



Human and Ecological Health Effects and Risk Assessment of Per- and Polyfluoroalkyl Substances (PFAS)

1 Introduction

Since their identification as contaminants of emerging concern in the early 2000s, per- and polyfluoroalkyl substances (PFAS) have been the focus of numerous studies that have evaluated their potential to cause adverse effects in humans, laboratory animals, and ecological species. The results of those studies, briefly summarized here, indicate that certain PFAS have been associated with health effects in both human and nonhuman species.

Certain perfluoroalkyl acids (PFAAs) and other PFAS are known to accumulate in humans, non-human mammals, fish, and plants. Perfluoroalkyl sulfonates (PFSAs) with six or more fluorinated carbons (that is, PFHxS and longer chain) and perfluoroalkyl carboxylates (PFCAs) with seven or more fluorinated carbons (that is, PFOA and longer chain) are substantially more bioaccumulative in humans and other mammalian species than shorter chain PFAAs. In species that inhabit or depend on aquatic ecosystems, PFAAs may also bioconcentrate and/or biomagnify. In fish, PFAAs with eight or more fluorinated carbons (PFNA and longer chain for PFCAs; PFOS and longer chain for PFSAs) are considered to be bioaccumulative. In general, PFSAs are more bioaccumulative than PFCAs with the same number of fluorinated carbons (Conder et al. 2008; Martin et al. 2003 Ref#633). In plants, short-chain PFAAs tend to be more bioaccumulative than long-chain PFAAs. (see Section 5.5 and 5.6 of the Guidance Document). Information about detected PFAS concentrations in biota is included in Section 6.5 of the Guidance Document.

This fact sheet also summarizes some of the specific challenges that PFAS pose in conducting human and ecological site risk assessments. Some of these include the limitations of the studies of adverse effects as well as possible complicating factors of exposure via multiple routes.

Additional information and references on these and other related topics are available in the Guidance Document.

2 Human Health Effects

Human health effects of PFAS are discussed in Sections 7.1 and 17.2 of the Guidance Document. Table 1 summarizes current animal toxicology and human epidemiology information for PFOA and PFOS, the two PFAS with the most health effects data.

Some PFAS have been linked to multiple health endpoints in studies of the general population and communities with contaminated drinking water. Laboratory animal toxicology studies and human epidemiological studies suggest health effects that may occur as a result of long-term exposure to PFOA and PFOS at environmentally relevant concentrations.

ITRC has developed a series of fact sheets that summarizes recent science and emerging technologies regarding PFAS. The information in this and other PFAS fact sheets is more fully described in the **ITRC PFAS Technical and Regulatory Guidance Document (Guidance Document)** (<https://pfas-1.itrcweb.org/>).

The purpose of this fact sheet is to summarize:

- Human health effects
- Ecological effects
- Site risk assessment challenges

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Table 1. Some health effects of PFOA and/or PFOS identified from published studies (not exhaustive).

Source: PFAS-1, Figure 7-1.

Animal	Human (associations)
Liver effects	Liver effects (increased serum enzymes)
Immunological effects	Increased serum cholesterol
Developmental effects	Immunological effects (decreased vaccination response)
Endocrine effects (thyroid)	Developmental effects (decreased birth weight)
Reproductive effects	Endocrine effects (thyroid disease)
Tumors (liver, testicular*, pancreatic*)	Cardiovascular effects (pregnancy induced hypertension)
	Cancer* (testicular, kidney)

**PFOA Only*

The toxicological effects of other PFAS that have been studied are generally similar to those of PFOA and PFOS. However, long-chain PFAAs are generally toxic at lower doses than short-chain PFAAs. This is because, as discussed above, long-chain PFAAs are more bioaccumulative than short-chain PFAAs and therefore build up to higher levels in the body from the same dose compared to short-chain PFAAs. Human bioaccumulation of PFAAs can occur regardless of the route of exposure. Of the four PFAS that have been tested for carcinogenicity in rodents, two PFAAs - PFOA, PFOS, and HFPO-DA (GenX) - a perfluorinated ether carboxylate (PFCECA)- caused tumors; another PFAA, PFHxA, did not. The majority of the thousands of PFAS known to exist, including many that are in commercial use and/or are found in drinking water or other environmental media, have very limited or no toxicity data. This is a critical data gap in health effects information for PFAS.

Certain long-chain PFAAs have human half-lives of several years, and they have been detected in the blood serum of almost all U.S. residents (CDC 2022 Ref#2266; Olsen et al. 2017; CA OEHHA 2011). These serum levels result from exposures to both the long-chain PFAAs and to other PFAS that are their precursors from sources that include food and food packaging, consumer products, and house dust. Decreasing serum levels of PFOS and PFOA in the U.S. general population likely results from the phaseout of their production and use in many products. Higher serum levels of PFAS are found in communities where contaminated drinking water or recreationally caught fish are consumed and in workers with occupational exposure.

Because developmental effects are considered to be sensitive endpoints for long-chain PFAAs, exposures during developmental lifestages (for example, fetus, infant) are important. PFAAs are known to cross the placenta to reach the fetus and are transferred from the mother to breast milk. In the general population, exposures to long-chain PFAAs (in breast-fed infants can be higher than in their mothers. Additionally, when an infant’s formula is prepared with contaminated water or the mother of a breastfed infant drinks contaminated water, exposure to the infant can be higher than in adults who consume the contaminated water. See section 17.2.3.1 of the Guidance Document for more information and references.

Historically, animal toxicity data were used as the basis for state and federal PFAS toxicity factors (reference doses, cancer slope factors) and guidelines. One reason for the reliance on animal data has been that there is concurrent exposure to multiple PFAS in the human study populations, making it difficult to determine the impact of individual PFAS. However, California EPA (CA OEHHA 2023 Ref#2717) and/or USEPA have developed draft reference doses for PFOA (USEPA 2023 Ref#2698), PFOS (USEPA 2023 Ref#2699), PFHxS (USEPA 2023 Ref#2857), and PFDA (USEPA 2023 Ref#2711), and a draft cancer slope factor for PFOA (USEPA 2023 Ref#2698; CA OEHHA 2023 Ref#2717) based on human general population data, and some European values are also based on human data.

3 Ecological Effects

Ecological health effects of PFAS are discussed in Section 7.2 of the Guidance Document. Biomonitoring studies across a variety of organisms, habitats, and geographies show that certain PFAS compounds can accumulate in wildlife and that exposures are occurring on a global scale (Reiner and Place 2015; Giesy and Kannan 2001). However, little is known about whether or how these exposures are translating into adverse effects in wildlife. Wildlife species may accumulate

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PFAS by the consumption of contaminated plants or prey items; or through the ingestion or uptake of PFAS present in soil, sediments, or water. Whether a given PFAS also bioconcentrates and/or biomagnifies depends on the chemical properties of the individual PFAS, the trophic level of the species, physiological factors such as biological sex, and whether exposure occurs in fresh or marine waters (see Sections 5.5 and 5.6 of the Guidance Document). Because of their propensity for bioaccumulation, even extremely low or undetectable concentrations of PFAS in the environment may present potential health risks to organisms through direct exposure to impacted abiotic media, and/or indirectly through the food chain.

There is a large body of aquatic toxicity data for PFAS, with relatively fewer controlled laboratory experiments for terrestrial taxa, notwithstanding typical laboratory mammals. Overall, there are comparatively more ecological effects data available for PFOS and PFOA than for other PFAS. Furthermore, acute exposure scenarios in laboratory tests are more commonly found than chronic exposure scenarios to PFAS.

Additionally, data for freshwater species are more abundant than those for saltwater. Direct toxicity data are relatively limited for benthic invertebrates and sediment-dwelling species for sensitivity to PFAS from bulk sediment exposures. For PFOS, effects on both invertebrates and fish occur at lower concentrations following chronic exposures compared to acute exposures. Although data are limited for amphibians, those that are available suggest that the effects of PFAS to amphibians fall within the range of effects concentrations for reported fish following acute and chronic exposures.

In the terrestrial environment, there are more published studies with apical endpoints for mammalian species than other classes of organisms. Toxicity tests on laboratory mammals (for example, mice) have shown that exposure to PFAS may result in adverse effects on the hepatic, endocrine and immune systems; development; and certain types of cancers. Toxicity testing with terrestrial plants, invertebrates and avian species has been performed but data are currently sparse for PFAS other than PFOS or PFOA.

Despite the growing body of literature on ecotoxicity of PFAS, there still remain significant data gaps. While there are many known PFAS, standard laboratory testing has been limited to a relatively small subset of PFAS compounds. Furthermore, effects of PFAS mixtures remains largely unexplored. Finally, there is a need to expand PFAS testing for terrestrial taxa, especially reptiles and amphibians.

4 Site Risk Assessment

Site risk assessment challenges specific to PFAS are discussed in Sections 9 and 17.3 of the Guidance Document.

Human Health Risk Assessment

In the general population, the predominant PFAS human exposure pathways are illustrated in Figure 1.

- Food and food packaging
- Consumer products
- Ingestion of drinking water (areas with PFAS-contaminated water supplies)
- Infants (breast milk or formula)
- Contact in the workplace

Figure 1. Predominant human exposure pathways.

Source: PFAS-1, Figure 9-5.

The highest exposures to PFAS can occur during early life stages (Goeden, Greene, and Jacobus 2019). Exposures to infants from breast milk of exposed mothers or via formula prepared with contaminated water are higher compared to older age groups. At PFAS-contaminated sites, the relevant exposure routes and scenarios will depend on the PFAS

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source (for example, AFFF release, industrial site release) and on the uses of the site and adjoining properties, particularly whether PFAS have migrated to groundwater on- and off-site.

Numerous state, national, and international regulatory and advisory agencies have developed human toxicity values for various PFAS that could be potentially used in conducting risk assessments or in support of establishing policies for PFAS risk management at a site. The mobility, persistence, and bioaccumulative properties of PFAS are discussed in the Guidance Document, and can all contribute to complications in calculating toxicity values as well as challenges in evaluating possible cumulative effects.

Ecological Risk Assessment

Ecological risk assessment (ERA) for PFAS is challenging because of limited data and technical complexity. Identification of ecological risk-based toxicity thresholds is one challenge for many PFAS. As of June 2022, there are no federal PFAS guidelines or media screening thresholds available for ecological receptors. However, the USEPA has released draft ambient water quality criteria for PFOA (USEPA 2022 Ref#2300) and PFOS (USEPA 2022 Ref#2302) for public comment. Several states have established some criteria that are intended to protect aquatic organisms in their respective surface waters. Screening thresholds and guidelines have been adopted in some jurisdictions using published effects data for species pertinent to the geography and habitats within these jurisdictions. Most available guidelines are protective of freshwater aquatic life exposed to PFOS or PFOA. In addition to these regulatory guidelines, recent peer-reviewed reports provide medium-specific benchmarks for aquatic life, birds, and mammals for several PFAS, not just PFOS and PFOA (Ankley et al. 2020; Conder et al. 2020; Divine et al. 2020, Argonne National Laboratory 2021). The reports also provide guidelines for performing ERA for PFAS.

A second major challenge with toxicity assessment for ERA is accounting for the large number of receptor types and the associated unknown variable sensitivity to PFAS. Although it is commonly understood that sensitivity to contaminants can vary widely across kingdoms or across classes of animals, the challenge for PFAS may be greater due to the lack of knowledge about this family of compounds. A third major challenge in effects assessment for PFAS is considering the toxicity of mixtures. At this time there are only limited data available to sufficiently understand the toxicity of more than just a few chemicals with respect to direct toxicity to lower trophic level organisms or exposure to upper trophic level wildlife. Detections of PFAS in tissues of top predators within both aquatic and terrestrial ecosystems point to ongoing exposure from bioaccumulative and possibly biomagnifying PFAS (see Section 5.5.3 of the Guidance Document). There are some published studies of the uptake and elimination of PFAS within aquatic organisms including fish and frogs. Bioconcentration factors and bioaccumulation factors are available to aid in conducting quantitative food chain modeling to upper trophic level wildlife.

5 References and Acronyms

The references cited in this fact sheet and further references can be found at <https://pfas-1.itrcweb.org/references/>. Reference numbers are included in this fact sheet for non-unique citations in the Guidance Document reference list.

The acronyms used in this fact sheet and in the Guidance Document can be found at <https://pfas-1.itrcweb.org/acronyms/>.



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