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

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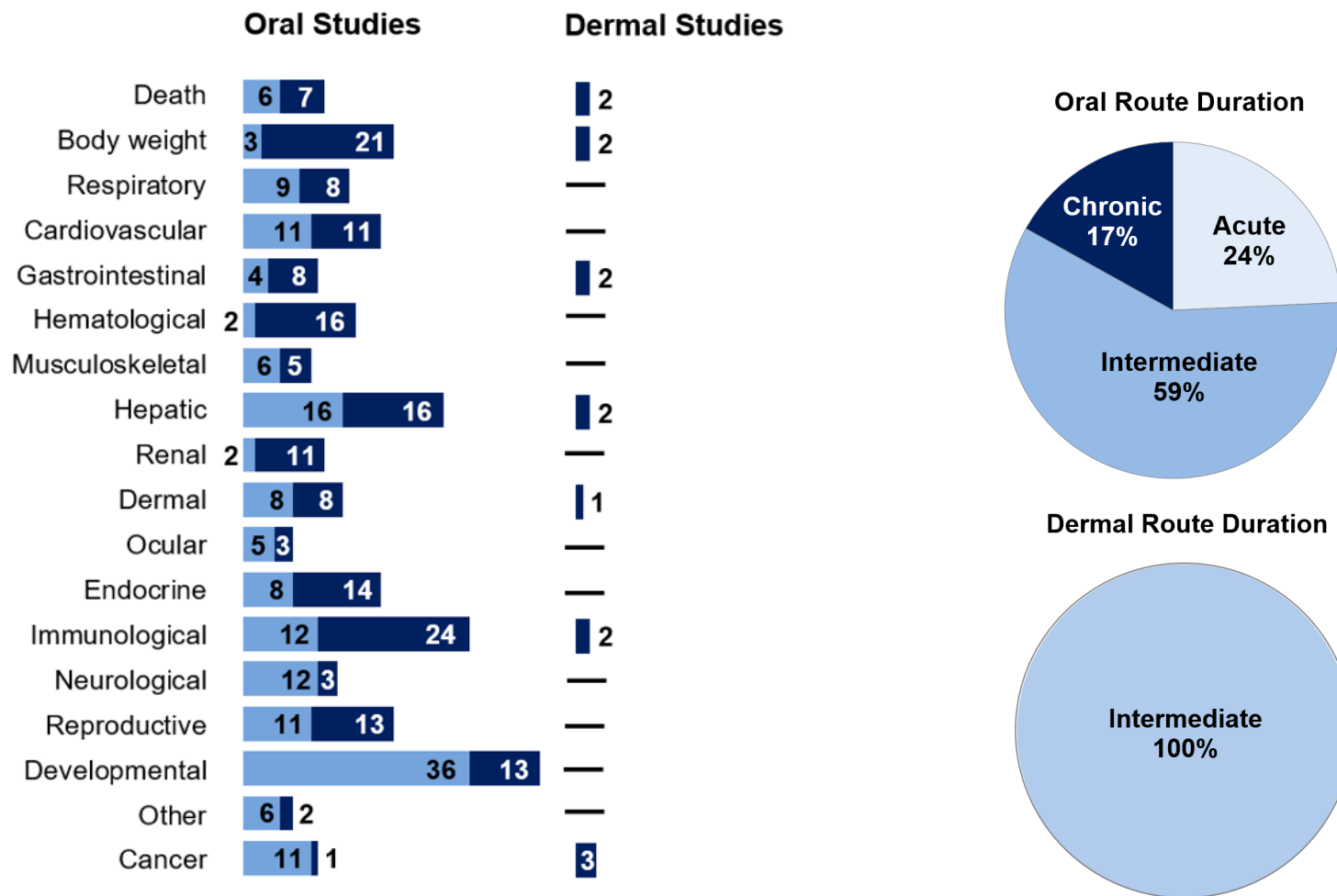
*Includes studies discussed in Chapter 2; the number of studies include those finding no effect; some studies examined multiple endpoints.

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 an 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 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 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).

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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 sensitive developmental endpoints in highly exposed populations would be 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 a whole-weight basis, in adipose tissue. CDFs 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 breast 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

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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 CDFs 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 absorption (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.

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Studies regarding urinary or fecal excretion of CDFs in humans were not located; however, elimination of CDFs through human 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). Additional studies are needed to determine the primary route of excretion in humans.

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 is 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 exposure risk.

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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 un-adsorbed 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 bio-transfer 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 (2022) database.