EPA/635/R-24/172Fc
www.epa.gov/iris

IRIS Toxicological Review of Perfluorodecanoic Acid (PFDA) and Related Salts

CASRN 335-76-2

July 2024

Integrated Risk Information System
Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

EXECUTIVE SUMMARY

Summary of Occurrence and Health Effects

Perfluorodecanoic acid (PFDA, CASRN 335-76-2),[1] and its related salts are members of the group per- and polyfluoroalkyl substances (PFAS). This Toxicological Review applies to PFDA as well as salts (including nonmetal or alkali metal salts) of PFDA that would be expected to fully dissociate in aqueous solutions of pH ranging from 4 to 9 (e.g., in the human body). Thus, while this Toxicological Review would not necessarily apply to nonalkali metal salts of PFDA because of the possibility of PFDA-independent contributions of toxicity, it does apply to PFDA salts including ammonium perfluorodecanoate (PFDA NH4, CASRN 3108-42-7) and sodium perfluorodecanoate (PFDA-Na, CASRN 3830-45-3), and other nonmetal or alkali metal salts of PFDA. The synthesis of evidence and toxicity value derivation presented in this Toxicological Review focuses on the free acid of PFDA, given the currently available toxicity data.[2]

Concerns about PFDA and other PFAS stem from the resistance of these compounds to hydrolysis, photolysis, and biodegradation, which leads to their persistence in the environment. PFAS are not naturally occurring in the environment; they are synthetic compounds that have been used widely over the past several decades in industrial applications and consumer products because of their resistance to heat, oil, stains, grease, and water. PFAS in the environment are linked to industrial sites, military fire training areas, wastewater treatment plants, and commercial products (see Section 1.1.3. for information specific to PFDA).

The Integrated Risk Information System (IRIS) Program is developing a series of five PFAS assessments (i.e., perfluorobutanoic acid [PFBA], perfluorohexanoic acid [PFHxA], perfluorohexanesulfonic acid [PFHxS], perfluorononanoic acid [PFNA], PFDA, and their associated salts) (see December 2018 IRIS Program Outlook) at the request of EPA National Programs. Specifically, the development of human health toxicity assessments for exposure to these PFAS represents only one component of the broader PFAS strategic roadmap at EPA that is aimed at characterizing potential health effects of individual PFAS and groups of PFAS

[1]The CASRN given here is for linear PFDA; the source PFDA used in the animal toxicity study NTP (2018) was reported to be >97% pure, giving this CASRN. For the human studies [e.g., Valvi et al. (2017)] the purity of the PFDA source was not provided by the study authors. None of the available studies explicitly state that only the linear form was used. Therefore, there is the possibility that some proportion of the PFDA used in the studies were branched isomers and thus observed health effects may apply to the total linear and branched isomers in a given exposure source.

[2]Candidate values for different salts of PFDA were also calculated by multiplying the candidate value for the free acid of PFDA by the ratio of molecular weights. For example, for the ammonium salt the ratio would be: $\frac{MW\ ammonium\ salt}{MW\ free\ acid} = \frac{531}{514} = 1.033$. This same method of conversion can be applied to other salts of PFDA, such as the potassium or sodium salts, using the corresponding molecular weights.

(https://www.epa.gov/pfas/pfas-strategic-roadmap-epas-commitments-action-2021-2024). For example, the EPA Office of Water (OW) has finalized a National Drinking Water Regulation (NPDWR) to establish Maximum Contaminant Levels (MCLs) for individual PFAS (PFOS, PFOA, PFNA, PFHxS, and hexafluoropropylene oxide dimer acid [HFPO-DA]) and mixtures of two or more PFAS (involving PFHxS, PFNA, PFBS, and HFPO-DA) (https://www.epa.gov/sdwa/and-polyfluoroalkyl-substances-pfas) and has finalized a framework for estimating noncancer health effects from PFAS mixtures (U.S. EPA, 2024c). Additionally, the EPA Center for Computational Toxicology and Exposure (CCTE) has developed a tiered toxicity testing strategy for evaluating PFAS using new approach methods (NAMs) that will inform future category grouping and read-across efforts to fill data gaps for PFAS with limited or no toxicity data (https://www.epa.gov/chemical-research/pfas-chemical-lists-and-tiered-testing-methods-descriptions).

The systematic review protocol (see Appendix A) for these five PFAS assessments outlines the related scoping and problem formulation efforts, including a summary of other federal and state assessments of PFDA. The protocol also lays out the systematic review and dose-response methods used to conduct this review (see also Section 1.2). The systematic review protocol was released for public comment in November 2019 and was updated based on those public comments. Appendix A links to the updated version of the protocol, which summarizes the history of the revisions.

Human epidemiological studies have examined possible associations between PFDA exposure and health outcomes, in particular liver serum biomarkers, antibody responses, sensitization and allergic responses, fetal growth restrictions, semen parameters, reproductive hormones, pubertal development, neurodevelopment, thyroid hormones, urinary effects, serum lipids, adiposity, cardiovascular disease, atherosclerosis, and cancer. With the exception of immune (i.e., decreased antibody responses) and developmental (i.e., decreased birth weight) outcomes, the ability to draw judgments regarding these associations based on the available human evidence is limited by the overall quality of the epidemiological studies (studies were generally *low* confidence), the small number of studies per health outcome, and, in some studies, the lack of a quantifiable measure of exposure.

Animal studies of PFDA exposure exclusively examined the oral exposure route; therefore, an inhalation assessment was not conducted and an RfC was not derived (see Section 5.2.3). The available animal studies of oral PFDA exposure examined a variety of noncancer endpoints, including those relevant to liver, immune, developmental, male, and female reproductive, endocrine, urinary, cardiometabolic, and other health effects. Limited evidence was identified evaluating PFDA-induced carcinogenicity in animals.

Overall, the available ***evidence indicates*** that PFDA exposure is likely to cause liver, immune, developmental, and male and female reproductive effects in humans, given sufficient

exposure conditions.[3] Specifically, for liver effects, the primary support for this hazard conclusion included evidence of increased relative liver weights, altered serum biomarkers of liver injury (e.g., serum enzymes) and histopathology (including necrosis) in rats. For immune effects, the primary supporting evidence included decreased antibody responses in children. Developmental effects were identified as a hazard based primarily on consistent findings of dose-dependent decreases in fetal weight in mice supported by evidence of decreased birth weight from studies of exposed humans in which PFDA was measured during pregnancy. The primary basis for the hazard judgment on male reproductive effects involved coherent responses across sperm counts, testosterone levels, and male reproductive histopathology and organ weights in adult male rats. For female reproductive effects, the primary hazard judgment was based on decreased uterus weight and estrous cycle effects in adult female rats. Selected quantitative data from these identified hazards were used to derive lifetime and subchronic organ-specific reference doses (osRfDs) (see Table ES-1) and the overall lifetime and subchronic RfDs (see Table ES-2).

The available ***evidence suggests*** that PFDA exposure might have the potential to cause cardiometabolic and neurodevelopmental effects in humans under sufficient exposure conditions[4] based on findings from human studies; however, because of inconsistency issues, imprecision, and/or sensitivity, these health hazards were not used in the derivation of toxicity values. Likewise, some human and animal evidence was also identified for endocrine, urinary, and other health effects (e.g., hematological), but the ***evidence is inadequate*** to assess whether PFDA may cause these health effects in humans and was not advanced for the derivation of toxicity values.

Table ES-1. Organ-specific RfDs for health effects with evidence available to synthesize and draw summary judgments for the derivation of toxicity values

Organ/system	Integration judgment	Toxicity value	Value (mg/kg-d)	Confidence	UF_A	UF_H	UF_S	UF_L	UF_D	UF_C	Basis
Immune (developmental immune effects)	Evidence indicates (likely)	Lifetime osRfD and subchronic osRfD	2×10^{-9}	*Medium*	1	10	1	1	3	30	Decreased serum antibody concentrations for both tetanus and diphtheria in children at age 7 yr and PFDA measured at age 5 yr Grandjean et al. (2012); (Budtz-Jørgensen and Grandjean, 2018a)

[3]The "sufficient exposure conditions" are more fully evaluated and defined for the identified health effects through dose-response analysis in Section 5.

[4]Given the uncertainty in this judgment and the available evidence, this assessment does not attempt to define what might be the "sufficient exposure conditions" for developing these outcomes (i.e., these health effects are not advanced for dose-response analysis in Section 5).

Organ/system	Integration judgment	Toxicity value	Value (mg/kg-d)	Confidence	UF_A	UF_H	UF_S	UF_L	UF_D	UF_C	Basis
Developmental	Evidence indicates (likely)	Lifetime osRfD and subchronic osRfD	2×10^{-9}	*Medium-low*	1	10	1	1	3	30	Decreased birth weight in male and female children (Wikström et al., 2020)
Liver	Evidence indicates (likely)	Lifetime osRfD	ND[a]								
		Subchronic osRfD	6×10^{-7}	*Medium*	3	10	10	1	3	1,000	Increased relative liver weight in SD female rats (NTP, 2018)
Male Reproductive	Evidence indicates (likely)	Lifetime osRfD	ND[a]								
		Subchronic osRfD	3×10^{-6}	*Medium-Low*	3	10	10	1	3	1,000	Decreased absolute whole epididymis weight in SD rats (NTP, 2018)
Female Reproductive	Evidence indicates (likely)	Lifetime osRfD	ND[a]								
		Subchronic osRfD	1×10^{-6}	*Medium-Low*	3	10	10	1	3	1,000	Increased number of days spent in diestrus in SD rats (NTP, 2018)

ND = not determined; RfD = reference dose (in mg/kg-day) for lifetime exposure; subchronic RfD = reference dose (in mg/kg-d) for less-than-lifetime exposure; osRfD = organ- or system-specific reference dose (in mg/kg-d); UF_A = animal to human uncertainty factor; UF_C = composite uncertainty factor; UFD = evidence base deficiencies uncertainty factor; UF_H = human variation uncertainty factor; UF_L = LOAEL to NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

[a]For hepatic, male reproductive, and female reproductive effects, derivation of candidate lifetime values was not attempted given the high degree of uncertainty associated with using PODs from a 28-day rodent study to protect against effects observed in a chronic setting.

Table ES-2. Overall Lifetime and subchronic RfDs

Organ/system	Integration judgment	Toxicity value	Value (mg/kg-d)	Confidence	UF_A	UF_H	UF_S	UF_L	UF_D	UF_C	Basis
Immune/ developmental	Evidence indicates (likely)	Lifetime osRfD and subchronic osRfD	2×10^{-9}	*Medium*	1	10	1	1	3	30	Decreased serum antibody concentrations for tetanus and diphtheria in children at age 7 yr and PFDA measured at age 5 yr Grandjean et al. (2012); (Budtz-Jørgensen and Grandjean, 2018a) Decreased birth weight in male and female children (Wikström et al., 2020)

ND = not determined; RfD = reference dose (in mg/kg-day) for lifetime exposure; subchronic RfD = reference dose (in mg/kg-day) for less-than-lifetime exposure; osRfD = organ- or system-specific reference dose (in mg/kg-day); UF_A = animal to human uncertainty factor; UF_C = composite uncertainty factor; UF_D = evidence base deficiencies uncertainty factor; UF_H = human variation uncertainty factor; UF_L = LOAEL to NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Lifetime and Subchronic Oral Reference Dose (RfD) for Noncancer Effects

Both of the identified hazards with quantitative information to support the derivation of candidate lifetime values (i.e., immune, and developmental) were selected as the basis for the RfD of 2×10^{-9} mg/kg-day.[5,6] The specific effects were decreased serum antibody concentrations in children (male and female) (Budtz-Jørgensen and Grandjean, 2018a); (Grandjean et al., 2012) and decreased birth weight (male and female) (Wikström et al., 2020). The PODs for these two osRfDs were similar (i.e., 6.04×10^{-8} and 5.44×10^{-8}, respectively). Identical UFs were applied resulting in the same RfD for both effects. $BMDL_{1/2SD(HED)}$ values for decreased antibody concentrations for both tetanus and diphtheria at age 7 years and PFDA measured at age 5 years were nearly identical (6.04×10^{-8} and 5.98×10^{-8} mg/kg-day, respectively) and were used as the point of departure (POD) for this endpoint. For decreased birth weight in males and females (Wikström et al., 2020), a $BMDL_{5RD(HED)}$ of 5.44×10^{-8} mg/kg-day was identified for this endpoint and was used as the POD. The osRfDs for both outcomes were calculated by dividing the POD_{HED} by an identical composite

[5]The candidate values for different salts of PFDA would be calculated by multiplying the candidate value for the free acid of PFDA by the ratio of molecular weights. For example, for the ammonium salt the ratio would be: $\frac{MW\ ammonium\ salt}{MW\ free\ acid} = \frac{531}{514} = 1.033$. This same method of conversion can be applied to other salts of PFDA, such as the potassium or sodium salts, using the corresponding molecular weights.

[6]Note that the RfD for the free acid presented in this document and an RfD for the anion of PFDA (perfluorodecanoate, $C_{10}F_{19}O_2^-$, CASRN 73829-36-4) would be practically identical given the molecular weights between the two compounds differ by less than 0.5% (i.e., by the weight of a single hydrogen atom).

uncertainty factor of 30 to account for interindividual differences in human susceptibility (UF_H = 10), and deficiencies in the toxicity evidence base (UF_D = 3). It is important to emphasize that both critical effects supporting this RfD are observed during the developmental period.

The same approach was selected as the basis for the subchronic RfD of 2×10^{-9} mg/kg-day. The subchronic and lifetime RfDs are identical given that the duration extrapolation uncertainty factor (UF_S) is 1 for both values. A UF_S of 1 was selected since the immune and developmental osRfDs are based on effects observed during the developmental period after exposure during gestation, which is recognized as a susceptible lifestage; therefore, exposure during this time window can be considered more relevant to the induction of sensitive effects on these outcomes than chronic and subchronic exposures (see Sections 5.2.1 and 5.2.2 for more details).

Confidence in the Oral Reference Dose (RfD) and Subchronic RfD

The overall confidence in the RfD and subchronic RfD is **medium** and is driven by *medium* confidence in the immune osRfD (the developmental osRfD was *medium-low* confidence), noting that there was *medium* confidence in the quantification of the PODs for both immune (Budtz-Jørgensen and Grandjean, 2018a); (Grandjean et al., 2012) and developmental (Wikström et al., 2020) endpoints using BMD modeling (Budtz-Jørgensen and Grandjean, 2018a); (Grandjean et al., 2012).

Noncancer Effects Following Inhalation Exposure

No studies that examine toxicity in humans or experimental animals following inhalation exposure were available and no acceptable physiologically based pharmacokinetic (PBPK) models are available to support route-to-route extrapolation; therefore, no RfC was derived.

Evidence for Carcinogenicity

Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), EPA concluded there is *inadequate information to assess carcinogenic potential* for PFDA by either oral or inhalation routes of exposure. Therefore, the lack of adequate data on the carcinogenicity of PFDA precludes the derivation of quantitative estimates for either oral (oral slope factor [OSF]) or inhalation (inhalation unit risk [IUR]) exposure.