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 CDDs 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 CDDs.

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

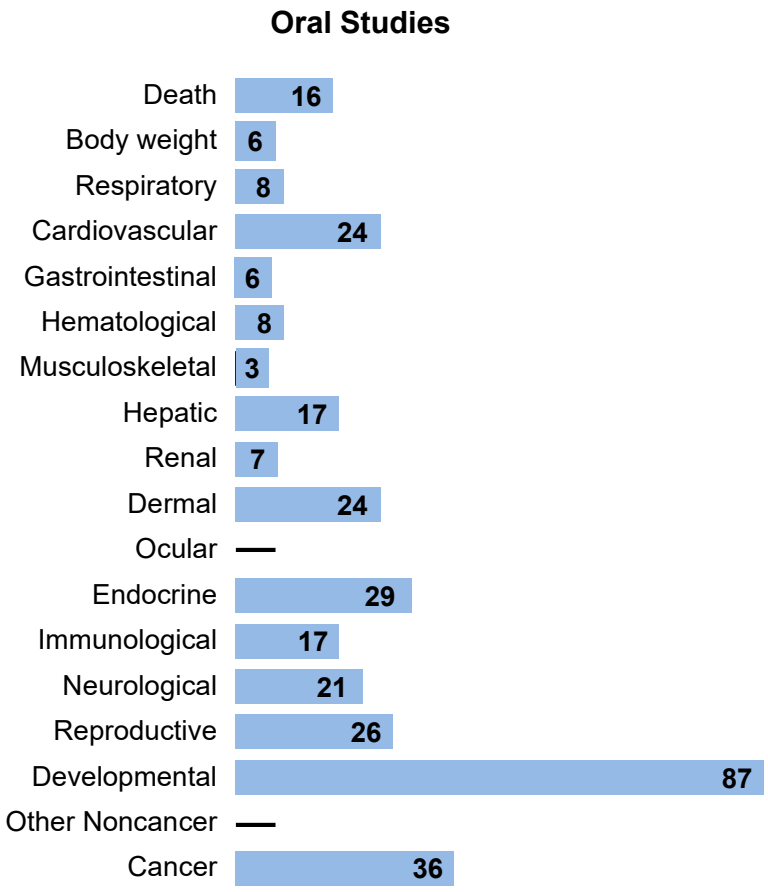
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to CDDs that are discussed in Chapter 2 are summarized in Figures 6-1, 6-2, and 6-3. The purpose of this figure is to illustrate the information concerning the health effects of CDDs. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figures 6-1, 6-2, and 6-3 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.

Figure 6-1. Summary of Existing Human Health Effects Studies on Chlorinated Dibenzo-*p*-Dioxins (CDDs) by Route and Endpoint*

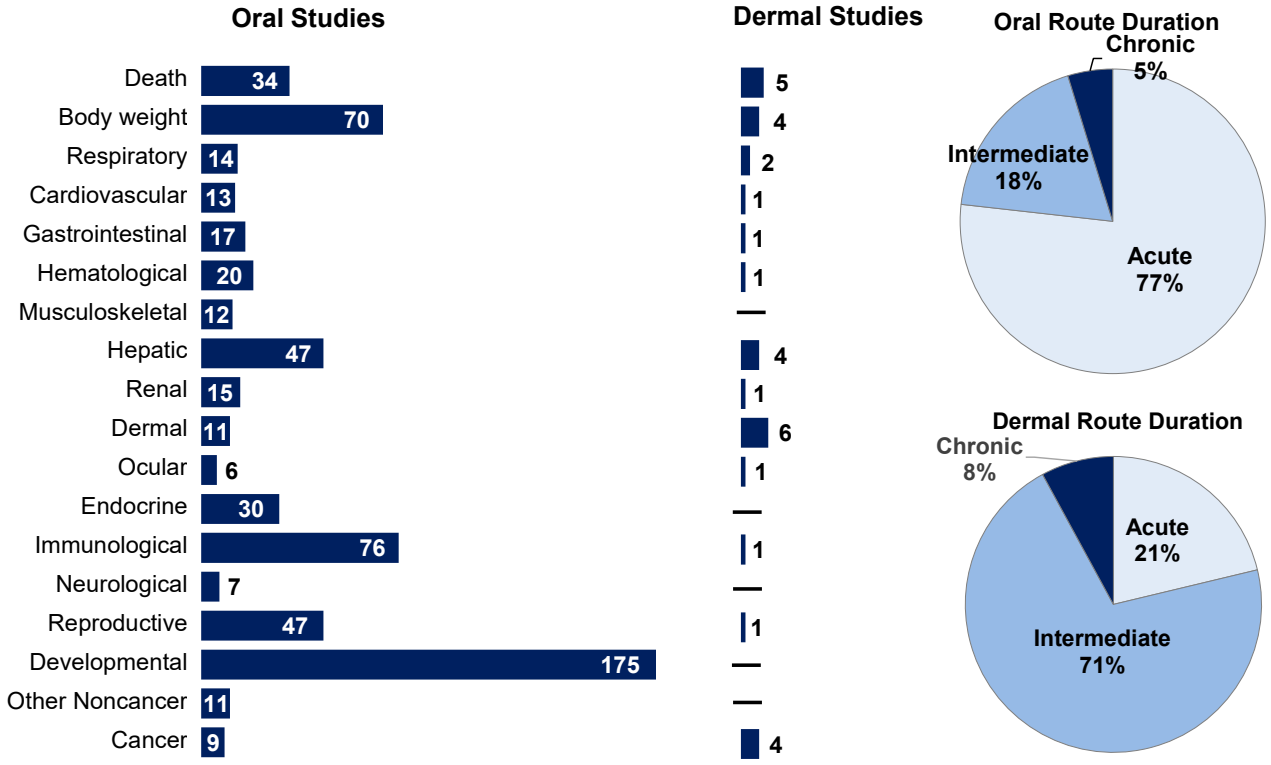
Potential body weight, liver, and kidney effects were the most studied endpoints
The majority of the studies examined oral exposure in **humans**



*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; studies may have examined more than one endpoint. No inhalation or dermal studies in humans were located.

Figure 6-2. Summary of Existing Animal Health Effects Studies on 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (2,3,7,8-TCDD) by Route and Endpoint*

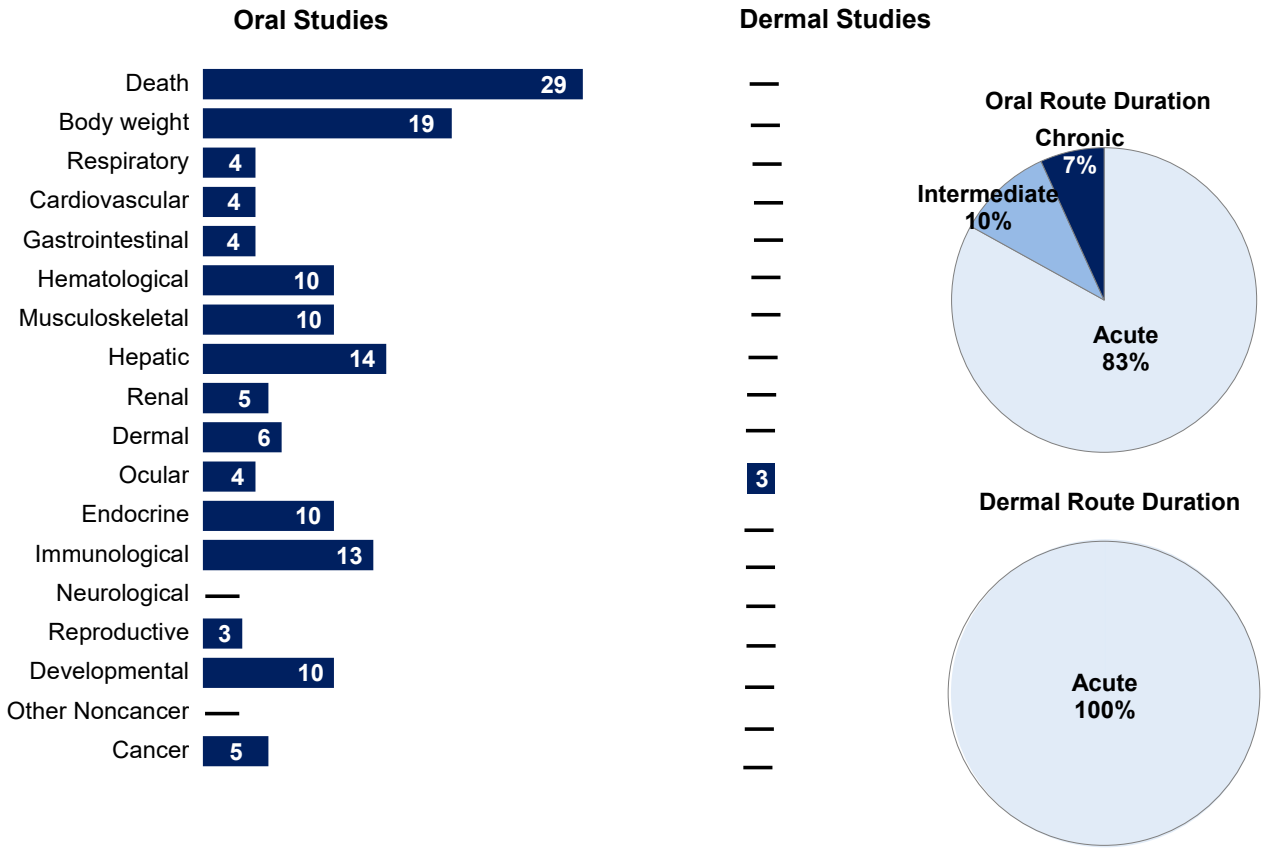
Potential body weight, liver, and kidney effects were the most studied endpoints
The majority of the studies examined oral exposure in animals



*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; studies may have examined more than one endpoint. No inhalation studies in animals were located.

Figure 6-3. Summary of Existing Health Effects Animal Studies on Other Chlorinated Dibenzo-*p*-Dioxins (CDDs) by Route and Endpoint*

Potential body weight, liver, and kidney effects were the most studied endpoints
The majority of the studies examined oral exposure in animals



*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; studies may have examined more than one endpoint. No inhalation studies in animals were located.

Acute-Duration MRLs. Acute-duration exposure of humans to 2,3,7,8-TCDD can cause chloracne and hepatic effects (Goldman 1972; Reggiani 1980). Specifying the route of exposure in these human cases is difficult because the individuals were probably exposed by a combination of routes. Furthermore, human data did not provide any information regarding exposure levels, and co-exposure to other chemicals confound the results. Also, in most cases, the exposed subjects were examined long after exposure occurred. No inhalation studies were identified that could be used to derive inhalation MRLs for 2,3,7,8-TCDD or other CDD congeners. Since inhalation exposure is a relevant route for humans, additional studies are needed to evaluate dose-response relationships. The acute oral toxicity of 2,3,7,8-TCDD has been extensively studied in animals; the most sensitive targets of toxicity are developmental, immunological, reproductive, hepatic, and endocrine endpoints. The database was considered adequate for derivation of an acute-duration oral MRL for 2,3,7,8-TCDD.

No information was located regarding health effects of other congeners in humans, and limited data exist about effects caused by an acute-duration exposure to these congeners in animals. Although studies are available for several other CDD congeners—2-MCDD, 2,3,7-TrCDD, 1,2,3,4-TCDD, 1,2,3,7,8-PeCDD, 1,2,4,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD—the databases were not considered adequate for derivation of acute-duration oral MRLs. The information would be useful for populations living near hazardous waste sites that may be exposed to CDDs for acute durations.

Intermediate-Duration MRLs. Intermediate-duration exposure of humans to CDDs has occurred after industrial accidents or in population groups (e.g., Vietnam War veterans, Vietnamese communities, and pesticide production workers and applicators) exposed to CDD-contaminated herbicides. As stated above, the route of exposure and exposure levels cannot be exactly determined. The oral toxicity of 2,3,7,8-TCDD following oral exposure has been extensively evaluated in animals. The main adverse effects in animals following intermediate-duration oral exposure to 2,3,7,8-TCDD include developmental toxicity, immunotoxicity, reproductive toxicity, and hepatotoxicity. However, the database was not considered adequate for derivation of an intermediate-duration oral MRL for 2,3,7,8-TCDD because the lowest adverse effect level was for a serious health outcome (decreased pup survival). The intermediate-duration oral toxicity data for 2,3-DCDD, 2,7-DCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD have also been evaluated; however, the data were not considered adequate for derivation of MRLs. No data were located regarding toxicity or toxicokinetics in animals after intermediate-duration inhalation exposure to CDDs. Information obtained

from a 90-day inhalation exposure study would be relevant to people living near hazardous waste sites who may be exposed to CDDs for similar durations or much longer time periods.

Chronic-Duration MRLs. A number of epidemiology studies have examined the toxicity of CDDs following chronic-duration exposure to phenoxy herbicides and chlorophenols contaminated with 2,3,7,8-TCDD. Although a number of effects have been observed, interpretation of the results is confounded by a number of factors including lack of adequate exposure information, long postexposure periods, concomitant exposure to other chemicals, and small cohorts. Follow-up medical surveillance of subjects with known past high exposure to 2,3,7,8-TCDD would provide information on the possibility that adverse effects could manifest later in adult life when compounded by normal age-related changes. In addition, further research is needed in areas for which the animal data have demonstrated exposure related effects, but the human data are inconclusive. Chronic-duration oral studies of 2,3,7,8-TCDD in animals have identified several targets of toxicity; adverse developmental, reproductive, and immunological effects were observed at the lowest dose tested. These data were used to derive a chronic-duration oral MRL for 2,3,7,8-TCDD. The chronic-duration oral toxicity of 2,7-DCDD was also evaluated; however, the database was not considered adequate for derivation of an MRL because immunotoxicity has not been evaluated. Chronic-duration oral studies are not available for other congeners.

No studies were located regarding chronic effects of CDD exposure by the inhalation route. Toxicokinetic inhalation data and chronic-duration studies would be useful for assessing the risk levels for people living near municipal, medical, and industrial waste incinerators who can be exposed for chronic durations to CDDs by this route.

Health Effects.

Reproductive. Data from studies on reproductive effects in humans (Aschengrau and Monson 1989; Egeland et al. 1994; Forsberg and Nordstrom 1985; Henriksen et al. 1996; Phuong et al. 1989; Smith et al. 1982; USAF 1991; Wolfe et al. 1985, 1995) are inconclusive and are limited by confounding factors such as small cohorts, co-exposure to other chemicals, and inadequate exposure data. Better controlled epidemiological studies measuring 2,3,7,8-TCDD exposure levels or 2,3,7,8-TCDD body burdens would be useful to assess the human reproductive toxicity risk. Reproductive effects have been observed in oral animal studies. Increased incidences of pre- and post-implantation losses were observed in 2,3,7,8-TCDD-exposed rodents (Giavini et al. 1983; Neubert and Dillmann 1972; Smith et al. 1976; Sparschu et al. 1971a), rabbits (Giavini et

al. 1982), and monkeys (McNulty 1985). Adverse effects have also been observed in the reproductive organs (decreased weight), hormone levels, and gametes of male rats (Khera and Ruddick 1973; Moore et al. 1985) and nonpregnant female rats (Li et al. 1995a, 1995b). None of the acute-duration exposure studies assessed the potential of CDDs to impair fertility; data on fertility would be useful in assessing potential effects in humans exposed to CDDs for a short period of time. Reduced fertility (Bowman et al. 1989b; Hong et al. 1989; Murray et al. 1979; Schantz et al. 1992) and increased incidence of abortions (Bowman et al. 1989b; Hong et al. 1989; McNulty 1984; Schantz et al. 1992) were observed in animals exposed for intermediate or chronic durations. Reproductive effects have also been observed in animals exposed to mixed HxCDD (Schwetz et al. 1973), but not following exposure to 2-MCDD, 2,3-DCDD, 2,7-DCDD, 1,2,3,4-TCDD, or OCDD (Khera and Ruddick 1973). Data on the reproductive toxicity of CDD following dermal exposure are limited to a single animal study that found no adverse effects on reproductive organs of mice chronically exposed to 2,3,7,8-TCDD (NTP 1982a). No animal inhalation reproductive toxicity studies were located. Additional animal inhalation and dermal reproductive studies, particularly studies that assessed reproductive performance, would be useful to assess the possible risk in humans exposed to CDDs by these routes.

Developmental. Studies in humans and animals indicated that 2,3,7,8-TCDD can cross the placenta and is excreted in milk (Fürst et al. 1989; Schecter et al. 1989b, 1989d, 1990a). Studies on the developmental toxicity of 2,3,7,8-TCDD in humans are inconclusive. Some studies found significant increases in the risk of certain birth defects (Aschengrau and Monson 1990; Erickson et al. 1984; Hanify et al. 1981; Nelson et al. 1979; Phuong et al. 1989; Wolfe et al. 1985, 1995), while other studies found no significant alterations (Bisanti et al. 1980; Mastroiacovo et al. 1988; Townsend et al. 1982). However, a number of limitations (e.g., lack of exposure data, small sample sizes, and lack of reliable data for birth defects prior to 2,3,7,8-TCDD exposure) limit the interpretation of the results of these studies. Epidemiology studies that measure exposure concentrations or body burdens would be useful to determine if 2,3,7,8-TCDD and other CDD congeners are human developmental toxicants. Developmental toxicity has been observed in animals orally exposed to 2,3,7,8-TCDD (Abbott and Birnbaum 1989a; Abbott et al. 1992; Bjerke and Peterson 1994; Bjerke et al. 1994a, 1994b; Bowman et al. 1989a, 1989b; Brown et al. 1998; Courtney 1976; Couture-Haws et al. 1991b; Giavini et al. 1983; Gray and Ostby 1995; Gray et al. 1995; Håkansson et al. 1987; Huuskonen et al. 1994; McNulty 1985; Moore et al. 1973; Neubert and Dillmann 1972; Roman et al. 1998a, 1998b; Schantz et al. 1992; Silkworth et al. 1989b; Smith et al. 1976; Thomas and Hinsdill 1979; Weber et al. 1985), 2,7-DCDD (Khera and Ruddick

1973; Schwetz et al. 1973), mixed HxCDD (Schwetz et al. 1973), and OCDD (Schwetz et al. 1973). The most common effects were cleft palate, hydronephrosis, impaired development of the reproductive system, immunotoxicity, and death. No studies were located regarding developmental effects in animals after inhalation and dermal exposure. Such studies would be useful for extrapolating the possible risk to human populations exposed environmentally by these routes.

Immunotoxicity. Studies in humans did not provide conclusive evidence regarding immunotoxicity of CDDs (Ernst et al. 1998; Jansing and Korff 1994; Jennings et al. 1988; Jung et al. 1998; Mocarelli et al. 1986; Neubert et al. 1993, 1995; Reggiani 1980; Stehr et al. 1986; Svensson et al. 1994; Tonn et al. 1996; USAF 1991; Webb et al. 1989; Wolfe et al. 1985). Studies in animals indicated that CDDs are immunosuppressive (Kerkvliet 1995). 2,3,7,8-TCDD induced thymic atrophy or thymic weight changes after oral (Hanberg et al. 1989; McConnell et al. 1978b), dermal (Hebert et al. 1990), and parenteral exposure (Gorski et al. 1988; Olson et al. 1980a). Suppressed cell-mediated and humoral immunity was found in rodents after intermediate-duration exposure (Vos et al. 1973). Similarly, immunotoxic effects were found after oral exposure of rodents to 2,7-DCDD or to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD (Holsapple et al. 1986; NCI/NTP 1980). At least in mice, differences in responsiveness to CDDs' immunotoxicity *in vivo* segregated with the Ah locus (Nagayama et al. 1989; Vecchi et al. 1983).

Studies in animals aimed at identifying 2,3,7,8-TCDD-sensitive immune endpoints that can also be measured in humans would be valuable to determine correlative changes in the biomarker and immune function. However, this can be done only after establishing a database of normal values for the clinical immunology endpoints that may be used as biomarkers of immune function in immunotoxicity assessments. It is also important to determine in animals how well changes in lymphoid organs correlate with changes in the expression of lymphocyte subset/activation markers in peripheral blood. The role of the AhR in the immunotoxicity of 2,3,7,8-TCDD needs to be researched in species other than mice. In addition, the role of AhR-independent processes in 2,3,7,8-TCDD-induced immunotoxicity needs to be examined further. Such actions may include changes in intracellular calcium or in the activity of kinase/phosphatase systems, or interactions with hormone systems. A battery of immune function tests in human cohorts exposed to CDDs would be useful for detecting the immunotoxic responses in exposed individuals. The ability of CDD-exposed individuals to mount an integrated functional response

to a novel antigen, such as hepatitis B vaccine, would provide a broad measure of immune function in exposed human populations.

Neurotoxicity. Studies in Vietnam veterans could not conclusively demonstrate cognitive or other central nervous system deficits (Goetz et al. 1994). Neurological examinations revealed neurological effects in humans exposed to a CDD-contaminated environment (Pocchiari et al. 1979) and in occupational settings (Goldman 1972; Jirasek et al. 1976; Klawans 1987; Pazderova-Vejlupkova et al. 1981) shortly following exposure, but reports with comparison groups do not offer clear evidence that exposure to 2,3,7,8-TCDD is associated with chronic peripheral neuropathy (Suskind and Hertzberg 1984; Sweeney et al. 1993). No notable neurological effects were found in laboratory animals after oral or dermal exposure. The existing information suggests that in adults, no long-term neurologic affects were caused by high exposure to 2,3,7,8-TCDD-contaminated materials. However, the possibility exists that subtle central nervous system changes acquired in early adulthood could manifest later in adult life when compounded by normal age-related changes in the central nervous system (Goetz et al. 1994). Thus, it would be of interest to include tests of neurological function in ongoing prospective studies of 2,3,7,8-TCDD-exposed populations to determine if neurological effects occur as the exposed population ages.

Epidemiology and Human Dosimetry Studies. Epidemiology studies have investigated the toxicity of 2,3,7,8-TCDD in populations exposed in the workplace or in the contaminated environment (after industrial accidents or herbicide spraying) and in Vietnam veterans exposed to Agent Orange. The interpretation of the results of most of these studies is confounded by such factors as unknown levels of exposure, too short or too long postexposure periods, and small cohorts. Well-conducted epidemiological and occupational studies that quantify exposure levels would be useful to assess the risk for the main endpoints of concern (i.e., reproductive, developmental, immunotoxic effects, and cancer). Some studies have measured the levels of 2,3,7,8-TCDD and related compounds in serum lipid; these levels can then be used to estimate body burden at the time of exposure. There are a number of drawbacks associated with extrapolating body burdens back to the time of the original exposure using current serum 2,3,7,8-TCDD levels; these include uncertainty associated with 2,3,7,8-TCDD half-life in humans and having to use average serum 2,3,7,8-TCDD levels, average exposure durations, reference body weights, and percentage of body fat. There is a lack of consensus on the half-life of 2,3,7,8-TCDD in humans; half-lives of 5–12 years have been estimated (Pirkle et al. 1979; Schecter et al. 1994b; Wolfe et al. 1994). Additional human studies measuring 2,3,7,8-TCDD half-life would be useful in establishing dose-response

relationships for human effects. All the above limitations for assessing the body burden of 2,3,7,8-TCDD also apply to other CDDs where far less human toxicokinetic data are available. Thus, it would be useful to have congener-specific human toxicokinetic data on other CDDs and related compounds. Furthermore, human dosimetry studies would be useful in occupational settings to obtain results regarding levels of CDDs in the environment as opposed to levels in serum or adipose tissues.

Biomarkers of Exposure and Effect. Several studies reported results of measurements of CDD levels in the lipid fraction of adipose tissue, milk, and serum from members of the general population with unknown CDD exposure (Andrews et al. 1989; Ryan et al. 1985; Schecter et al. 1987b). The gas chromatography-mass spectrometry (GC/MS) tests used to detect CDD levels are sensitive and specific. Analytical testing for levels in biological fluids and tissues can be used for monitoring exposed populations. While chloracne is a known, readily identifiable effect of exposure to CDDs, it is not useful as a biomarker of exposure because of its variable expression in individuals with even very high levels of exposure to these agents. Further information on how aging and changes in body composition can influence the distribution of CDDs in tissues and body fluids would be valuable. A reverse transcriptase polymerase chain reaction method has been used to quantify CYP1A1 mRNA levels on total RNA extracts from human blood lymphocytes (Vanden Heuvel et al. 1993). This method was found to be much more sensitive than, for example, measuring EROD activity, and could potentially be used as a human exposure marker for CDDs and structurally related compounds. However, EROD activity measurements can be useful as a marker of exposure to the agents.

There are no specific biomarkers of effects for CDDs. Exposure to relatively high concentrations of CDDs can lead to the development of chloracne in humans. However, while the presence of chloracne indicates CDD or similar halogenated-chemical exposure, lack of chloracne does not indicate that exposure has not taken place, as evidenced in a cohort from the Seveso incident (Mocarelli et al. 1991). Additional studies could evaluate the feasibility of using body burden as a biomarker for predicting other effects of CDDs. Although the results of an earlier study suggested that 2,3,7,8-TCDD may form adducts with DNA, albeit at an extremely low rate (Poland and Glover 1979), later studies that have rigorously looked for 2,3,7,8-TCDD-DNA adducts have been negative (Randerath et al. 1988; Turteltaub et al. 1990). Expression of CYP1A1 mRNA, protein, and/or activity are sensitive biological responses in human tissues that can be observed following exposure to 2,3,7,8-TCDD and related compounds, and may be useful biomarkers of effects. Further studies to identify biomarkers of effects of CDDs would facilitate medical surveillance, leading to early detection of potentially adverse health effects and possible treatment.

Absorption, Distribution, Metabolism, and Excretion. There are no quantitative data regarding absorption in humans by the inhalation or dermal routes, but data from accidentally exposed individuals suggest that exposure by these routes may lead to a significant increase in body burden of CDDs (Patterson et al. 1994; Schecter et al. 1994b). Results from one human study indicated that >87% of an oral 2,3,7,8-TCDD dose in an oil vehicle was absorbed (Poiger and Schlatter 1986). Also, results from studies of absorption of CDDs from maternal milk by nursing infants showed that 90–95% of the dose of CDDs can be absorbed; hepta-substituted congeners and OCDD exhibited lower absorption rates (Abraham et al. 1994, 1996; Dahl et al. 1995; McLachlan 1993; Pluim et al. 1993b). The data indicate that 2,3,7,8-TCDD is effectively absorbed, and that absorption is vehicle-dependent (Fries and Marrow 1975; Lucier et al. 1986; Poiger and Schlatter 1980); oil vehicles were most effective (Olson et al. 1980b; Piper et al. 1973). Transpulmonary absorption of 2,3,7,8-TCDD also occurs in animals (Diliberto et al. 1996; Nessel et al. 1992). Dermal absorption of 2,3,7,8-TCDD in rats was found to be age-dependent (Anderson et al. 1993). In rats, following single equivalent intratracheal, oral, and dermal 2,3,7,8-TCDD doses, absorption was calculated as 95, 88, and 40% of the administered dose, respectively (Diliberto et al. 1996). The available information shows that absorption of 2,3,7,8-TCDD has been fairly well characterized in animals.

Based on analysis of CDDs in adipose tissue, milk, and blood, it appears that humans store exclusively 2,3,7,8-chlorine substituted congeners (Fürst et al. 1987; Van den Berg et al. 1986b). Data are available on tissue distribution of 2,3,7,8-TCDD in rats after inhalation, oral, and dermal exposure (Diliberto et al. 1996). The liver and adipose tissue are the major storage sites in animals. In general, distribution of CDDs is congener specific and depends on the dose and route of administration (Diliberto et al. 1996; Van den Berg et al. 1994). Age was also a factor in the distribution of 2,3,7,8-TCDD in mice (Pegram et al. 1995). The distribution of 2,3,7,8-TCDD-derived radioactivity in subcellular liver fractions has also been studied (Santostefano et al. 1996). 2,3,7,8-Chlorine substituted CDDs are the predominant congeners retained in tissue and body fluids from humans, rodents, and monkeys (Abraham et al. 1989; Van den Berg et al. 1983). Further dosimetry studies of various durations in which levels of 2,3,7,8-TCDD and related compounds are monitored in tissues suspected of being targets for 2,3,7,8-TCDD toxicity would provide valuable information. These data can be used to establish correlations between target-tissue doses and adverse effects.

Data regarding the biotransformation of CDDs in humans are limited to a self-dosing experiment that provided some evidence that 2,3,7,8-TCDD is partially excreted in the feces in the form of metabolites

(Wendling et al. 1990). The use of human cell systems in culture might be considered a useful addition to whole-animal studies for examining the metabolic fate of CDDs. Biotransformation of CDDs has been examined in several species, but the structure of metabolites has been elucidated only in the rat and dog (Poiger and Buser 1984). Although information regarding metabolism following inhalation or dermal exposure is lacking, there is no reason to believe that different pathways would operate after exposure by these routes.

Two studies were located that provided limited evidence of fecal excretion of 2,3,7,8-TCDD metabolites in adult humans (Sorg et al. 2009; Wendling et al. 1990). Several studies provided information regarding fecal excretion of CDDs in infants exposed through human milk (Abraham et al. 1994; McLachlan 1993; Pluim et al. 1993b). Elimination of CDDs through maternal milk is well documented (Fürst et al. 1994; Rappe et al. 1985; Schecter and Gasiewicz 1987a; Schecter et al. 1989d, 1989e). Fecal excretion is the main route of excretion of CDDs in animals after all routes of exposure (Diliberto et al. 1996). Estimates of 2,3,7,8-TCDD half-life in humans are available (Pirkle et al. 1989; Poiger and Schlatter 1986; Wolfe et al. 1994), but further information regarding the relationships between aging, fat redistribution, and half-lives in humans would be valuable.

Comparative Toxicokinetics. CDDs are efficiently absorbed from the gastrointestinal tract of mammals, but the vehicle plays an important role (Olson et al. 1980b; Piper et al. 1973; Poiger and Schlatter 1986; Van den Berg et al. 1987a). Distribution data in orally exposed rodents indicated that the highest postexposure levels were in the liver followed by the fat (Diliberto et al. 1996; Khera and Ruddick 1973; Olson 1986), but distribution is highly dose- and species-dependent. The studies to date suggest that compared with rodents, primates, including humans, accumulate significantly less CDDs in the liver than in adipose tissue (Neubert et al. 1990; Ryan et al. 1986; Van Miller et al. 1976). With the exception of the guinea pig, mammals retain only 2,3,7,8-substituted congeners. The high liver retention of 2,3,7,8-substituted congeners by rodents has been attributed to the presence of inducible storage sites, presumably CYP1A2 (Leung et al. 1990b). In all mammalian species studied, exposure by breastfeeding has a much greater contribution to the offspring 2,3,7,8-TCDD body burden than placental transfer. Metabolic capacities are species dependent. Rats, hamsters, and mice metabolize and eliminate CDDs much faster than the guinea pig. The metabolites were excreted predominantly via the bile and feces, with minor amounts excreted in the urine in all species (Diliberto et al. 1996; Fries and Marrow 1975; Weber and Birnbaum 1985). Whole-body half-lives ranged from 11 days in hamsters (Olson et al. 1980b) to >1 year in monkeys (Bowman et al. 1989b; McNulty et al. 1982) and were approximately 7–12 years in humans (Wolfe et al. 1994). The toxicity of CDDs has been associated with the parent compound and

not the metabolites (Mason and Safe 1986; Weber et al. 1982); therefore, metabolism and excretion represent a detoxification process. The data collected in later years indicate that differences in species susceptibility to CDDs cannot be explained by differences in toxicokinetics alone; it is likely that genetic factors have an important role. Based on this information, species-, congener-, and dose-specific toxicokinetic data need to be factored into human risk assessment for CDDs. Several models that describe the disposition of 2,3,7,8-TCDD in animals and humans were identified from the literature (Andersen et al. 1993, 1997a, 1997b; Carrier et al. 1995a, 1995b; Kissel and Robarge 1988; Kohn et al. 1993; Leung et al. 1988, 1990b). Although each new model that is published usually fills data gaps identified in earlier models, further research is necessary to increase their reliability for use in human risk assessment.

Children's Susceptibility. A limited number of human studies have examined health effects of CDDs in children. Data from the Seveso accident suggest that children may be more susceptible to the dermal toxicity of 2,3,7,8-TCDD (chloracne), but it is not known if this would be the case for other effects. Follow-up medical surveillance of the Seveso children (including measurement of serum 2,3,7,8-TCDD levels) would provide information on whether childhood exposure would pose a risk when the individual matures and ages. The available human and animal data provide evidence that 2,3,7,8-TCDD can cross the placenta and be transferred to an infant via human milk. Although information on the developmental toxicity of CDDs in humans is limited, there are extensive animal data that the developing organism is very sensitive to the toxicity of 2,3,7,8-TCDD. Several human studies have found significant alterations in markers of liver, thyroid, immune, and neurological function in young, breastfed infants of mothers with higher current background or general population CDD levels. Data suggest that the neurological effects are reversible; prospective studies of breastfed individuals would provide useful information on whether these children are at risk of developing additional effects as they age. Further data needs relating to developmental effects are discussed above under Developmental.

In general, the available toxicokinetic data did not examine potential differences between adults and children; toxicokinetic studies examining how aging and changes in body composition can influence distribution and turnover rates would be useful in assessing children's susceptibility to CDD toxicity. Most of the available mechanism-of-action data suggest that the toxicity of 2,3,7,8-TCDD is mediated through the AhR. It is not known whether there are any age-related differences in receptor binding or expression; studies in animals would be valuable to fill this information gap. No age-specific biomarkers of exposure or effect were identified for CDDs; the long half-life of 2,3,7,8-TCDD in humans suggests that there may not be a way to assess whether adults were exposed as children to 2,3,7,8-TCDD.

Additionally, there are no data to determine whether there are any interactions with other chemicals that would be specific for children. There is very little available information on methods for reducing 2,3,7,8-TCDD toxic effects or body burdens; it is likely that research in adults would also be applicable to children.

Physical and Chemical Properties. The physical and chemical properties of 2,3,7,8-TCDD are sufficiently characterized to predict the environmental fate of 2,3,7,8-TCDD (IARC 1977; Sax and Lewis 1987; Schroy et al. 1985; Shiu et al. 1988). Of all the CDDs, 2,3,7,8-TCDD has been the compound most studied. Not all isomers within each homologous class have been equally well studied for many of the physical and chemical properties. Information on physical and chemical properties of certain congeners (particularly 1,2,3,7,8,-PeCDD and 1,2,3,6,7,8-HxCDD) would be helpful in better understanding the different fate and transport pathways of the homologous groups.

Production, Import/Export, Use, Release, and Disposal. CDDs are not manufactured commercially in the United States except on a laboratory scale for use in chemical and toxicological research (CIL 1995). They are produced as undesired by-products during the manufacture of chlorophenols (e.g., PCP and 2,4,5-trichlorophenol) and during combustion processes (IARC 1977; NTP 1989; Podoll et al. 1986). CDDs are ubiquitous in the environment and have been found at low levels (ppt or lower) in air, water, soil, sediment, and foods. Continued monitoring of release data would provide useful information on trends. Current disposal methods are efficient and are subject to EPA and state regulations.

Environmental Fate. CDDs are subject to atmospheric transport and both wet and dry deposition (Kieatiwong et al. 1990). They are partitioned to air, water, sediment, and soil, and they accumulate in both aquatic and terrestrial biota. CDDs can volatilize to the atmosphere from water and soil surfaces; however, adsorption processes attenuate the rate of volatilization. They adsorb strongly to soils and are not likely to leach into groundwater (Eduljee 1987). In the aquatic environment, CDDs partition to sediment or suspended particulates. TCDD, HpCDD, and OCDD are subject to photolysis in air, water, and soil (Plimmer et al. 1973). 2,3,7,8-TCDD is biodegraded very slowly in soil and is thus likely to persist in the soil. A better understanding of environmental behavior of CDDs is needed with respect to the importance of vapor-phase versus particulate transport, the environmental behavior of different congeners, and the significance of processes that reintroduce CDDs into the atmosphere after deposition. Information regarding the degradation of other congeners, specifically OCDD, and their degradation

products in water, sediment, and soil would be useful in evaluating the various pathways of human exposure.

Bioavailability from Environmental Media. Toxicokinetic data in humans regarding absorption of CDDs following oral and dermal exposure are very limited (Poiger and Schlatter 1986). CDDs can be absorbed following oral exposure in both humans and animals (Birnbaum and Couture 1988; Fries and Marrow 1975; Koshakji et al. 1984; Norback et al. 1975; Olson et al. 1980b; Piper et al. 1973; Poiger and Schlatter 1980). The more highly chlorinated CDD congeners are absorbed to a lesser extent than 2,3,7,8-TCDD (Koshakji et al. 1984). Also, limited information is available on the bioavailability from fly ash (Van den Berg et al. 1983, 1985). 2,3,7,8-TCDD can be adsorbed following dermal contact (Banks and Birnbaum 1991; Poiger and Schlatter 1980; Shu et al. 1988); however, dermal absorption of 2,3,7,8-TCDD from soil is very low (Shu et al. 1988). More information is needed regarding oral and dermal exposure to determine the bioavailability of CDDs from food, water, and soil. Additional information is needed to examine the discrepancy noted in the mass balance from CDDs ingested from foods and eliminated in feces. For inhalation exposure, information on the bioavailability from fly ash and sediments would be useful. Information is also needed on the selective uptake of the 2,3,7,8-substituted CDD congeners.

Food Chain Bioaccumulation. CDDs are bioconcentrated in aquatic organisms, plants, and terrestrial animals. Shellfish (including crustaceans and bivalve mollusks) appear to accumulate CDDs nonselectively to relatively high concentrations in their tissues (Bopp et al. 1991; Brown et al. 1994; Cai et al. 1994; Conacher et al. 1993; Hauge et al. 1994; Rappe et al. 1991). In contrast, finfish appear to selectively accumulate primarily 2,3,7,8-TCDD and other 2,3,7,8-substituted isomers in their tissues (Rappe et al. 1991). Information from a larger number of species on the retention of 2,3,7,8-substituted CDD congeners and general information on retention and distribution of other CDDs would be useful in better understanding both aquatic and terrestrial food chains.

Exposure Levels in Environmental Media. CDDs have been detected in air, water, soil, sediment, plant material, and foods. Environmental monitoring studies show that the higher chlorinated CDDs are usually the ones most commonly found in environmental samples (Christmann et al. 1989; Clement et al. 1985, 1989; Pereira et al. 1985; Reed et al. 1990; Tashiro et al. 1989a; Tiernan et al. 1989). Current monitoring studies are needed to determine CDD levels in media surrounding hazardous waste sites. Using a model, the total average daily intake of 2,3,7,8-TCDD (by air, water, and food) for the general population was estimated to be 0.05 ng/day (range 0.008–0.3 ng/day) (FDA 2006; Travis and Hattemer-

Frey 1987). Dearfield et al. (2013), FDA (2006), Schecter et al. (1994a, 1994d, 1996a); and Schecter and Li (1997) have provided current information on CDD exposures from food. Food consumption accounts for >90% of background human exposure to 2,3,7,8-TCDD and other CDDs/CDFs in the general U.S. population (Dearfield et al. 2013; Hattemer-Frey and Travis 1989; Schaum et al. 1994). The average daily intake by nursing infants in the United States has been estimated to be 83 pg TEQs/kg (Schecter and Gasiewicz 1987a, 1987b). Since levels of CDDs and CDFs have declined in environmental media, including food items, as emissions have been reduced, these estimated intakes are likely higher than current intakes. A data need to estimate current daily intakes is identified. Dietary exposure studies should look at exposures for population sectors that have different diets (e.g., according to age, race/socioeconomic status, dietary preferences).

Exposure Levels in Humans. CDDs/CDFs have been found in blood (CDC 2024a, 2024b; Fingerhut et al. 1989; Needham et al. 1991; Päpke et al. 1989b, 1992, 1993), adipose tissue (EPA 1986a; Orban et al. 1994; Patterson et al. 1986a; Ryan et al. 1986; Schecter et al. 1986b; Stanley et al. 1986), and human milk of both the general population and workers exposed through industrial accidents or environmental contamination (Fürst et al. 1992; Pluim et al. 1993a; Ryan et al. 1993b; Schecter and Gasiewicz 1987b; Schecter and Tiernan 1985; Schecter et al. 1986a, 1986b, 1989e). Levels of 2,3,7,8-TCDD as well as other CDDs are generally higher in occupationally exposed individuals or those individuals exposed through industrial accidents or environmental contamination (Kahn et al. 1988; Schecter and Tiernan 1985; Schecter et al. 1986b, 1987a; Umbreit et al. 1986a, 1986b). CDDs have also been detected in human milk and blood of Canadian populations of native Inuit who consume large amounts of fish and marine mammals (Ayotte et al. 1997; Dewailly et al. 1992). Additional, recent biological monitoring data are needed, however, for those U.S. populations surrounding hazardous waste sites or municipal, medical, or industrial incinerators, for urban versus rural exposures, and for other potentially exposed populations including subsistence fishers and hunters (Liem et al. 1991; Startin et al. 1989; Wuthe et al. 1993). Recent information on tissue levels in the general population worldwide are for the most part lacking (Schecter et al. 1991a). As they are identified, exposed populations should be evaluated to characterize exposure levels and health effects. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Children in the general population are exposed to CDDs primarily through dietary exposures *in utero* via placental blood and in newborn infants via breastfeeding. Despite the fact that studies on the concentrations of CDDs in human milk have been conducted in various other countries, there is a need to determine the levels of CDDs in human milk in the United States. Additional

exposure studies also are needed to determine whether dietary modifications in mothers can reduce total CDD exposures in newborns and whether dietary modifications of the infant can also reduce lifetime exposure. For children in populations with potentially high exposure to CDDs, the primary exposure pathway is through their diet; however, additional exposure to CDDs via consumption of contaminated groundwater or soil, and dermal exposure to contaminated soil may increase their exposure levels. Studies of workers in various industrial settings that are exposed to CDDs (i.e., elevated CDD levels in adipose or blood serum) should be conducted to determine whether CDDs are routinely brought home by these workers on their clothing and shoes to assess whether this is an important exposure route for children.

Schecter and Li (1997) have calculated weight-adjusted intakes of CDDs derived from consumption of four types of fast foods for 6-year-old children. Additional information on dietary intake of CDDs from other types of foods should be conducted for various age groups of children to help identify the magnitude and sources of dietary exposure during childhood. Studies to verify these calculations would be helpful in assessing health risks to children.

The primary childhood specific means to decrease exposure to CDDs involves placing the infant on a cow's milk or soy-based baby formula and on maintenance of children on a long-term diet that is lower in animal fats (meat, dairy products, and fish) and higher in grains, fruits, and vegetables. It should be noted however, that because of the relatively short period of intake and the accepted benefits of breastfeeding, the maintenance of children on a long-term diet low in animal fat would likely be more beneficial in decreasing total lifetime CDD body burdens than cessation of breastfeeding. Additional means of reducing CDD exposures also should be investigated.

6.3 ONGOING STUDIES

Table 6-1 lists research studies identified in a search of the National Institutes of Health (NIH) Research Portfolio Online Reporting Tools Expenditures and Results (RePORTER 2022) that are currently being conducted that may fill some of the data needs discussed in Section 6.2.

Table 6-1. Ongoing Studies on Chlorinated Dibenzo-*p*-Dioxins (CDDs)

Investigator	Affiliation	Research description	Sponsor
Kaminiski NE	Michigan State University	Evaluate the mechanisms of IgM production suppression in response to dioxin-like compounds	NIEHS
Peterson PE	University of Wisconsin-Madison	Examining the relationship between *in utero* exposure to 2,3,7,8-TCDD and benign prostate hyperplasia in adults	NIEHS
Ko CI	University of Cincinnati	Examining the mechanisms of dioxin developmental toxicity	NIEHS

IgM = immunoglobulin M; NIEHS = National Institute of Environmental Health Sciences; 2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

Source: RePORTER 2022