

**Case Study Summary****Title: Differences Among Perfluorooctanoate (PFOA) Safe Doses****Presented by:**

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**1. Provide a few sentences summarizing the method illustrated by the case study.**

International risk assessments (or safe dose estimations) for certain chemicals, such as perfluorooctanoate (PFOA), are over 100,000-fold apart. Such differences lead to immense difficulty in public communication. The purpose of this workshop is to understand why such differences in risk judgment exist, and then to discuss the legal, policy and economic repercussions of this extraordinary divergence. Avenues of resolution will be sought.

**2. Describe the problem formulation(s) the case study is designed to address. How is the method described in the case useful for addressing the problem formulation?**

Several domestic and international institutions have established regulatory health-based guidance values for PFOA. These values vary considerably, for example, by over 100,000-fold between safe doses of PFOA determined by the U.S. Environmental Protection Agency (2022) and the Food Standards Australian and New Zealand (FSANZ, 2017). The European Food Safety Agency (EFSA, 2018), the German Federal Ministry for the Environment (2022), Health Canada (2018), the Israeli Ministry of Health, and the World Health Organization (WHO, 2022) all have values lying between these two extremes. A current list of selected international safe doses for PFOA and PFOS is shown in Table 1.

The principal reasons for these large differences in safe doses may be attributed to potential differences between country/region-specific legislative requirements, risk assessment practices, interpretation/weighting of animal toxicity and human data, understanding of the underlying mode of action, and/or considerations including expertise and other resources afforded an

agency's assessment and its peer review. These differing considerations may contribute to differing choices of:

- Critical effect (the first adverse effect or its known and immediate precursor as dose increases) and appropriate species, including humans;
- Point of departure for the subsequent extrapolation (generally a no-observe-adverse-effect-level or benchmark dose);
- Extrapolation of experimental animal data, when used, to humans by way of a physiologically-based toxicokinetic model, chemical-specific-adjustment factor, or default uncertainty factors for toxicokinetics and toxicodynamics;
- Extrapolation of average to sensitive human subgroup by way of a physiologically-based toxicokinetic model, chemical-specific-adjustment factor, or by default uncertainty factors for toxicokinetics and toxicodynamics; and
- Other uncertainty considerations, e.g., deficiencies in the database when compared with an ideal situation, that is, identification of a sensitive human subgroup NOAEL for the well-established critical effect—in essence, the defined safe chemical dose.

The most recent evaluation of safe dose for PFOA is an unfunded, international effort by the Alliance for Risk Assessment (ARA), which has been recently accepted for publication. This effort defined a likely range of the safe dose for PFOA that is generally supportive of those from several authorities as shown in Table 1 (Burgoon et al., 2023).

The development of guideline values for various environmental media, for example drinking water, based on these various safe doses is highly dependent on the exposure assumptions unique to each authority. For example, one country might have a higher rate of water consumption than another due to climate leading to a lower guideline value in drinking water, other parameters being equal. Also, the background levels of PFOA in food might differ among countries leading to the use of different relative source contributions, that is, a parameter used to portion the safe dose among different environmental media.

Because of differing exposure assumptions and background levels, the differences in guideline values for various environmental media will not be considered in this case study. However, while the development of guideline values can be country dependent, and therefore countries might have differing values for the same environmental media, generally the development of the underlying safe doses should be more uniform. Populations of humans are wonderfully different, but safe doses should not vary to the extreme that is evident with PFOA.

Thus, this case study is designed to directly address differences in PFOA's safe doses by examining the hazard identification and dose response assessment for perfluorooctanoate (PFOA) of 8 different international groups, discussing findings, and sharing insights. A science panel of experts in risk assessment, several with extensive experience in the assessment of PFOA and related chemicals, will also contribute to this examination. It is hope that avenues of potential resolution are developed.

Table 1. Safe Doses of PFOA from International Groups

Authority	Safe Dose ug/kg-day	Critical effect; Species; Point of Departure (POD)	Uncertainty Factors
Alliance for Risk Assessment (Burgoon et al., 2023)	0.01-0.07	Effects: liver, developmental, immune Species: monkey, rat, mouse PODs: 4.35 to 23 ug/ml of serum	<ul style="list-style-type: none"> <li>Animal to human kinetic factor = 1</li> <li>Animal to human dynamic factor = 3</li> <li>Human toxicodynamic factor = 3</li> <li>Human toxicokinetic factor = 8.4</li> <li>Database uncertainty factor = 1</li> <li>Human clearance = 0.23 ml/day-kg</li> </ul>
European Food Safety Authority (EFSA, 2018)	0.0008	Effect: immune Species: human POD: Modeled using a physiologically based pharmacokinetic model	<ul style="list-style-type: none"> <li>None applied</li> <li>BMDL10 is based on infants, which is expected to be a sensitive population group.</li> </ul>
Food Standards Australia New Zealand (FSANZ, 2017)	0.16	Effect: developmental Species: mouse POD: 4.9 ug/kg-day	<ul style="list-style-type: none"> <li>Within human variability = 10</li> <li>Animal to human extrapolation = 3</li> </ul>
German Federal Ministry for the Environment, 2022	0.02	Effect: Species: human POD: Insignificance threshold values derived on the basis of human toxicological data.	<ul style="list-style-type: none"> <li>Group made a risk assessment call of 0.1 ug/liter</li> <li>This value can be used to estimate the comparable safe dose of ~0.02 ug/kg-day by multiplying by 2 liters of water consumed per day, by dividing by 0.2 to adjust for a relative source contribution, and by dividing by a 60 kg body weight. Other assumptions are possible.</li> </ul>
Health Canada (2018)	0.02	Effect: liver Species: rat POD: 0.52 ug/kg-day	<ul style="list-style-type: none"> <li>Within human variability = 10</li> <li>Animal to human extrapolation = 2.5</li> </ul>
Israel Ministry of Health, 2023	0.02	Effect: not applicable Species: not applicable POD: water level of 100 ppt for 20 PFAS chemistries	<ul style="list-style-type: none"> <li>Adopted the European directive that sets a maximum value of 100 ppt for the sum of 20 PFAS compounds, including PFOA</li> <li>This value can be used to estimate the comparable safe dose of ~0.02 ug/kg-day by multiplying by 2 liters of water consumption per day, by dividing by 0.2</li> </ul>

Authority	Safe Dose ug/kg-day	Critical effect; Species; Point of Departure (POD)	Uncertainty Factors
			to adjust for a relative source contribution, and by dividing by a 60 kg body weight. Other assumptions are possible.
US Environmental Protection Agency (2022)	0.0000015 <sup>a</sup>	Effect: immune Species: human POD: 0.0000149 ug/kg-day	<ul style="list-style-type: none"> <li>• Within human variability = 10</li> </ul>
World Health Organization (2022)	0.02	Effect: not able to determine Species: not able to determine POD: PFOA water level of 100 ng/liter	<ul style="list-style-type: none"> <li>• WHO made a risk management call of 0.1 ug/liter</li> <li>• This value can be used to estimate the comparable safe dose of ~0.02 ug/kg-day by multiplying by 2 liters of water consumption per day, by dividing by 0.2 to adjust for a relative source contribution, and by dividing by a 60 kg body weight. Other assumptions are possible.</li> </ul>

- a) A revised value of 0.00003 ug/kg-day is currently under review; see: <https://www.federalregister.gov/documents/2023/03/29/2023-05471/pfas-national-primary-drinking-water-regulation-rulemaking#addresses>, and <https://www.regulations.gov/document/EPA-HQ-OW-2022-0114-0027>.

**3. Comment on whether the method is general enough to be used directly, or if it can be extrapolated, for application to other chemicals and/or problem formulations. Please explain why or why not.**

The creation of an international forum to explore differences in safe dose assessments is not a novel method, nor one without precedent. For example, this has previously been done for the chemical 2,3,7,8-TCDD (e.g., WHO, 2005). This method can be used directly with other chemistries with similar, extensive international exposures and concern.

**4. Discuss the overall strengths and weaknesses of the method.**

The method is both time consuming and expensive to conduct but has the opportunity to yield safe dose estimates that can be used with more confidence, and potentially result in improved international harmonization of risk assessment best practices. This in turn would allow easier communication with relevant publics and ease or enhance trading among interested nations.

**5. Outline the minimum data requirements and describe the types of data sets that are needed.**

At a minimum, safe doses among more than one international group are needed in order to develop a forum of any consequence. Also, the estimated safe doses should be at a minimum of 10-fold apart since the imprecision of estimated safe doses is perhaps an order of magnitude (Felter and Dourson, 1998). Moreover, these estimates should all be based on contemporary science since differences in safe dose can often be significant just because of the receipt of new information (Dourson and Lu, 1995).

**Does your case study:**

**A. Describe the dose-response relationship in the dose range relevant to human exposure?**

Yes, the estimation of safe doses is directly relevant to the range of potential human exposures.

**B. Address human variability and sensitive populations?**

Yes, the estimation of safe doses by different international group nearly always includes consideration of sensitive populations.

**C. Address background exposures or responses?**

Background responses are nearly always folded into the development of safe doses, but background concentrations are not routinely considered unless they are part of an epidemiology study where background exposure to the chemical of interest is a part of the investigation or if the compound of interest is also a natural endogenous or exogenous agent (e.g., ethylene oxide, formaldehyde). For PFOA in particular, background exposure is a common occurrence in the available epidemiology studies, and many of these studies incorporate an analysis of background exposures.

**D. Address incorporation of existing biological understanding of the likely mode of action?**

Yes, the estimation of safe doses by different international group nearly always includes consideration of the likely mode of chemical action. This information is often useful for the development of Chemical Specific Adjustment Factors. See for example, Meek et al. (1994), IPCS (2005) and US EPA (2014).

**E. Address other extrapolations, if relevant – insufficient data, including duration extrapolations, interspecies extrapolation?**

Yes, the estimation of safe doses by different international groups nearly always includes consideration of databases that differ by duration of chemical exposure, extrapolation from higher dose to lower, and extrapolation from experimental animals to humans, or from a

general population of humans to their more sensitive subgroups. Multiple documents attest to these various extrapolations.

#### **F. Address uncertainty?**

Yes, the estimation of safe doses by different international group nearly always includes consideration of uncertainty, generally in the form of uncertainty or adjustment factors that account for various types of missing data. Multiple documents attest to these various extrapolations.

#### **G. Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?**

Although the estimated safe dose by various groups is considered to be without risk (risk = zero), or nearly without any risk, to the sensitive and general population, the estimation of risk above this safe dose is not a relevant question for this case study.

#### **H. Work practically? If the method still requires development, how close is it to practical implementation?**

This method is workable now.

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