Range of the Perfluorooctanoate (PFOA) Safe Dose for Human Health: An International Collaboration

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Abstract

Many government agencies and other expert groups have estimated a dose-rate of perfluorooctanoate (PFOA) that would protect human health. Most of these evaluations are based on many of the same studies (whether of humans, laboratory animals, or both), and all note various uncertainties in our existing knowledge with regard to this chemical and its risks to human health. Nonetheless, the values of these various, estimated, safe-doses (known by various names) vary widely, with some being more than 100,000 fold different than others. This sort of discrepancy invites scrutiny and explanation.

The Steering Committee of the Alliance for Risk Assessment (*ARA*) called for scientists interested in attempting to understand and potentially narrow these disparities. An advisory committee of nine scientists from four countries was selected from nominations received, and a subsequent invitation to scientists internationally led to the formation of three technical teams (for a total of 24 scientists from 8 countries). The teams reviewed relevant information and independently developed ranges for estimated PFOA safe doses. All three teams determined that the available epidemiologic information could not form a reliable basis for a PFOA safe dose-assessment in the absence of mechanistic data that are relevant for humans at serum concentrations seen in the general population. Based instead on dose-response data from five studies of PFOA-exposed laboratory animals, we estimated that PFOA dose-rates 10 to 70 ng/kg-day are protective of human health.

Disclaimers

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HC and LD are salaried employees of Ramboll US Consulting, Inc., a consulting firm that provides scientific and technical support to a variety of clients in private and public sectors. Participation in the project and the preparation of the manuscript reflects the professional work of the authors and may not necessarily reflect the views of Ramboll US Consulting, Inc. or its parent company, Ramboll Group A/S. HC and LD did not receive outside funding to participate in this project or prepare the manuscript; the manuscript was prepared on their own time or supported by Ramboll as part of their usual employment responsibilities. Prior to preparing the manuscript, LD has been retained as an expert witness on behalf of defendants in litigation matters pertaining to certain PFAS.

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FP is an employee of RHP Risk Management, a consulting firm, serving a variety of clients in the private and public sector. RHP has performed consulting and testifying work on various matters including PFAS. Neither FP nor RHP has shared this work with any RHP client nor elicited input into the design, preparation, or review of this work prior to publication. The time spent on this manuscript was either supported by RHP or was performed on the author's own time.

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Introduction

The development of a safe, or subthreshold,[1] dose for perfluorooctanoate (PFOA) has been ongoing for several years. In 2002, a suggested value of 4,000 ng/kg-day was developed by a team of scientists for the State of West Virginia (DEP, 2002). This assessment was subsequently relied on, in part, by the U.S. Environmental Protection Agency (EPA, 2005) in a draft assessment for EPA's Office of Toxic Substances. Later, EPA (2009) estimated a safe dose of 200 ng/kg-day draft assessment for its Office of Water on more recently available dose-response data.

Outside the U.S., other groups were also estimating safe doses for PFOA, including the European Food Safety Authority (EFSA, 2008) and the United Kingdom (COT, 2009), with both estimating a value of 1,500 ng/kg-day.

EPA (2016) revised its assessment by using a 10-fold lower safe dose (thus estimating 20 ng/kg-day), and five years later, revised the value again, this time lowering it quite substantially, to 0.0015 ng/kg-day (EPA, 2021).

Other authorities, such as the Drinking Water Inspectorate (2021), Health Canada (2018), the European Food Safety Authority (2018), Food Standards of Australian and New Zealand

[1] The term "safe" dose (aka "reference dose") is used throughout this text and is intended to represent a dose just below the population threshold. This population threshold is a point in the dose scale where the first adverse effect, that is the critical effect, is anticipated in a sensitive group of humans. The safe dose can be more formally defined as an estimate (with imprecision spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of adverse effects during a lifetime.

(FSANZ, 2017) and the Agency for Toxic Substances and Disease Registry (ATSDR, 2018) also have developed or revised their safe doses. These various values have been described previously (e.g., Mikkonen et al., 2020). The World Health Organization (2022) has also recently reviewed this information.

Table 1 lists some of these currently estimated safe doses for PFOA. The wide range in estimated values is striking. This disagreement among expert groups was noted by the Steering Committee of the Alliance for Risk Assessment (*ARA*)[2] as an issue that might be addressed via collaboration of interested and expert scientists.

It was not the intention of this collaboration to exhaustively review the literature on PFOA, since many authorities have already adequately done this. Nor was it the intention of this work to critique any individual authority's approach, although presumably not all approaches can be "correct," insofar as they disagree by orders of magnitude. Of course, there is still much to learn before we can arrive at maximally informed estimates of a truly safe dose of PFOA to protect human health. The intent of this work is to estimate a plausible range for such a dose now, anticipating that results of future research will refine and improve on current estimates.

Methods

The Steering Committee of the Alliance for Risk Assessment (*ARA*) solicited nominations from interested scientists and managers in the early fall of 2022 to form an advisory committee that would shepherd the project entitled "The Perfluorooctanoate (PFOA) Safe Dose".[3] After reviewing nominations, an Advisory Committee was selected from nominations received as shown in Appendix 1.

The Advisory Committee assembled a list of relevant publications on PFOA safe dose and opened a call for interested scientists in the late fall of 2022 to participate in an international collaboration to investigate this issue. After nominations from scientists interested in this collaboration were reviewed by the Advisory Committee, three independent teams of scientists were selected as also shown in Appendix 1, assuring that various scientific experts were represented in each team.

The overall objective of each team was to review relevant information and various agency positions on PFOA in order to determine their safe dose ranges. The teams considered the following criteria in their evaluation: known or suspected mode of action (MOA), overall consistency in response among studies, coherence between experimental animal and epidemiology data, and robustness of the overall dose response. The science teams were directed to review and discuss relevant literature and positions independently of each other and in the following manner:

- First, focus on PFOA's MOA for its critical effect(s),

[2] See: https://tera.org/Alliance%20for%20Risk/ARA_Steering_Committee.htm

[3] See: https://tera.org/Alliance%20for%20Risk/Projects/pfoahumanhalflife.html

- Then focus on determination of the critical studies for one or more of its critical effect(s),
- Finally, focus on the choice of extrapolation method including the choice of uncertainty factors.

The sequence of work was interspersed with periodic Zoom conference calls in which the teams shared and discussed their independently developed results and attempted consensus around the various focus topics.

Results

The results provided below are summarized by the charges given to the three teams. Teams worked independently on each charge and then shared results prior to the periodic international Zoom meetings.

PFOA's Mode of Action

Overall, each of the teams found it difficult to identify a particular MOA finding because little information exists on MOAs other than perhaps for the liver effects found in rodents due to peroxisome proliferator-activated receptor (pPAR) activation. However, since humans and rodents have strikingly different pPAR activations, the relevance to development of a safe dose range for PFOA based on rodent data is uncertain. Each of the teams found that answers to questions regarding relevance of these findings and their associated MOAs in humans were thought to not likely come from human studies, but at the same time experimental models were needed that more closely resemble humans.

There was general agreement that a likely MOA involved fatty acid mimicry. Fatty acids serve several functions in multiple systems of the body including the ability of the cell to maintain normal fatty acid homeostasis. Membrane fluid dynamics due to the insertion of PFOA into plasma membranes was raised as a possible MOA. Such fluidity might be expected due to PFOA's chemical similarity to plasma lipids and limited volume of distribution from the sole clinical study in humans (suggesting quick sequestration). Insertions of PFOA molecules into the membrane without associated hydrogen bonding might make such membranes less efficient, and if given sufficient dose, might be expected to cause a host of effects. While this was considered a plausible hypothesis, it was not known how much PFOA would be needed per cell membrane to cause leakage or fluidity.

Discussion then segued into the widely different choices of critical effect[4] and their tentative MOA evident among national authorities. Not all critical effects were thought to be relevant to

[4] Critical effect is defined here as the first adverse effect, or its known and immediate precursor, that occurs as dose is increased. It is recognized that multiple effects may be critical (occurring at or around the same dose), and that

risk assessment intended to protect human health. For example, while observed associations between PFOA body-burdens in populations and diminished levels of serum antibodies following immunization to one or more specific types of vaccines might prompt additional investigation, the current body-burden/antibody level data were not deemed suitable for developing a safe dose since the assessments were based upon secondary immune response, rather than primary, which contradicts the WHO immunotoxicology guidelines (derived from Van Loveren et al., 1999), as a reliable quantitative measure of immune function. Moreover, as several team-members noted, it was unclear whether small decreases in "vaccine responses" are clinically significant because vast inter- and intra-individual human variability in natural vaccine response exists. This variability precludes any definitive statement in the choice of this endpoint as the critical effect. Finally, a SciPinion panel (Garvey et al., 2023) on immunotoxicity of PFOA suggests that the vaccine threshold of 0.1 IU/ml was not helpful for risk assessment since it is a surrogate of protection and basic immunity is presumed at even lower antibody concentrations (WHO, 2009), most recently 0.01 IU/ml.

Clinical effects in many of the other human observational studies, such as increases in cholesterol and decreases in birth weight, were of small magnitude or imprecisely estimated. Investigators generally reported that these differences were within normal laboratory reference ranges in relation to PFOA blood concentrations and thus might reflect pharmacological bias or reverse causality due to the fatty acid mimicry based on PFOA's chemical structure. Although cholesterol changes did not appear to be definitive and were deemed not likely to be the critical effect, studying other inflection points or hormetic responses seemed worthwhile. Reverse causality or confounding by physiological determinants of exposure and effect biomarkers may apply to more than one effect.

An argument can be made that small decreases (in antibody concentrations or birth weight) or small increases (in cholesterol) associated with PFOA blood concentrations can lead to a shift in the population distribution of these clinical parameters, and potentially result in a higher proportion of individuals that experience increased risk of clinical disease. The basis of this argument, however, is an assumption that a causal relationship exists between PFOA and clinical disease (e.g., increases in frequency and occurrence of infectious diseases, hypercholesterolemia, or long-term developmental outcomes associated with low birth weight) and there is currently insufficient evidence of these adverse effects.

A final discussion ensued over whether the dose response information was adequate to develop a safe dose range. This question led to discussion of inflection points or potentially hormetic responses that might yield useful information, such as human observational studies showing an increase in cholesterol but the sole human clinical study on PFOA showed decreases (Convertino et al., 2018).

After presentations, clarifying questions and discussion, the consensus positions summarized in Table 2 and shown below were developed:

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critical effects in experimental animals may not reflect these same effects found or expected in humans. However, if the critical effect is prevented, then it is assumed that all subsequent adverse effects are prevented.

1. Several MOAs could be envisioned but not enough evidence exists to establish any one of these MOAs with certainty.
2. Some effects appear to be irrelevant for the determination of a safe dose from current epidemiology data, specifically cholesterol changes and vaccine status.
3. Studying inflection points or perhaps hormesis might help resolve why we have 100,000-fold differences in estimated PFOA safe doses internationally. While differences among such groups can often span a range of 3-fold due to differing times of analyses and methods, this large difference in PFOA is clearly not acceptable for informing confident decision-making, nor can all groups be correct.

Determination of Studies for PFOA's Critical Effect(s)

After reviewing the plethora of relevant information, none of the teams independently considered the epidemiology data, composed primarily of observational studies, to be sufficient to determine a critical effect. The results from these studies were considered to be not only potentially confounded, with confounding that was not readily quantified, but also to have serum concentrations from unidentified sources of exposure to PFOA that were not significantly different from background in most studies, making it difficult or impossible to assign a clear exposure-response association, much less causation. Because of these multiple and significant concerns, all three teams focused on experimental animals for consideration of the critical effect.

However, each team independently reached a different conclusion about the critical effect. One team considered monkey studies as most relevant due to the closeness to humans with PPAR-alpha activation for potential liver effects and general physiology, and the difficulty in interpretation of rodent developmental effects. Non-adverse liver effects were seen at all the doses tested in monkeys (3, 10, 20, and 30 mg/kg-day). These effects correlated roughly with non-adverse liver effects seen in the human observational studies and was consistent with the sole human clinical study by Elcombe et al. (2013).[5] Although these liver effects were not considered to be adverse in monkeys, mortality was also observed in monkeys at the higher doses leading to a clear No Observed Adverse Effect Level/Low Observed Adverse Effect Level (NOAEL/LOAEL) boundary. One member from this team reached out to the investigators of the monkey studies to ask for any additional data but none were available.

Another team selected rodent developmental studies rather than liver changes, and specifically Lau et al. (2006) as most relevant due to the consistency in response of several rodent species considering that the likely MOA was fatty acid mimicry. Specifically, PFOA has access to mid-chain fatty acid transport, and biliary and renal excretion and resorption. And while such mimicry might be readily handled by organs such as the liver, it might more readily disturb fatty acid homeostasis in the developing organism, thus supporting the selection of developmental

[5] The human clinical study of Elcombe et al. (2013) is in the same range and showed no overt effects (50 – 1200 mg/week ÷ 7 days ÷ 70 kg ~ 0.1 – 2.4 mg/kg-day).

effects as the critical, or perhaps co-critical effect. Moreover, pPAR-alpha induced liver effects occurred in rodents at about a 10-fold higher dose than those evoking developmental toxicity.

The third team did not judge that the liver effects seen in monkeys, or perhaps other species, were appropriate, since the effects seen were not adverse. Nor did this team consider the developmental effects by Lau et al. (2006) appropriate due to statistical issues associated with the study. Rather, this team was of the general opinion that the overall database was insufficient at this time to make a reliable judgment of critical effect and supported this position with the observation that different health agencies around the world have come to very different decisions. While these differences may not be direct evidence for the overall weakness in the database, the WHO (2022) came to the same conclusion. Specifically, the overall database was considered too uncertain to determine a scientifically based judgment of critical effect. Instead, WHO (2022) made a risk management recommendation.

After these presentations, clarifying questions and discussion, the following consensus positions were developed as summarized in Table 2 and shown below:

1. Should human studies be used for the development of the critical effect?
   No, existing human observational studies cannot be used reliably for this purpose. For example, changes in cholesterol appear to have only a small effect at low doses and an opposite effect at higher doses. These studies may support the choice of critical effect with some of the experimental animal work, however.
2. Should vaccine responses be used for the development of the critical effect?
   No, existing human observational vaccine findings are not primary immune responses and of questionable clinical relevance. Based on epidemiological study results, it is premature to assume that a population shift in the distribution of antibody concentrations – if one exists – results in increased risk of susceptibility to diseases. Moreover, higher dose worker exposures do not suggest immune responses.[6]
3. Should experimental animal studies be used for the development of the critical effect?
   The overall uncertainty in the database, both epidemiology and experimental animal, is sufficient to give pause to the development of a credible critical effect for PFOA. This conclusion is similar to what WHO (2022) found and for the same or similar reasons.
4. However, in recognition of the importance of managing PFOA potential health risk, and despite the overall difficulties in the experimental animal studies, a provisional approach was explored as follows:
   - Frank toxicity in both monkeys and rats has been observed in a dose related manner. We might be able to tie these effects into other liver and or developmental endpoints. One member volunteered to conduct a Benchmark Dose (BMD) approach on the relevant monkey and rodent studies, and send this to all three teams for consideration (information available upon request).
   - One team member asked participants to critique and improve upon Green and Crouch (2019).

[6] Experimental animal work indicates some immune toxicity but only at doses higher than those suggested in human observational studies.

- PFOA is the fluorinated version of the naturally occurring caprylic acid. A big difference between these two chemicals is their half-lives in the human body. Considering whether potential long-term toxicity from caprylic acid matches any of the findings with PFOA may prove useful.

Choice of Extrapolation Method

All teams developed a range in the PFOA safe dose. One team decided to build a range in the safe dose based on several studies of developmental effects in mice. The first study was Lau et al. (2006) with a NOAEL of 23 ug/ml for dose dependent growth deficits in offspring. Other studies considered were Onishchenko et al. (2011), Koskela et al. (2015), Loveless et al. (2006), and Macon et al. (2011). The resulting safe dose range from this collection of studies was 0.011 to 0.27 ug/kg-day.

A second team remained of the opinion that the overall database was insufficient at this time to make a reliable judgment of critical effect. Nevertheless, in order to develop a provisional range, this team focused on two mouse studies, specifically the developmental/reproduction study of Abbott et al. (2007) and the immunotoxicity study of DeWitt et al. (2016), with a range in the NOAELs from 0.3 to 0.94 mg/kg-day. The resulting safe dose range was 3 to 9.4 ug/kg-day from these two values. This team also developed a separate range by adjusting the kinetic comparison between mice and humans based on the work of Zhang et al. (2013) to develop a range of 0.3 to 515 ug/kg-day.

The last team considered liver effect as best meeting the criteria laid out initially and that the results in monkey were most relevant due to comparability of pPAR-alpha activation for potential liver effects and general physiology with humans, despite the small numbers of animals and some inconsistency with the reported observations. Butenhoff et al. (2002) showed liver weight increases in monkeys and Green and Crouch (2019) developed a benchmark concentration from these data of 19 ug/ml based on data from this study.

Discussion around these various ranges centered on whether the use of a clearance value from human study Zhang et al. (2013), as describe by Campbell et al. (2022), would be a better choice than clearance values from human observational studies described by Lorber and Egeghy (2011). Also discussed was whether the use of a database uncertainty factor would be reasonable, given the large uncertainty in the overall database. Some concern was also expressed over the use of Onishchenko et al. (2011) and Koskela et al. (2015) due to the small number of experimental animals and potential use of pup-based statistics. Lastly, the large range in the second team's calculation appeared to be due to conflating the mouse to human uncertainty factor for toxicokinetic variability with the within human uncertainty factor for toxicokinetic variability. Separating these two seemed reasonable to all participants.

The following consensus positions were developed as summarized in Table 2 and shown below:

1. The various positions of the three science teams appear to overlap, so that developing a provisional range in the PFOA safe dose, based on differing experimental animal studies, seemed reasonable. After discussion by all three teams, there was an agreement to develop a range of the safe dose based on liver effects in monkeys and developmental and immunological effects in mice.
2. The use of human data for this exercise was not entertained, consistent with the earlier consensus of all three science teams that human data were not adequate for identifying safe doses.
3. PFOA has an enormous database, but still has some uncertainty, especially in choosing the critical effect. A factor of 3-fold for this area of uncertainty should be considered.[7]
4. The use of the average clearance value (either mean, median, mode or geometric versions of these) from the Zhang et al. (2013) human study should be used with any of the experimental animal points of departure if in ug/ml of serum, or by comparison with kinetic information from the relevant species if the points of departure are in units of dose. Moreover, the Zhang et al. (2013) also shows human variability that can be used to develop a data-derived value for within human toxicokinetics. A preliminary analysis by Team 1 gives this a value of ~9-fold.

Development of a Provisional Safe Dose Range

A specific provisional range in the PFOA safe dose was subsequently developed based on information from the various consensus calls regarding PFOA's underlying MOA for various effects, its likely critical effect(s), and the extrapolation of experimental or human data to the presumed sensitive subgroup. The range of the PFOA safe dose is provisionally estimated to be 0.01 to 0.07 ug/kg body weight-day (10-70 ng/kg body weight-day) based on points of departure and uncertainty factors from the studies described in Table 3.

Discussion

The study of Macon et al. (2011) was not considered useful for development of a safe dose range because the statistics in this study appeared to be based on pups and not the maternal experimental animal. Using pups as the basis of the assessment is not in accordance with US EPA (1991) guidelines. In addition, neither Onischenko et al. (2011) nor Koskela et al. (2016) were used because of too few animals and limited doses used in these studies, and furthermore, the statistics also appeared to be based on pups and not the maternal experimental animal. The use of these studies for risk assessment is likewise not in accordance with US EPA (1991).

[7] After the meeting several members pointed out that a comprehensive two-generation reproductive toxicity study was conducted in Sprague-Dawley Rats by Butenhoff et al. (2004). EPA used this study to help justify a database UF of 1.

PFAS in general, and PFOA in particular, differ from many other chemicals and mixtures for which safe doses have been estimated. Exposure-response data for the two populations that have been most highly exposed to PFOA are limited in scope. These two PFOA-exposed groups were (i) workers who manufactured PFOA, and/or were otherwise occupationally highly exposed and (ii) a small group of end-stage cancer patients who were administered large doses of PFOA as a cancer chemotherapeutic drug (Elcombe et al., 2013; Convertino et al., 2018). Notably, though, observations in both such groups fail to indicate that PFOA presents a significant risk of toxicity.

As noted above, the observational epidemiologic data that associate PFOA body burdens *in the general public* with various biological endpoints cannot, in our judgment, serve as reliable basis for safe dose-assessment. These studies were considered to be not only unquantifiably confounded but also to have exposures that were not significantly different from background, which makes the interpretation of any association problematic. We recommend that the reliability of the results from these epidemiological studies are reconsidered after mechanistic data become available that supports (or argues against) the hypothesized MOAs; however, in the absence of mechanistic data relevant to humans at serum concentrations seen in the general population, the uncertainties of the reliability of the human data that show small differences in clinical biomarkers are substantial.

At present, the best that can be done, we believe, is to rely on dose-response data from PFOA-exposed laboratory animals. Mice and rats tend to be good models for humans for most chemicals; but for PFOA, mice and rats are rather less reliable human-models. Monkeys are much better models; but, of course, the numbers of monkeys that have been PFOA-exposed are small; and the endpoints that have been examined remain limited. Future research using non-human primates might well yield useful information for purposes of human health risk assessment.

With regard to the potential carcinogenicity of PFOA, there was general agreement that the EPA's proposed change in the categorization of PFOA from "suggestive evidence" to "likely carcinogen" is not justified. The EPA's determination was based primarily on the evidence of liver tumors in rodents and reported associations between PFOA concentrations and incidence of renal cell carcinoma (RCC) in humans. However, rodent liver tumors are observed only at doses associated with peroxisomal proliferation, a response that is not relevant to human exposures. Epidemiological studies, on the other hand, have not adequately considered the potential for confounding by impaired renal function, which is associated with both PFOA clearance and kidney cancer. Kidney cancer is frequently associated with impaired renal function and alterations in renal function that resulted in decreased PFOA excretion would result in a consequent increased PFOA concentration in serum. Cross-sectional analyses of adults exposed at background levels (Shankar et al. 2011) and of children exposed at high levels (Watkins et al. 2013) found a positive association between lower kidney function and higher measured serum PFOA. Dhingra et al. (2016), performed an analysis of cross-sectional studies reporting associations between PFOA and renal function, and concluded that pharmacokinetic confounding led to the observed associations. While Shearer et al. (2021) adjusted their results for estimated glomerular filtration rate (eGFR), adjusting for eGFR alone would not adequately

control for this potential confounding due to the extensive role of renal transporters in the clearance of PFOA.

The international process described in this brief communication has several advantages. Many of the scientists who volunteered for this task are well published in the area of PFOA, or in one or more of PFOA's designated critical effects, or in one or more of the extrapolation methods used to determine the provisional range of its safe dose. Many of these scientists are also intimately familiar with one or more of the agency positions on PFOA. Despite these credentials and familiarity, or perhaps because of them, uniformity of thought was not present, at least initially, and the Zoom call meetings were often lively but respectful. Therefore, the eventual consensus of 27 scientists from 8 countries over 6 months can perhaps be afforded a higher degree of trust than position developed with fewer or less diverse viewpoints.

This process, however, also has its drawbacks. First, it depended on group or self-nominations and from individuals from groups that may or may not appreciate a particular agency position. This concern was addressed in two ways. First, nominations to the Advisory Committee were solicited by the Steering Committee from known experts in the field along with an open nomination process. Members were then selected by the Alliance for Risk Assessment Steering Committee after a review of credentials. This Steering Committee is composed of 5 scientists, 3 from governments, one from a university and one from an environmental science non-government organization. In turn, members of the 3 science teams were selected by the Advisory Committee after an open nomination process and review of proffered biographical sketches/resumes. Balances were maintained among affiliations within each science team. A second drawback is that no funding was received for this work, making it difficult to follow-up on nuances of data that needed additional consideration.

The suggested provisional safe dose range of this international collaboration is 0.01 to 0.07 ug/kg-day. This range encompasses the single value of Health Canada (2018) and the projected range of values for the WHO (2022) and lies slightly below the value of Food Standards of Australia and New Zealand (FSANZ, 2017; Australian Government, 2022). However, this range is well above the single values of both EFSA (2021) and EPA (2021). The principal reasons for the larger disparity between this provisional range with these latter two single values is the unanimous judgment of the international collaboration that human data are not sufficiently credible as a basis of the PFOA safe dose. In this regard, Health Canada, the WHO and Food Standards of Australia and New Zealand are in agreement with the Collaboration---the use of human data is not sufficiently credible as the basis for the PFOA safe dose.

Additional thoughts from other colleagues are welcome. We continue to believe that,

> *…It is the mark of an instructed mind to rest satisfied with the degree of precision which the nature of the subject permits and not to seek an exactness where only an approximation of the truth is possible.* Aristotle

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Table 1. Safe Doses of PFOA and PFOS from International Authorities

Authority	Safe Dose ug/kg-day	Point of Departure (POD)	Uncertainty Factors
Alliance for Risk Assessment (this paper)	0.01-0.07	Various (see text): 4.35 to 23 ug/ml of serum	a) Animal-human kinetic factor = 1 b) Animal-human dynamic factor = 3 c) Human toxicodynamic factor = 3 d) Human toxicokinetic factor = 8.4 e) Database uncertainty factor = 1 f) Human clearance = 0.23 ml/day-kg
European Food Safety Authority (EFSA, 2018)	0.0008	Modeled using a physiologically based pharmacokinetic model.	• None applied • BMD from the general population included potentially sensitive subgroups and risk factors for disease rather than disease outcomes.
Food Standards Australia/New Zealand (2017)	0.16	4.9 ug/kg-day	• Within human variability = 10 • Animal to human extrapolation = 3
Health Canada (2018)	0.02	0.52 ug/kg-day	• Within human variability = 10 • Animal to human extrapolation = 2.5
US Environmental Protection Agency (2021)	0.0000015	0.0000149 ug/kg-day	• Within human variability = 10
World Health Organization (2022)	0.02	PFOA water level of 100 ug/liter	• WHO made a risk management call of 100 ug/liter • This value can be used to estimate the comparable safe dose of 0.02 using 2 liters of water consumption per day, a 60 kg body weight and a 20% relative source contribution.

a) Factor is not needed since PODs are based on serum concentrations.
b) The use of a 3 is the US EPA default position (US EPA, 2014); the IPCS (2005) default is 2.5.
c) The use of a 3 is both the US EPA and IPCS default positions.
d) This value of 8.4 is derived by dividing the value of 0.79 ml/day/kg, which is the arithmetic mean clearance of average group from Zhang et al. (2013, Table 2) by a value of 0.094 ml/day/kg, which is the arithmetic 95%

lower bound clearance of sensitive group from Zhang et al. (2013, Table 2).

e) Data base factor of 1 was considered appropriate for most PODs.

f) This value of 0.23 ml/day/kg is the geometric mean clearance from Zhang et al. (2013, Table 2) assuming steady state.

Table 2. International Collaboration Consensus Statements

Consensus on Mode of Action	Several MOAs could be envisioned but not enough evidence exists to establish any one of these MOAs with certainty.
	Certain effects appear to be irrelevant for the determination of a safe dose, specifically cholesterol changes & vaccine status.
	Studying inflection points or perhaps hormesis might help resolve why we have 100,000-fold differences in the PFOA safe dose internationally.
Consensus on Critical Effect	Existing human observational studies cannot be used reliably for developing the critical effect.
	Existing human observational vaccine findings are not primary immune responses and not of clinical relevance.
	The overall uncertainty in the database is sufficient to give pause to the development of a credible critical effect for PFOA. However…
	In recognition of the importance of managing PFOA potential health risk, a provisional approach could be developed based on several experimental animal studies.
Consensus on Extrapolation Method	The various positions of the three science teams overlap, so developing a provisional range in the PFOA safe dose, based on differing experimental animal studies, seemed reasonable.
	Human data are not an acceptable basis of the safe dose.
	PFOA has an enormous database, but still has some uncertainty, suggesting that a 3-fold factor may be reasonable.
	A clearance value from the Zhang et al. (2013) should be used with any of the experimental animal points of departure and can be used for a data-derived value for human toxicokinetics.

Table 3. Experimental Animal Studies as the Basis of the Provisional Safe PFOA Dose.*

Reference	Safe Dose ug/kg-day	Point of Departure (POD)
Butenhoff et al. (2002).	0.06	**Monkey**: Point of Departure = 19 ug/ml from Green and Crouch (2019) based on a serum PFOA benchmark concentration (BMC) for *increased liver weight*
Lau et al. 2006	0.07	**Mouse**: Point of Departure = 1 mg/kg-day or 23 µg/ml No Observed Adverse Effect Level (NOAEL) for *dose-dependent growth deficits* for gestation days 1-17
Loveless et al. (2006)	0.01	**Mouse**: Point of Departure = 4.35 µg/ml based on a serum PFOA benchmark concentration by New Jersey/New Hampshire (Post et al., 2021) for *lipid parameters/relative liver weight* in male mice
Abbott et al. (2007)	0.03	**Mouse**: Point of Departure = 0.3 mg/kg-day (10.4 ug/ml) NOAEL for *neonatal survival* found
DeWitt et al. (2016)	0.07	**Mouse**: Point of Departure = 0.94 mg/kg-day (no serum values available) NOAEL for *immune suppression* found

* See Appendix 2 for details of the various calculations.

Appendix 1

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Appendix 2

Monkey: Point of Departure = 19 ug/ml from Green and Crouch (2019) based on a serum PFOA benchmark concentration (BMC) for *increased liver weight* in Butenhoff et al. (2002).

- Monkey to human toxicokinetic factor = 1 [Factor is not needed since BMD is based on serum concentration]
- Monkey to human toxicodynamic factor = 2.5 [IPCS (2005) default or 3 EPA (2014) default]
- Human toxicodynamic factor = 3 [default of IPCS (2005) and EPA (2014)]
- Human toxicokinetic factor = 8.4 [0.79 ml/day/kg arithmetic mean clearance of average group from Zhang et al. (2013, Table 2) ÷ 0.094 ml/day/kg arithmetic 95% lower bound clearance of sensitive group from Zhang et al. (2013, Table 2)]
- Database uncertainty factor = 1 (Although it could be argued that the small number of animals in the study justifies an additional uncertainty factor; the counter-argument is that these are primates. See also footnote 7.)

- RfD serum concentration = 0.25 ug/ml [19 ug/ml ÷ (1 x 3 x 3 x 8.4 x 1) = 0.25]
- RfD = 0.06 ug/kg-day [0.25 ug/ml x 0.23 ml/day/kg [geometric mean clearance from Zhang et al. (2013, Table 2) assuming steady state]

Mouse: Point of Departure = 1 mg/kg-day or 23 µg/ml No Observed Adverse Effect Level (NOAEL) for *dose-dependent growth deficits* in the Lau et al. 2006 for gestation days 1-17

- Mouse to human toxicokinetic factor = 1 (Factor is not needed since BMD is based on serum concentration)
- Mouse to human toxicodynamic factor = 2.5 [IPCS (2005) default or 3 EPA (2014) default]
- Human toxicodynamic factor = 3 [default of IPCS (2005) and EPA (2014)]
- Human toxicokinetic factor = 8.4 [0.79 ml/day/kg arithmetic mean clearance of average group from Zhang et al. (2013, Table 2) ÷ 0.094 ml/day/kg arithmetic 95% lower bound clearance of sensitive group from Zhang et al. (2013, Table 2)]
- Database uncertainty factor = 1 (Although it has been argued that problems with this study might justify an additional uncertainty factor; the counter-argument is that US EPA uses a value of 1. See also footnote 7.)

- RfD serum concentration = 0.30 ug/ml [23 ug/ml ÷ (1 x 3 x 3 x 8.4 x 1) = 0.30]
- RfD = 0.07 ug/kg-day [0.30 ug/ml x 0.23 ml/day/kg [geometric mean clearance from Zhang et al. (2013, Table 2) assuming steady state]

Notes:

- It could be argued that the fetal toxicity is secondary to disruption of lipid metabolism in

the dam, as evidenced by the increased maternal liver weight at all doses.

- Several authorities consider the 1 mg/kg/d dose to be a LOAEL, but effects at the lowest dose were only observed in dams. Resulting US State RfDs range from 0.005 – 0.020 ug/kg-day (Post et al., 2021).

Mouse: Point of Departure = 4.35 µg/ml based on a serum PFOA benchmark concentration by New Jersey/New Hampshire (Post et al., 2021) for *lipid parameters/relative liver weight* in male mice from Loveless et al. (2006)

- Mouse to human toxicokinetic factor = 1 (Factor is not needed since BMD is based on serum concentration)
- Mouse to human toxicodynamic factor = 2.5 [IPCS (2005) default or 3 EPA (2014) default]
- Human toxicodynamic factor = 3 [default of IPCS (2005) and EPA (2014)].
- Human toxicokinetic factor = 8.4 [0.79 ml/day/kg arithmetic mean clearance of average group from Zhang et al. (2013, Table 2) ÷ 0.094 ml/day/kg arithmetic 95% lower bound clearance of sensitive group from Zhang et al. (2013, Table 2)]
- Database uncertainty factor = 1 (See footnote 7.)

- RfD serum concentration = 0.058 ug/ml [4.35 ug/ml ÷ (1 x 3 x 3 x 8.4 x 1) = 0.058]
- RfD = 0.01 ug/kg-day [0.058 ug/ml x 0.23 ml/day/kg [geometric mean clearance from Zhang et al. (2013, Table 2) assuming steady state]

Notes:
- It could be argued that a toxicodynamic UF of 0.1 could be applied for rodent to human differences in response to PPAR activation.

Mouse: Point of Departure = 0.3 mg/kg-day (10.4 ug/ml) NOAEL for *neonatal survival* found in Abbott et al. (2007)

- Mouse to human toxicokinetic factor = 1 (Factor is not needed since BMD is based on serum concentration)
- Mouse to human toxicodynamic factor = 2.5 [IPCS (2005) default or 3 EPA (2014) default]
- Human toxicodynamic factor = 3 [default of IPCS (2005) and EPA (2014)].
- Human toxicokinetic factor = 8.4 [0.79 ml/day/kg arithmetic mean clearance of average group from Zhang et al. (2013, Table 2) ÷ 0.094 ml/day/kg arithmetic 95% lower bound clearance of sensitive group from Zhang et al. (2013, Table 2)]
- Database uncertainty factor = 1 (See footnote 7)

- RfD serum concentration = 0.14 ug/ml [10.4 ug/ml ÷ (1 x 3 x 3 x 8.4 x 1) = 0.14]
- RfD = 0.03 ug/kg-day [0.14 ug/ml x 0.23 ml/day/kg [geometric mean clearance from Zhang et al. (2013, Table 2) assuming steady state]

Mouse: Point of Departure = 0.94 mg/kg-day (no serum values available) NOAEL for *immune suppression* found in DeWitt et al. (2016).

Based on Lau et al. 2006, the serum level associated with in the mouse repeated dosing at 1 mg/ kg-day is 23 µg/ml. Therefore, dosing at 0.94 mg/kg/d is estimated to be associated with a serum level of 22 µg/ml.

- Mouse to human toxicokinetic factor = 1 (Factor is not needed since BMD is based on serum concentration)
- Mouse to human toxicodynamic factor = 2.5 [IPCS (2005) default or 3 EPA (2014) default]
- Human toxicodynamic factor = 3 [default of IPCS (2005) and EPA (2014)].
- Human toxicokinetic factor = 8.4 [0.79 ml/day/kg arithmetic mean clearance of average group from Zhang et al. (2013, Table 2) ÷ 0.094 ml/day/kg arithmetic 95% lower bound clearance of sensitive group from Zhang et al. (2013, Table 2)]
- Database uncertainty factor = 1 (See footnote 7.)

- RfD serum concentration = 0.29 ug/ml [22 ug/ml ÷ (1 x 3 x 3 x 8.4 x 1) = 0.29]
- RfD = 0.07 ug/kg-day [0.29 ug/ml x 0.23 ml/day/kg [geometric mean clearance from Zhang et al. (2013, Table 2) assuming steady state]