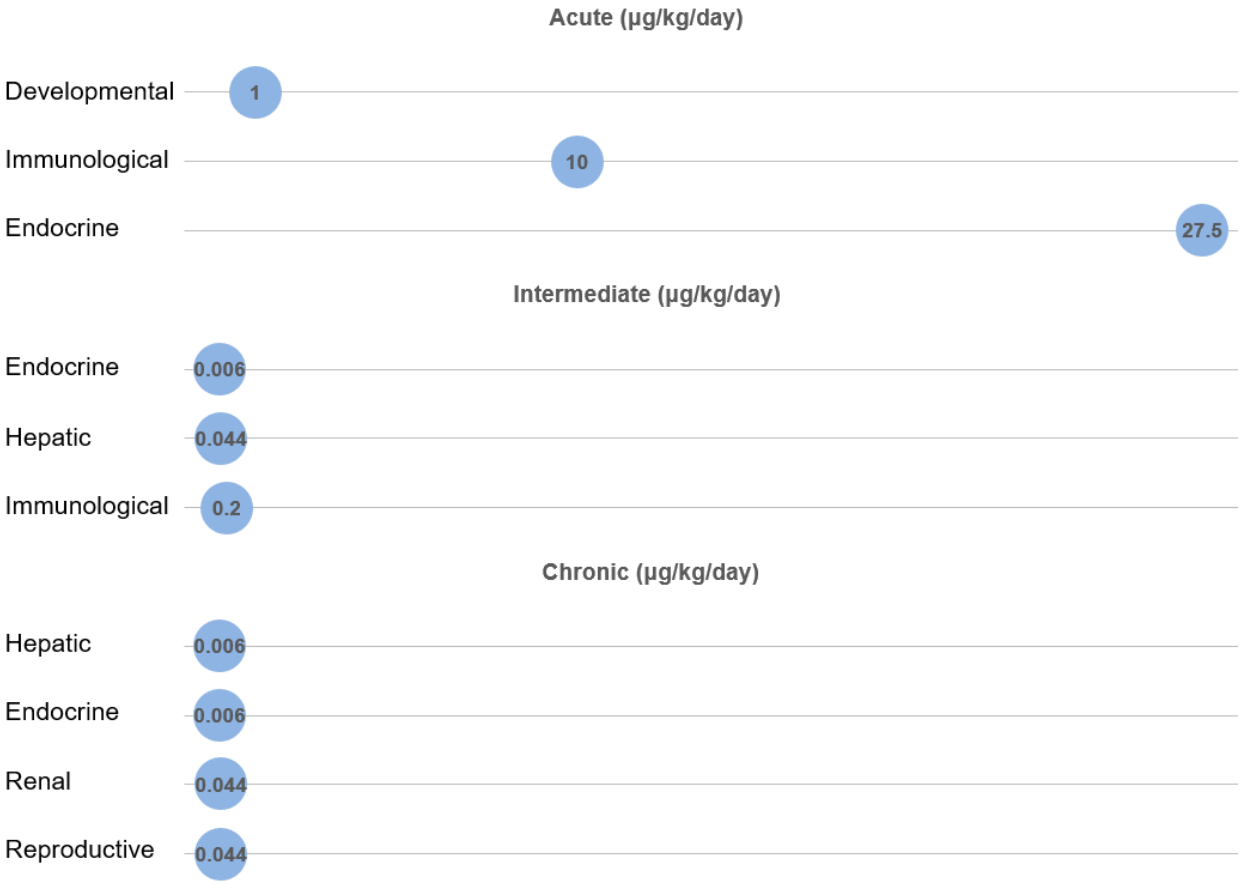


Figure 1-8. Summary of Sensitive Targets of 1,2,3,6,7,8-Hexaachlorodibenzofuran – Oral

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.

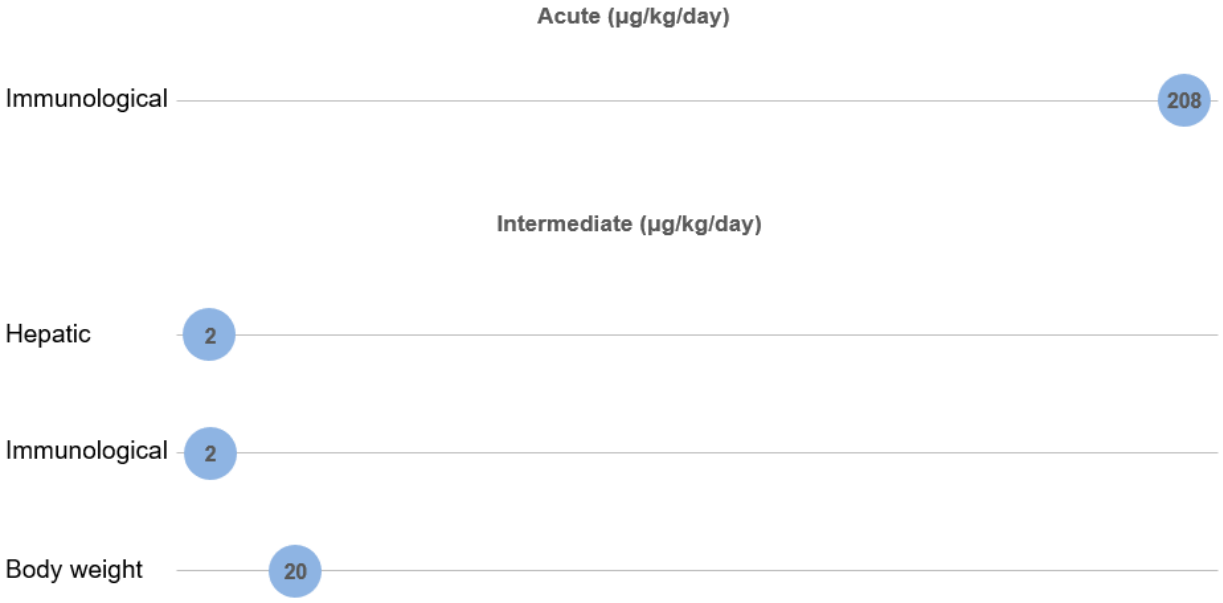


Table 1-1. Minimal Risk Levels (MRLs) for 1,2,3,7,8-Pentachlorodibenzofuran[a]

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