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 perfluoroalkyls 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 perfluoroalkyls.

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 Existing Information on Health Effects

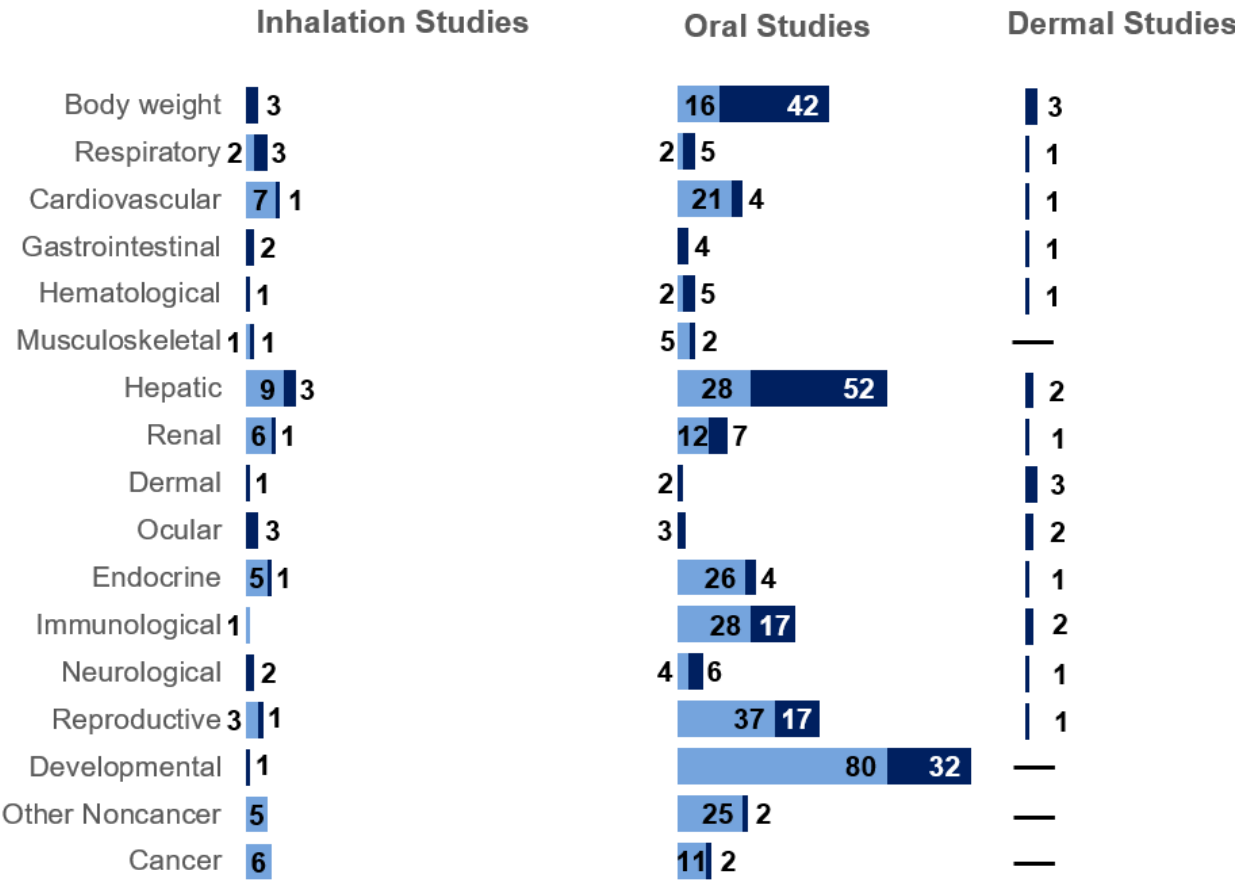
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to PFOA, PFOS, and other perfluoroalkyls that are discussed in Chapter 2 are summarized in Figures 6-1, 6-2, and 6-3, respectively. The purpose of these figures is to illustrate the information concerning the health effects of perfluoroalkyls. 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 Figures 6-1, 6-2, and 6-3, most of the data on the toxicity of PFOA, PFOS, and other perfluoroalkyls come from epidemiological studies in humans; oral exposure is the assumed route of exposure for the epidemiological studies. The epidemiology database consists of health evaluations of subjects exposed in occupational settings (primarily PFOA and PFOS), highly exposed residents living near a PFOA facility, and studies of the general population. The most commonly examined endpoints in the epidemiological studies were developmental, hepatic, reproductive, and immunological effects.

Figure 6-1. Summary of Existing Health Effects Studies on PFOA by Route and Endpoint*

Potential body weight, hepatic, and developmental effects were the most studied endpoints

The majority of the studies examined oral exposure in **humans** (versus **animals**)

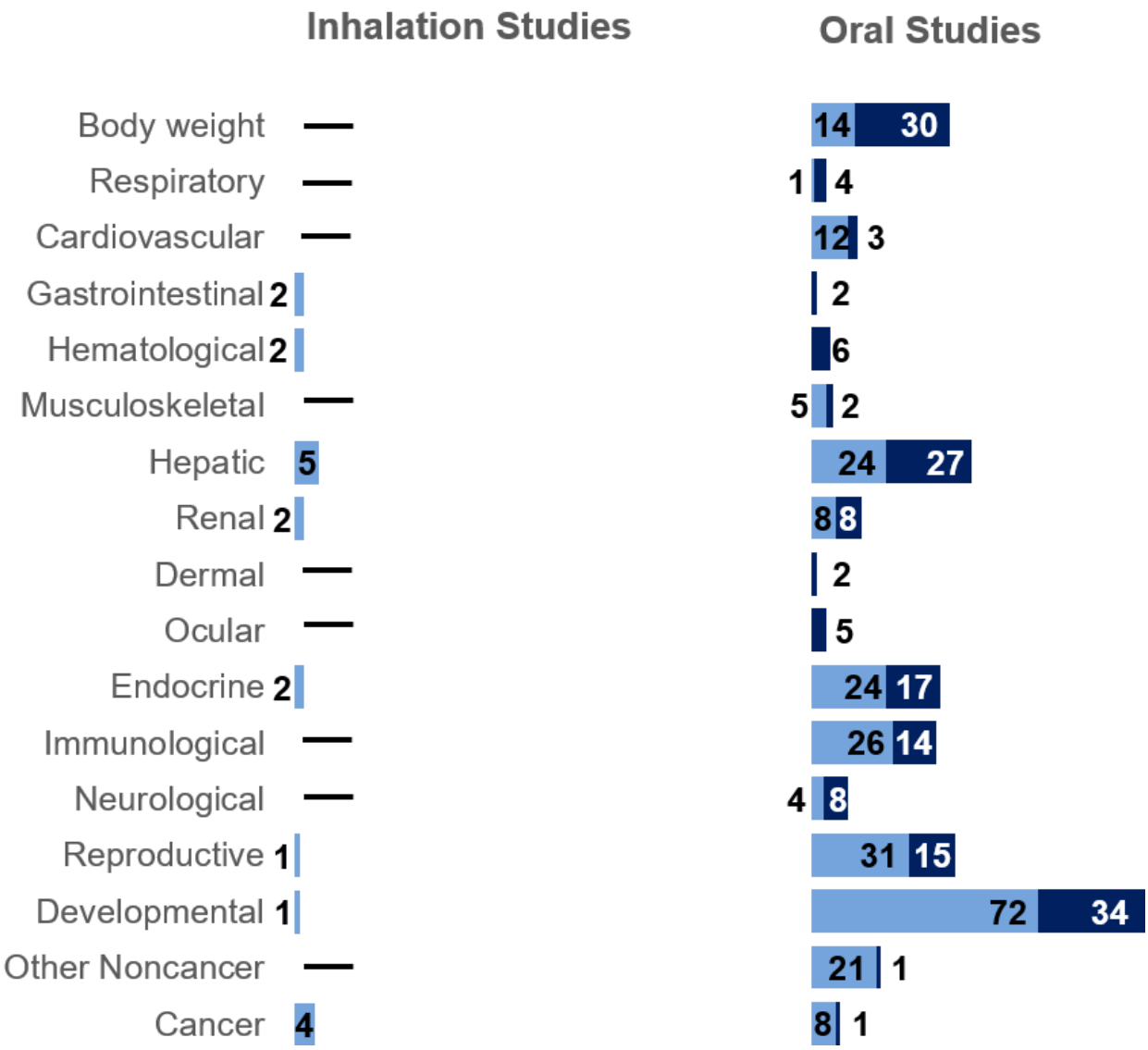


*Oral exposure was the presumed route of exposure for human studies involving environmental exposure. Human and animal studies may have examined more than one endpoint. A "—" indicates that no studies are available.

Figure 6-2. Summary of Existing Health Effects Studies on PFOS by Route and Endpoint*

Potential developmental, hepatic, and reproductive effects were the most studied endpoints

The studies examined oral exposure in **humans** (versus **animals**)

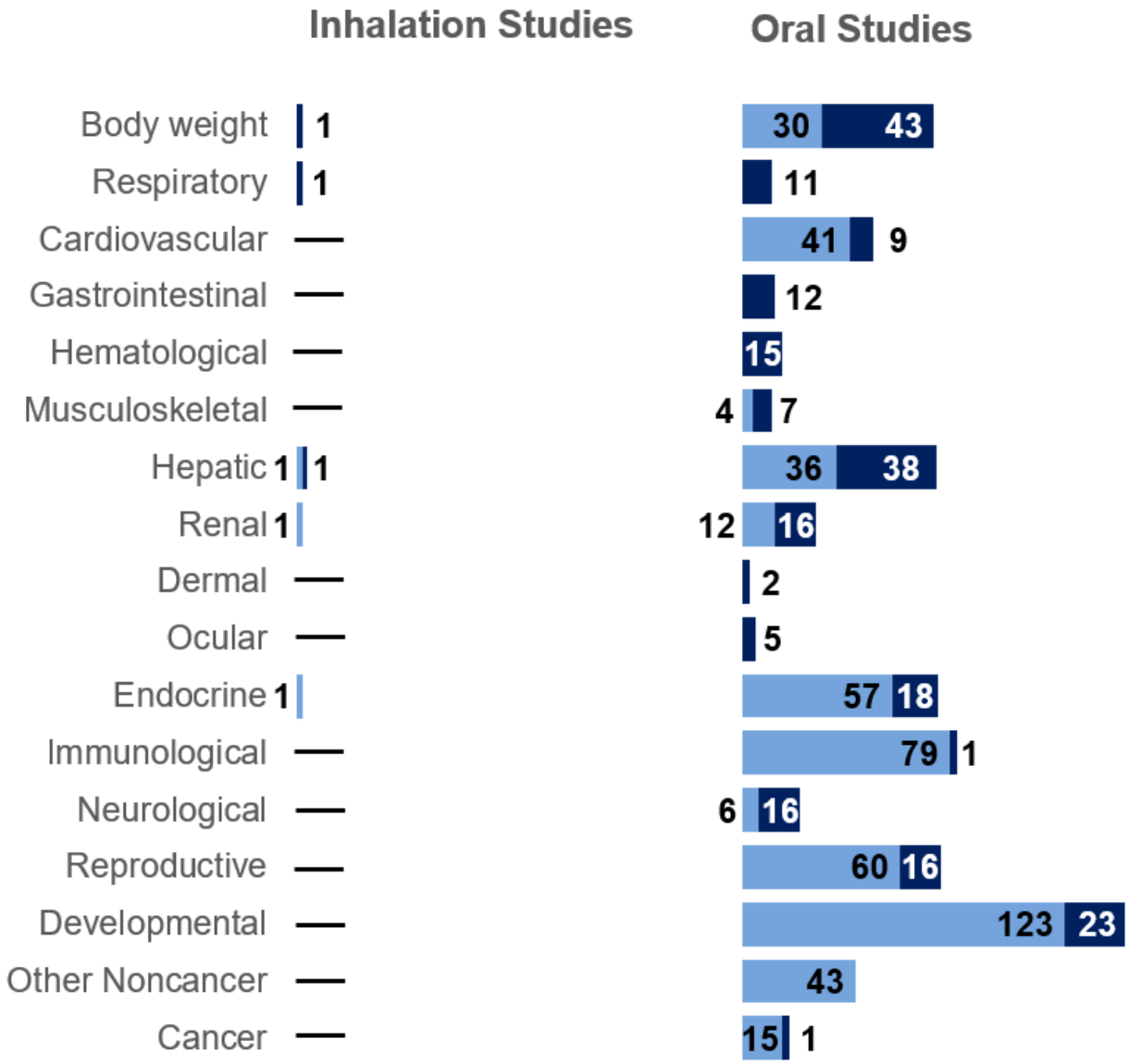


*Oral exposure was the presumed route of exposure for human studies involving environmental exposure. Human and animal studies may have examined more than one endpoint. A "—" indicates that no studies are available.

Figure 6-3. Summary of Existing Health Effects Studies on Other Perfluoroalkyls 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**)



*Oral exposure is the presumed route of exposure for human studies involving environmental exposure. Most human studies examined multiple perfluoroalkyls. Human and animal studies may have examined more than one endpoint. A "—" indicates that no studies are available. Includes data for PFBA, PFHxA, PFHpA, PFNA, PFDA, PFUnA, PFBS, PFHxS, PFDoDA, and FOSA.

Most of the information regarding the effects of perfluoroalkyls in animals has been derived from oral studies; considerably less information is available from inhalation and dermal exposure studies. PFOA and PFOS have been the most extensively studied members of this class of chemicals, and oral administration has been the preferred route of exposure in animal studies. Information regarding other perfluoroalkyls covered in this profile is limited to acute-duration oral studies with PFHxS, PFNA, PFDA, PFBA, PFDoDA, PFHxA, and FOSA; intermediate-duration oral studies with PFHxS, PFNA, PFDA, PFUnA, PFBS, PFBA, PFDoDA, and PFHxA; and a chronic-duration oral study with PFHxA. An acute-duration-inhalation study with PFNA is also available. The most commonly examined endpoints were hepatic, body weight, developmental, reproductive, and immunological effects.

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.

Acute-Duration MRLs. The available acute inhalation database for PFOA was considered inadequate for derivation of an MRL due to lack of measured serum PFOA levels in the available animal studies and the lack of PBPK model parameters that could be used to predict serum levels. The inhalation database for PFNA was not considered adequate due to the limited endpoints examined and the short exposure duration of the only available study. No inhalation data were available for PFOS or the other perfluoroalkyls. A number of studies have evaluated the acute toxicity of PFOA and PFOS following oral exposure and have identified several sensitive targets of toxicity. Smaller numbers of studies evaluated potential sensitive targets of acute toxicity for PFNA and PFDA. However, toxicokinetic differences between humans and laboratory animals, particularly the relative short half-life in rodents compared to humans, preclude derivation of an acute MRL for these compounds. For other perfluoroalkyls (PFHxS, PFBA, PFDoDA, FOSA), the available studies were not considered adequate for identification of critical targets; did not examine sensitive targets that were identified for other perfluoroalkyls, such as developmental and immunological endpoints; or involved a single exposure. No acute oral data were identified for PFUnA, PFHpA, or PFBS. Research is needed to develop a PBPK model that would allow for extrapolation from rodents to humans. Additionally, toxicity studies are needed for most perfluoroalkyls to identify critical targets of toxicity and/or establish dose-response relationships. These

studies should examine developmental and reproductive endpoints that have been established as the most sensitive targets of toxicity for PFOA and PFOS.

Intermediate-Duration MRLs. No intermediate-duration inhalation studies were identified for perfluoroalkyls. Oral studies suggest that developmental and immune effects are the most sensitive targets of toxicity; similar effects are likely to occur following inhalation exposure because perfluoroalkyls are not metabolized. Inhalation studies are needed to establish dose-response relationships and to establish whether the respiratory tract is a sensitive target of toxicity. The intermediate-duration oral databases were considered adequate for derivation of MRLs for PFOA and PFOS. The MRL for PFOA is based on altered bone development measured in mature mice exposed *in utero*. The principal study only tested one PFOA dose level and only examined long bones; additional studies utilizing several dose levels, examining other types of bone, and testing a second species would provide support for the MRL. A modifying factor was used for PFOS due to the lack of PBPK modeling parameters; additional studies are needed that would allow for predicting steady-state serum PFOS levels for immunotoxicity studies in laboratory animals. An important decision made in the derivation of intermediate oral MRLs was to use the time-weighted average serum concentrations (C_{TWA}) of PFOA or PFOS as the basis for extrapolations of the dose-response PODs from animal studies to human equivalent doses (HEDs). However, the available data on the toxicity of PFOA and PFOS do not provide convincing evidence that toxicity outcomes are more likely to be determined by C_{TWA} rather than C_{max}. Since the PBPK model used for dosimetry modeling of the animal studies predicted that C_{TWA} is lower than C_{max} in the principal studies for the MRLs, selection of C_{TWA} as the internal dose metric results in lower values for MRLs. Therefore, use of C_{TWA}, rather than C_{max} is a health-protective decision that might be more adequately evaluated with additional studies that evaluate associations between C_{max}, C_{TWA}, and toxicity outcome responses.

Intermediate-duration MRLs were also derived for PFHxS and PFNA; however, these were based on marginal databases and additional dose-response studies are needed to support the basis of the MRL. The databases were not considered adequate for PFUnA, PFBS, PFBA, or PFDoDA due to the lack of studies examining potential sensitive targets (developmental and/or immune effects). No intermediate-duration oral studies are available for PFDA, PFHpA, or FOSA. Intermediate-duration oral studies are needed for these seven perfluoroalkyls to provide information on sensitive targets and establish dose-response relationships. These studies should include measurement of serum perfluoroalkyl levels, which would allow for estimating HEDs.

An additional uncertainty in the MRLs was the confidence in the elimination half-lives for perfluoroalkyls used in the empirical model for calculating HEDs. Estimated half-lives for PFOA and PFOS vary and contributors to this variability have not been completely characterized. The empirical model used to calculate HEDs is linear; therefore, the change in the HED is approximately proportional to the change in the half-life. A halving of the half-life would result in a doubling of the HED. Studies that can improve confidence in the half-life estimates would increase confidence in MRLs.

Chronic-Duration MRLs. The lack of chronic-duration inhalation studies for perfluoroalkyls precluded derivation of chronic MRLs. Chronic toxicity studies examining a wide range of endpoints are needed to identify the most sensitive target and establish concentration-response relationships. A small number of chronic duration oral studies have been identified in laboratory animals. Four studies examined the chronic toxicity of PFOA, PFOS, or PFHxA. These studies were not considered suitable for derivation of MRLs because they did not evaluate immunotoxicity which was a sensitive target following shorter term exposures. Studies examining this potentially sensitive endpoint are needed to identify the most sensitive target following chronic exposure.

Health Effects. Over 600 studies have evaluated the toxicity of perfluoroalkyls; epidemiological studies account for over 400 of the toxicity studies. Evidence from epidemiological studies suggest associations between perfluoroalkyl exposure and several health outcomes including liver damage, increases in serum lipids, thyroid disease, immune effects, reproductive toxicity, and developmental toxicity. The primary health effects observed in laboratory animals are liver, developmental, and immune toxicity. Although a large number of studies evaluating health effects are available, there is a need for additional studies to address data gaps. Future laboratory animal studies should include measurement of serum perfluoroalkyl levels, as this would provide valuable information for comparing effects observed in laboratory animals to effects observed in humans.

Hepatic Effects. Evidence from acute, intermediate, and/or chronic oral studies in rats, mice, and monkeys indicates that the liver is a sensitive target of PFOA, PFOS, PFHxS, PFNA, PFDA, PFUnA, PFBA, PFBS, PFDoDA, and PFHpA toxicity. The effects observed in rodents differ from those observed in humans. In humans, exposure to PFOA, PFOS, PFNA, and PFDA appear to result in increases in serum lipid levels, particularly total cholesterol levels. However, animal studies have found decreases in serum lipid levels associated with exposure to most perfluoroalkyls. It is not known if the species differences are due to different mechanisms of toxicity or differences in

exposure levels (serum levels observed in animal studies are orders of magnitude higher than those in human studies).

Immune Effects: Epidemiological data suggest an association between PFOA, PFOS, PFHxS, and PFDA and decreased antibody response to vaccines. This is supported by acute- and intermediate-duration studies of PFOA and PFOS in laboratory animals. There is also evidence of immunotoxicity following a single injection of PFNA; some of the immune effects persisted 4 weeks post-exposure. Shorter-term studies are needed for other perfluoroalkyls. In addition, chronic-duration studies evaluating immune endpoints, particularly immunosuppression, for all perfluoroalkyls would allow for identification of the critical targets of toxicity.

Reproductive Effects. Decreases in mammary gland development have been demonstrated in several PFOA mouse studies. The effect levels observed in these studies are very low, although there is some indication that at lower doses, the changes in mammary gland development do not affect lactation. Additional studies are needed to evaluate the adversity of these alterations. This endpoint has not been evaluated for other perfluoroalkyls and studies are needed to determine whether it is also a sensitive effect for these compounds.

Developmental Effects. Based on the results of laboratory animal studies, developmental endpoints are targets of PFOA, PFOS, PFHxS, PFNA, PFDA, PFUnA, and PFBA toxicity following acute- and/or intermediate-duration oral exposure. Studies are needed to evaluate potential developmental effects for PFHxS following intermediate-duration oral exposure. Additionally, cross-fostering studies would provide information that could be used to evaluate the health impact of lactational exposure to perfluoroalkyls. Epidemiological studies in children suggest altered responses to vaccination; two animal studies have evaluated immune effects following perinatal exposure to PFOA and PFOS, but data are lacking for other perfluoroalkyls.

Potential Interactions between Perfluoroalkyls. A common limitation of the epidemiological data is co-exposure to multiple perfluoroalkyls. There are limited data on possible interactions between perfluoroalkyls and possible effects on toxicity and toxicokinetics. Animal studies examining the possible interactions between perfluoroalkyls would be useful for interpreting the epidemiological study results; this is especially important since humans are typically exposed to multiple perfluoroalkyls and many of them are likely to have similar mechanisms of action.

Mechanisms of Toxicity. Many of the effects observed in rodents, particularly liver and developmental effects, involve the activation of PPARα; humans and nonhuman primates are less responsive to PPARα agonists than rats and mice. However, the results of studies in PPARα-null mice suggest that PPARα-independent mechanisms also play a role in the liver, immunological, and developmental toxicity. Additional studies are needed on the mechanisms of toxicity to assess whether the effects observed in laboratory animals are relevant to humans. Mechanistic studies would also provide support for the critical effects used to derive the MRLs for PFOA, PFOS, PFHxS, and PFNA.

Epidemiology and Human Dosimetry Studies. As previously mentioned, information is available regarding the effects of exposure to perfluoroalkyls in humans derived from health evaluations of subjects exposed in occupational settings, residents living near a PFOA manufacturing facility with high levels of PFOA in the drinking water, and the general population. Although many studies found statistically significant associations between serum perfluoroalkyl levels and the occurrence of an adverse health effect, the findings were not consistent across studies. Interpretation of the human data is limited by the reliance of cross-sectional studies, which do not establish causality, and the lack of exposure data. Studies on serum lipids suggest that the dose-response curve is steeper at lower concentrations and flattens out at higher serum perfluoroalkyl concentrations (Steenland et al. 2010a); additional studies that could be used to establish dose-response relationships would be valuable. Mechanistic studies examining the association between perfluoroalkyl exposure and serum lipid levels would also provide valuable insight. Clarification of the significance and dose-response relationships for other observed effects is also needed. Longitudinal studies examining a wide range of endpoints would be useful for identifying critical targets of toxicity in humans exposed to perfluoroalkyls. The available human studies have identified some potential targets of toxicity; however, cause-and-effect relationships have not been established for any of the effects, and the effects have not been consistently found in all studies. Mechanistic studies would be useful for establishing causality. When possible, health assessments should include subjects of different race/ethnicity and age to determine potential race/ethnicity- and age-based susceptibilities. Another limitation of the epidemiological studies is co-exposure to other perfluoroalkyls; studies that statistically controlled for co-exposure to other pollutants would decrease this uncertainty. As noted previously, there is a need for studies evaluating potential interactions between perfluoroalkyls.

Biomarkers of Exposure and Effect. Data are available regarding levels of perfluoroalkyls in serum from the general population, highly exposed residents, and perfluoroalkyl workers. Information is needed regarding the toxicokinetics (see also below) of perfluoroalkyls in humans to be able to relate levels of

these compounds in serum to exposure to specific perfluoroalkyls; data on matched serum and urine samples would be valuable. Also needed is further information on the relationship between serum and liver concentrations of perfluoroalkyls in humans.

Absorption, Distribution, Metabolism, and Excretion. Several epidemiological studies have examined the kinetics of serum perfluoroalkyl concentrations following a change in environmental or occupational exposure, from which estimates of terminal elimination half-lives in adults are available for PFOA, PFOS, PFHxS, PFBA, and PFBS. Other studies provide data on the renal clearances of PFOA and PFOS, binding of PFOA, PFOS, and PFHxS to human plasma protein, tissue levels (primarily blood, maternal and fetal cord serum, and breast milk). Data on other aspects of the toxicokinetics of perfluoroalkyls in humans are not available and could serve to improve predictions of internal dosimetry associated with exposures to perfluoroalkyls (bioavailability, kinetics of tissue distribution and elimination, binding in tissues, external-internal dose relationships, all aspects of toxicokinetics in children and aging populations).

Toxicokinetics of perfluoroalkyls have been studied much more extensively in rodents (rats and mice) and less extensively in Cynomolgus monkeys; however, a number of data gaps have been identified:

- Absorption studies; oral absorption data are available for PFOA, PFOS, and PFBA, but are more limited for other perfluoroalkyls and for other exposure routes. Studies elucidating the mechanisms of pulmonary and gastrointestinal absorption are also needed.

- Studies have shown that elimination kinetics, and therefore, internal dose-external dose relationships, are dependent on structure, including the terminal acid group (carboxylate or sulfonate), carbon chain length, and carbon chain branching. These structural features affect plasma and tissue protein binding, renal and biliary clearances, tissue levels, maternal-fetal transfer, and lactational transfer of perfluoroalkyls. Studies examining differences between perfluoroalkyls would be useful for extrapolating health effects and toxicokinetic data across compounds.

- Toxicokinetic studies have found sex- and dose-dependent subcellular distribution of PFOA in rats. Further studies on the mechanisms for dose-dependency, characterization of subcellular binding proteins, and mechanistic linkages between subcellular distribution and toxicity of perfluoroalkyls are needed.

- The distribution and elimination of PFOA and PFOS are greatly influenced by binding interactions with albumin and other high molecular weight plasma proteins; available data suggest that binding to plasma proteins, as well as the volume of distribution, may be sex- and species-specific. Interactions with albumin have been partially characterized to the extent that binding capacity and affinity constants have been estimated, but the rates of association and dissociation have not been reported.

- Liver uptake and renal clearance of PFOS also appeared to be time-dependent in a PBPK model used to predict plasma and liver in concentrations of PFOS in a chronic rat study (Harris and Barton et al. 2008). Mechanisms underlying these time dependencies have not been elucidated.

Comparative Toxicokinetics. Toxicokinetic studies conducted in various rodent species (mice, rats, hamsters, rabbits) and in Cynomolgus monkeys have revealed profound species and sex differences as well as dose dependencies in the tissue distribution and elimination kinetics of PFOA and PFOS. Studies conducted in rats have revealed contributing mechanisms for sex differences in elimination of PFOA; slower elimination of PFOA in male rats compared to female rats has been attributed to sex hormone-modulated renal tubular transport of PFOA that results in markedly lower renal clearance of PFOA in the sexually mature male rat (see Section 3.5.1, Excretion). Sex differences in elimination of PFOA have also been observed in hamsters; unlike the rat, male hamsters excreted absorbed PFOA more rapidly than female hamsters. Sex differences in elimination of PFOA have not been observed in other rodent species, in Cynomolgus monkeys, or in limited observations made in humans. Sex differences in elimination rates of perfluoroalkyls in humans have not been demonstrated in population studies of serum elimination kinetics or renal clearance. Although the few studies that estimated elimination half-lives or renal clearances in male and female humans have not found significant sex differences, these outcomes may reflect the relatively low serum concentrations in these subjects compared with studies that were conducted in nonhuman primates and rodents (i.e., sex differences in elimination may vary with dose and/or plasma concentration). Additionally, the failure to account for the influence of reduced estrogen levels (in postmenopausal women) and reduced testosterone levels (in older males) in occupational and/or site-related epidemiological studies may also account for the lack of findings of sex-related differences.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in the Health Effects subsection above. It is not known whether children are more or less susceptible than adults to the effects of exposure to perfluoroalkyls because there are no studies that specifically addressed this question. Several studies have examined the possible associations between perfluoroalkyl exposure and health outcomes in children living in an area with high PFOA contamination and in the general population. Although some studies have found statistically significant associations, they are not adequate for establishing causality. Follow-up studies of the C8 population could allow for a longitudinal assessment of health effects in children and would be useful in determining whether the observed effects are due to perfluoroalkyl exposure. Toxicokinetics information in children is needed. Half-life studies have been conducted in adults; there is the need to understand if these are applicable to children. There are no

studies that have examined whether young animals are more or less susceptible than adults to perfluoroalkyls toxicity. Additional information on this issue would be useful.

Physical and Chemical Properties. Perfluoroalkyls have unique and complex physical and chemical properties (Kissa 2001; Schultz et al. 2003). Sources are available that provide helpful insights into the structural aspects and surfactant nature of these substances; however, many of the properties are still not well understood (CEMN 2008; Kissa 2001; Schultz et al. 2003). In general, specific properties such as physical state, melting point, boiling point, density, solubility, vapor pressure, micelle formation, and acid dissociation in water have not been determined or are not well described for these compounds. Measurements of these endpoints are needed. Information regarding the potential association of these species in water would be useful. Where determination of a particular endpoint is not possible, a thorough description of the physical and chemical properties as they relate to that endpoint would be helpful. Perfluoroalkyls discussed in this profile exist as a mixture of linear and branched isomers. Isomer-specific data would also be useful for the various physical-chemical properties. Wang et al. (2013b) identified several of the fluorinated compounds that are currently being used by major manufacturers as alternatives to PFOA and PFOS. These compounds are being used as processing aids in the emulsion polymerization of PTFE and other polymers as well as surface treatment uses, metal plating uses, firefighting foams, and other miscellaneous uses such as food contact materials. A data need exists to determine the physical and chemical properties of these replacement substances.

The production, use, import, and export of perfluoroalkyls have changed dramatically since 2000. Most nations no longer produce or use PFOS or PFOA (China is a notable exception). Major fluoropolymer manufacturers in the United States have altered their chemical processes to use alternative fluorinated substances in their production processes. Information regarding the production, import, and export volumes of these substances is needed.

Recommended methods for the disposal of perfluoroalkyls have not been located. In the past, perfluoroalkyl-containing waste has been disposed of in on- and off-site landfills, through sludge incorporation, and through incineration (3M 2007b, 2008b; ATSDR 2005). New disposal methods that avoid release of these substances into the open environment and prevent contamination of nearby soil, sediment, and groundwater should be developed. The eventual breakdown of fluorotelomer-based polymers with the eventual release of substances such as PFOA is not well understood. Early researchers have concluded that the half-life for this process is >1,000 years; however, more recent data suggest much shorter time scale of 1–2 decades (Rankin et al. 2014; Washington and Jenkins 2015; Washington et al.

2009, 2014, 2015). Additional studies on the potential release of perfluoroalkyls from the eventual degradation of fluoropolymers in landfills would be useful.

Environmental Fate. Perfluoroalkyls are very stable compounds and are resistant to biodegradation, direct photolysis, atmospheric photooxidation, and hydrolysis (3M 2000; EPA 2008a; OECD 2002, 2007; Schultz et al. 2003). The chemical stability of perfluoroalkyls and the low volatility of these substances in ionic form indicate that perfluoroalkyls will be persistent in water and soil (3M 2000; Prevedouros et al. 2006). K_{oc} values ranging from 17 to 230 indicate that PFOA will be mobile in soil and can leach into groundwater (Davis et al. 2007; Prevedouros et al. 2006). Environmental fate and potential pathways of PFOA exposure at and near the DuPont Washington Works site have been discussed (Small 2009). Wang et al. (2013b) identified several of the fluorinated compounds that are currently being used by major manufacturers as alternatives to PFOA and PFOS. Environmental fate and toxicity research of newer replacement substances is ongoing (De Silva et al. 2016; Gomis et al. 2018; Kabore et al. 2018).

Bioavailability from Environmental Media. Perfluoroalkyls are widely detected in humans and animals, indicating that several of these substances are bioavailable. The bioaccumulation potential of perfluoroalkyls is reported to increase with increasing chain length (de Vos et al. 2008; Furdui et al. 2007; Martin et al. 2004b). In living organisms, perfluoroalkyls bind to protein albumin in blood, liver, and eggs and do not accumulate in fat tissue (de Vos et al. 2008; Kissa 2001). The mechanism of perfluoroalkyl uptake in animals is not fully understood; additional studies would be helpful (de Vos et al. 2008). Perfluoroalkyls discussed in this profile exist as a mixture of linear and branched isomers. Data regarding the bioavailability of branched versus linear substances would be useful. A data need exists to determine the bioavailability of the replacement substances identified in Wang et al. (2013b) used in place of PFOA and PFOS.

Food Chain Bioaccumulation. High levels of certain perfluoroalkyls in animals have been measured in apex predators, such as polar bears, which indicates that some perfluoroalkyls possess the ability to bioaccumulate (de Vos et al. 2008; Houde et al. 2006a; Kannan et al. 2005; Smithwick et al. 2005a, 2005b, 2006). Perfluoroalkyl sulfonates with carbon chain length lower than 8 tend to bioaccumulate less than PFOS. Ongoing monitoring of perfluoroalkyl levels in animals may help to determine whether efforts to phase out these substances will have had an effect on their biomagnification. A data need exists to determine the bioaccumulation potential of the new replacement substances used in place of PFOA and PFOS.

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

Concentrations of perfluoroalkyls have been measured in surface water from several locations across the United States (Boulanger et al. 2004; Kannan et al. 2005; Kim and Kannan 2007; Nakayama et al. 2007; Simcik and Dorweiler 2005; Sinclair et al. 2004, 2006). Continued monitoring for perfluoroalkyls in surface water would be useful. Data are available regarding levels of perfluoroalkyls in outdoor air, indoor air, indoor dust, food, food packaging, and consumer products (3M 2001; Barber et al. 2007; Begley et al. 2005; Food Standards Agency 2006; Fromme et al. 2007b; Harada et al. 2005b, 2006; Jogsten et al. 2009; Kim and Kannan 2007; Kubwabo et al. 2005; Moriwaki et al. 2003; Tittlemier et al. 2007; Washburn et al. 2005). Comprehensive studies monitoring for perfluoroalkyls in these matrices within the United States are needed. Elevated concentrations of perfluoroalkyls have been measured in air, water, soil, and sediment near fluorochemical industrial facilities (3M 2007b, 2008b, 2008c; Barton et al. 2006; Davis et al. 2007; Hansen et al. 2002). Additional research is needed to evaluate how soil physical and chemical properties influence the bioavailability of perfluoroalkyls. Continued monitoring for perfluoroalkyls in these matrices are needed to assess exposure of individuals working at these locations and individuals who live near these facilities. A data need also exists to perform environmental monitoring of the replacement substances identified in Wang et al. (2013b) used in place of PFOA and PFOS, particularly near manufacturing locations.

Exposure Levels in Humans. Trudel et al. (2008) provided a thorough assessment of the exposure of the general population to PFOS and PFOA. 3M (2008b) provided an assessment of exposure of individuals to PFOA on-site at a fluoropolymer facility. Uptake values and exposure pathways determined in these studies should be examined further. Conclusions made in these assessments are expected to be adjusted as future monitoring data are made available. Large-scale monitoring of perfluoroalkyls in human serum in the United States is ongoing (Calafat et al. 2006a). Future results of human monitoring studies would be useful for assessing human exposure to these substances over time. The results of these studies can be examined for correlations between human perfluoroalkyl levels and the phasing out of perfluoroalkyls by companies of the fluorochemical industry. Levels of perfluoroalkyls in human urine have been reported (Jurado-Sanchez et al. 2014). Higher exposure levels for individuals who reside in areas where substances such as PFOA contaminated both public and private water supplies

have been documented (Emmett et al. 2006a, 2009). Continued biomonitoring of legacy compounds such as PFOA and PFOS as well as other perfluoroalkyls is needed.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Trudel et al. (2008) provided a thorough assessment of the exposure of children to PFOS and PFOA. These conclusions should be reexamined with respect to future biomonitoring data when they become available. Data are available regarding the levels of perfluoroalkyls in young children (Kato et al. 2009b; Olsen et al. 2004b; Toms et al. 2009). NHANES monitoring data for 2013–2014 for children of ages 3–11 years have recently been released (CDC 2018; Ye et al. 2018a). Data provided from these efforts will be useful in assessing the exposure of young children to perfluoroalkyls.

Concentrations of perfluoroalkyls have been measured in human breast milk and cord blood (Apelberg et al. 2007a, 2007b; Fei et al. 2007; Inoue et al. 2004; Kärrman et al. 2007; Midasch et al. 2007; So et al. 2006b; Völkel et al. 2008). Additional monitoring for perfluoroalkyls in these media would be useful. Continued biomonitoring of legacy compounds such as PFOA and PFOS as well as replacement substances is needed.

6.3 Ongoing Studies

A number of federal agencies are sponsoring ongoing studies; a list of these studies are available at https://www.atsdr.cdc.gov/pfas/PFAS-health-effects.html.