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

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Abstract

Many governments and other groups have estimated a safe dose for perfluorooctanoate (PFOA) for humans. Most of these evaluations (i) are contemporary; (ii) are based on many of the same underlying studies (whether of humans, laboratory animals, or both), and (iii) note similar uncertainties in existing databases. Nonetheless, the values of these various, estimated, safe-doses (otherwise known as "reference doses") vary widely, with some being more than 100,000 fold smaller than others. This sort of discrepancy begs examination.

The Steering Committee of the Alliance for Risk Assessment (*ARA*) called for scientists interested in attempting a resolution to this disparity. An advisory committee of nine scientists from four countries was selected from nominations received, and a subsequent invitation to the international community led to the formation of three independent teams (total of 24 scientists from 8 countries). The teams reviewed relevant information and independently developed ranges for estimated PFOA safe doses. We found that the current epidemiologic data could not form a reliable basis for a PFOA safe dose-assessment. Based instead on dose-response data from five studies in PFOA-exposed laboratory animals, we developed a provisional range for the PFOA safe dose of 10 to 70 ng/kg-day.

Disclaimers

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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

[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

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. Then, EPA (2009) developed 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 have also developed safe doses for PFOA, including the European Food Safety Authority (EFSA, 2008) and the United Kingdom (COT, 2009), both estimating values of 1,500 ng/kg-day.

EPA (2016) changed its assessment by using a 10-fold lower safe dose (thus estimating 20 ng/kg-day), and five years later, changed the value again, this time down 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), the Food Standards of Australian and New Zealand (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).

Table 1 shows 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 scientists. Thus, the Steering Committee initiated an international collaboration to develop a range in the PFOA safe dose based on current data and related knowledge.

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 denigrate any individual authority's approach, although presumably not all approaches can be "correct," however defined. Of course, there is still much to learn before we can arrive at the "truly safe" dose of PFOA to protect human health: the results of future research will hopefully get us even closer.

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

population (including sensitive subgroups) that is likely to be without an appreciable risk of adverse effects during a lifetime.

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

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

reviewing nominations, the following scientists were selected by the Steering Committee as members of the Advisory Committee:

- Lyle D. Burgoon with Raptor Pharm & Tox, Ltd, USA
- Harvey J. Clewell with Ramboll, Global
- Tony Cox with Cox Associates, USA
- Michael L. Dourson with TERA, USA
- Tamara House-Knight with GHD, Global
- Ravi Naidu with CRC CARE, Australia
- Paul Nathanail, United Kingdom
- James S. Smith with US DoD, USA
- Nitin Verma with Chitkara University, India

The Advisory Committee then 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, the following scientists were selected and arranged into three independent teams, assuring that various sectors were represented in each team:

Team 1

- Lyle D. Burgoon, RaptorPharmTox, USA, consultant
- Paul Nathanail, LQM, UK, consultant
- Shanon E. Ethridge, International Association for Plumbing and Mechanical Officials Research and Testing, USA, NGO
- Vijay Kannappan, Cook Medical, USA, industry
- Michael I. Luster, NIOSH (retired), USA, government
- Therese Manning, Environmental Risk Sciences Pty Ltd, Australia, consultant
- Tiago Severo-Peixe, State University of Londrina, Brazil, university
- Andrea Wojtyniak, Geosyntec, Canada, consultant

Team 2

- Harvey J. Clewell, Rambol, USA, consultant
- Tamara House-Knight, GHD, Global, consultant
- Linda Dell, Ramboll, Global, consultant
- James A. Deyo, Environmental Protection Authority, New Zealand, government
- Bernard K. Gadagbui, Toxicology Excellence for Risk Assessment, USA, NGO
- Travis R. Kline, Geosyntec Consultants, USA, consultant

- Katie Richardson, Senversa, Australia, consultant
- Anurag Sharma, Nitte University, India, university

Team 3

- James S. Smith, NMCPHC, USA, government
- Nitin Verma, Chitkara University, India, university
- Wolfgang Dekant, University of Würzburg (retired), Germany, university
- Philip Goodrum, GSI, USA, consultant
- Laura C. Green. Green Toxicology LLC, USA, consultant
- Tom Jonaitis, RegTox Solutions Inc., Canada, consultant
- Frank Pagone, RHP Risk Management, USA, consultant
- Jackie Wright, Environmental Risk Sciences Pty Ltd, Australia, consultant

The charge to the Teams was determined by the Advisory Committee to be as follows:

- You have been selected for participation in small, independent science teams during the next several months to review relevant information and positions on PFOA in order to determine its safe dose range, and afterwards to determine the safe dose range of PFOS. As you all know, the relevant literature for these PFAS chemistries is voluminous, most recently summarized by the WHO (2022). However, your team is free to pursue literature that you deem relevant to purpose, realizing that choices made will need to be justified.

- Since many approaches to the review of relevant literature, discussion, consensus (by which we mean, "agreed upon by a majority of us") building, and reporting are possible, we wish for you to focus sequentially.
    - First please focus on PFOA's mode of action for its critical effect(s) [deadline December 16],
    - Then focus on determination of the critical studies for one or more of its critical effect(s) [deadline January 27],
    - Then focus on the choice of extrapolation method including the choice of uncertainty factors [deadline March 10], and
    - Then finally please identify additional data gaps [deadline March 31].

- The sequence will be periodically interrupted by Zoom conference calls for the purpose of team presentations and attempted consensus around the various focus topics.

- This sequence will then be repeated for PFOS.

- Leadership within each team is also for you to choose, although we have provided two members of the advisory committee to assist. We anticipate that consensus positions will periodically be shared with the broader interested community, followed by publication(s) in relevant journals.
- We appreciate your willingness to take on this task and would be more than happy to answer any questions you might have. Please feel free to contact any one or more of us [The Advisory Committee] with questions. However, during your teams review and discussion please maintain independence from the two other teams.

All deadlines in the charge were met by all teams.

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.

Charge 1: PFOA's Mode of Action

After the three teams had reviewed information on PFOA's mode of action (MOA), a Zoom conference call was scheduled. The meeting was opened by restating the charge for this phase of the effort, which is a focus on PFOA's mode of action for its critical effect(s) in humans.

Team 1's findings were summarized as:

- Widely different choices of critical effect[4] and their tentative mode of action (MOA) are evident among national authorities; and not all critical effects may be relevant to risk assessment intended to protect human health.
- For example, one member opined that while observed associations between (i) PFOA body-burdens in populations and (ii)diminished levels of serum antibodies following to one or more specific types of vaccination might suggest additional investigation, the current body-burden/antibody level data not suitable for developing a Reference Dose (RfD) since the assessments were based upon secondary immune response, rather than primary, which contradicts the WHO Immunotoxicology panels guidelines as a reliable quantitative measure of immune function.. Moreover, as several team-members noted, it is unclear whether small decreases in "vaccine responses" are clinically significant.
- A second member added that comments on the level of uncertainty for differing choices of critical effect by each government position might be helpful for the next phase of our work (to select a critical effect among the many suggested candidates).

[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 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. .

- An team member added that most sample sizes in rodents are too small to be readily helpful for risk assessment.
- Another team member asked whether membrane fluid dynamics was due to lodging of PFOA into plasma membranes, which might be expected due to its chemical similarity to plasma lipids and limited volume of distribution from the sole clinical study in humans. Such insertions without associated hydrogen bonding might make such membranes less efficient.

Team 2 then summarized their findings as:

- Clinical effects in many of the human observational studies, such as increases in cholesterol and decreases in vaccine titer and birth weight, are of small magnitude or are imprecise. Investigators generally report differences within normal laboratory reference ranges in relation to PFOA blood concentrations. These findings might reflect pharmacological bias or reverse causality due to the fatty acid mimicry evident in PFOA's chemical structure.
- Several of the critical effects found in experimental animals need pPAR activation; since humans and rodents have strikingly different pPAR activations, this has direct relevance to development of a safe dose range for PFOA based on data from experimental animals.
- A vast inter- and intra-individual human variability in natural vaccine response exists that precludes any definitive statement in the choice of this endpoint as the critical effect.
- Reverse causality may apply to more than one effect.
- Answers to questions regarding relevance of these findings and their associated MOAs in humans will not likely come from human studies, but at the same time we need experimental models that more closely resemble humans.

The chair then asked if any conflicts were evident between the presentations and discussion of topics between teams 1 and 2. None were identified. A member of Team 1 then asked whether we could go through Team 1's list of government positions and at some point opine whether each team was likely to have under- or over-predicted the likely range in the PFOA safe dose. No one disagreed with this suggestion.

Team 3 then summarized their findings as:

- It was difficult to discuss any particular MOA as the critical effect had not yet been selected.
- Overall, we have little information on MOA other than perhaps for the liver effects found in rodents due to pPAR activation.
- Do we have areas where the dose response information is good enough 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 showing decreases (Convertino et al., 2018).
- Although cholesterol changes did not appear to be definitive and not likely to be the critical effect, studying other inflection points or hormetic responses seemed like a good idea.
- Humans are much less sensitive than experimental animals to pPAR related events.

- Membrane fluid dynamics was again raised as a possible clue to the inculcation of PFOA into plasma membranes, which might be expected, if given sufficient dose, to cause a host of effects. While this is a plausible hypothesis, it was not known how much PFOA would be needed per cell membrane to cause the expected leakage or fluidity.

The chair then led the three teams in a general discussion. Items noted included:

- A SciPinion panel (Garvey et al., 2023) on immunotoxicity of PFOA found that the vaccine threshold of 0.1 IU/ml was not helpful for risk assessment since it is just a guideline. Additional discussion mentioned that this value is not an appropriate biomarker nor should it be considered as a threshold. Its use in the development of a safe dose is not credible. No one disagreed with these findings or statements.
- Could the varying COVID responses world-wide be studied in relation to differing PFOA serum concentrations? One team member thought that this was likely already happening.
- 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 and vaccine status. No one disagreed with this statement.
- Studying inflection points or perhaps hormesis might help resolve why we have 100,000-fold differences in the PFOA safe dose internationally. While differences among such groups can often be a factor of 3 due to differing times of analysis and methods, this difference in PFOA is clearly not acceptable, nor can all groups be correct.

Charge 2: Determination of critical studies for PFOA's critical effect(s)

After the three teams had reviewed information on determination of critical studies for PFOA's critical effect(s), a zoom conference call was scheduled. The meeting was opened by restating the charge for this phase of the effort, a focus on PFOA's mode of action (MOA) for its critical effect(s). The call started with presentations and clarifying questions, and then continuing with discussion and consensus statements. Afterwards, the chair invited Team 3 to present.

- Team 3 went over its findings. The team considered the following criteria in their evaluation of potential critical effects:
- Dose response,
- Known or suspected MOA,
- Consistency,
- Coherence between experimental animal and epidemiology data, and
- Robustness of the overall response.

After reviewing the plethora of relevant information, Team 3 did not consider the epidemiology data, composed primarily of observational studies, to be sufficient to determine a critical effect and instead focused on experimental animal work.

Team 3 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 some non-adverse liver effects seen in the human observational studies and was consistent with the sole human clinical study that, while short term, showed no adverse liver effects.
- 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 NOAEL/LOAEL boundary.
- One member of Team 3 reached out to the investigators of the monkey studies to ask for any additional data. No additional data were available.

Team 2 then went over its findings. After reviewing the relevant plethora of information, Team 2 also did not consider the epidemiology data, composed primarily of observational studies, to be sufficient to determine a critical effect. These studies were considered to be:

- Confounded, and confounding was not readily quantified, which created a hurdle with the use of human data, and
- Exposures were not significantly different from background in most studies to assign an association, much less causation.

Because of these concerns, Team 2 also focused on experimental animals for consideration of the critical effect.

In contrast to Team 3, Team 2 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 and the fact that the likely MOA was fatty acid mimicry. This selection was based on:

- PFOA access to mid-chain fatty acid transport, and biliary and renal excretion and resorption.
- 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 its selection as the critical, or perhaps co-critical effect.
- PPAR-alpha induced liver effects occurred in rodents at about a 10-fold higher dose than those evoking developmental toxicity.

Other issues/questions raised included:

- A member of Team 3 raised the idea that a developmental study in rabbits might also be worth considering since rodents do not always representative human development as well. Team 2 agreed to review the available rabbit developmental study.

- A member of Team 1 raised the issue of statistical problems with the Lau et al. (2006) study in particular, and for most, if not all of the experimental animal work in general.
- Several, but not all, human observational studies show a decrease in birth weight when PFOA is sampled in the 3rd trimester of pregnancy, but not at earlier sampling times.
- Monkey and rodent No-Observed-Adverse-Effect-Level (NOAEL) and Low-Observed-Adverse-Effect-Level (LOAEL) interfaces are approximately the same at around 1 to 3 mg/kg-day.[5]

Team 1 then summarized its findings, which were based on a very nice summary of studies by several members. Like Teams 2 and 3, Team 1 did not feel that any of the human studies were sufficiently reliable to be used to determine the critical effect, and for the various reasons already indicated. Nor did Team 1 feel that the liver effects seen in monkeys, or perhaps other species, were appropriate, since the effects seen were not adverse. Nor did Team 1 consider the developmental effects appropriate due to statistical issues mentioned above.

Team 1 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 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 chair led the all three teams to develop the following consensus positions:

- 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 have only a small effect and are not dose responsive. These studies may support the choice of critical effect with some of the experimental animal work, however.
- Should vaccine responses be used for the development of the critical effect?
    - No, existing human observational vaccine findings are not primary immune responses and not of clinical relevance. Moreover, higher dose worker exposures do not suggest immune responses.[6]
- 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.

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[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).

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

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 will be explored along the following lines:

- 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 Teams 1, 2, and 3 for consideration.
- A member of Team 3 asked participants to critique and improve upon Green and Crouch's work in this regard from 2019 (as submitted to MassDEP, and available at https://greentoxicology.com/Reports/PFAS_comments_to_MADEP.pdf).
- PFOA is the fluorinated version of the naturally occurring caprylic acid. A big difference between these two chemicals is ½ life in the human body. One member volunteered to conduct a limited literature review on the toxicity of caprylic acid, and Teams 1, 2, and 3 will conduct a thought experiment to probe whether potential long-term toxicity from caprylic acid matches any of the findings with PFOA.
- Team 2 will look at the rabbit developmental toxicity study.

Charge 3: Choice of extrapolation method

After the three teams had reviewed information on PFOA's choice of extrapolation, a zoom conference call was scheduled. The meeting opened by restating the charge for this phase of the effort, a focus on PFOA's choice of extrapolation. The call then started with presentations and clarifying questions, and then continuing with discussion and consensus statements. Afterwards, Team 2 presented.

Team 2 went over its findings, where it was collectively decided to build a range in the safe dose based on several studies. The first study was the Butenhoff et al. (2002) where liver weight increases in monkeys were observed and from Green and Crouch (2019) developed a benchmark concentration of 19 ug/ml. Dividing this concentration by an uncertainty factor of 1-fold for laboratory animal to human variability (since this was a study in primates), and a human clearance factor by Lorber and Egeghy (2011) as reported by Post (2021), resulted in an RfD of 0.27 ug/kg-day.

The second study considered by Team 2 was Lau et al. (2006) with a NOAEL of 23 ug/ml for dose dependent growth deficits in offspring. An uncertainty factor for experimental animals to humans of 10 was used as well as a human clearance factor of Lorber and Egeghy (2011) as reported by Post (2021). The resulting RfD was 0.3 ug/kg-day.

Other studies considered were Onishchenko et al. (2011), Koskela et al. (2015), Loveless et al. (2006), and Macon et al. (2011). An uncertainty factor for experimental animals to humans of 10 was used with each study as well as a human clearance factor by Lorber and Egeghy (2011) as reported by Post (2021). The resulting RfDs varied from 0.011 to ~0.6 ug/kg-day.

Clarify questions and discussion included:

- Would not the use of a clearance value from human study Zhang et al. (2013), as describe by Campbell et al. (2022), be a better choice than clearance values from human observational studies described by Lorber and Egeghy (2011)? Team 2 responded that this would be the case and a revision of these tentative RfD values would be appropriate.
- Would not the use of a database uncertainty factor be reasonable given the large uncertainty in the overall database? Team 2 thought that the data for PFOA was extensive, but perhaps a factor of 3 might be appropriate since a 2-generation study was not available.
- Some concern was expressed over the use of the Onishchenko et al. (2011), Koskela et al. (2015) due to the small number of experimental animals.
- It was also argued that a UF of 0.1 for experimental animal to human toxicodynamics should be applied for differences in response to PPAR activation between rodents and humans. While appropriate, no one seemed willing to invoke this science-based factor.

Team 1 then summarized its findings, members of whom were still of the general 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, Team 1 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.

Team 1 then developed an RfD range of 3 to 9.4 ug/kg-day from these two values by dividing this range by the classic 100-fold uncertainty factor. Team 1 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.

Clarify questions and discussion included:

- Would not the use of a database uncertainty factor be reasonable given the large uncertainty in the overall database? The general consensus was that such a factor might be needed, but if so, a factor of 3-fold might be more appropriate than a value of 10-fold, since a 2-generation study was not available.
- The large range in the second RfD 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. Perhaps separate these two? Everyone seemed to agree with this.

Findings of Team 3 were then described. This team had previously considered dose response, known or suspected MOA, consistency, coherence between experimental animal and epidemiology data, and robustness of the overall response in their evaluation of potential critical effects. In general, Team 3 considered liver effect as best meeting these criteria 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 few numbers of animals and some inconsistency with the reported observations. Team 3 did not state a range in the provisional RfD, but it would be similar to what Team 2 had proposed.

After these presentations, clarifying questions and discussion, the following consensus positions were developed:

- 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. The use of human data for this exercise was not entertained, consistent with the unanimous consensus of all three science teams from the second conference call.
- 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]
- 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.
- The development of a specific provisional range in the PFOA safe dose based on information from this meeting will be tasked to a subgroup of volunteers who will then send around a draft for consensus review.

Development of a Provisional Safe Dose Range

The results shown below summarize the consensus of findings from 3 teams of scientists working independently over 6 months regarding PFOA's underlying mode of action for various effects, its likely critical effect(s), the extrapolation of experimental or human data to the presumed sensitive subgroup, and other tasks as appropriate.

The range of the PFOA safe dose is 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 following studies.

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]

[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.

- 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]

Note that a subsequent evaluation of Macon et al. (2011) determined that it was not 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 appeared to be based on pups and not the maternal experimental animal. The use of these studies for risk assessment is not in accordance with multiple US EPA guidelines.

Discussion

PFAS in general, and PFOA in particular, differ from many other chemicals and mixtures for which safe doses have been estimated. Among other things, this is because 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 (Convertino et al., 2018). Notably, though, observations of 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.

At present, the best that can be done, we believe, is to rely on dose-response data from PFOA-exposed laboratory animals. Indeed, risk assessors routinely do this for other chemicals and chemical-classes. The difference here, though, is that 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.

The international process described in this brief communication has several advantages. First, many 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. Second, many of these scientists are also intimately familiar with one or more of the agency positions on PFOA; several of these scientists are familiar with more than one agency position. Third, despite these credentials and familiarity, or perhaps because of them, uniformity of thought was not present, at least initially, and the Zoom call meetings, conducted alternatively at different times (to balance out the pain of midnight 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 compared with an agency position developed with fewer scientist and/or 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 values of Health Canada (2018) and the projected value 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 our colleagues who are not otherwise part of this collaboration are welcome. However, we encourage our colleagues to keep in mind the finding of our predecessors, and specifically 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 (Roberts et al., 2016)	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.