Case Study #2 Summary

Title: The safe dose range of perfluorooctane sulfonate (PFOS)

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

   Our three, international teams of life-scientists, chosen in the same manner as described by Buroogn et al. (2023), sought to develop a range of reliable, evidence-based, safe-doses for perfluorooctane sulfonate (PFOS). We collaborated virtually, via Zoom, email-exchanges, and sometimes phone calls. We relied on (i) each of our prior work on, and understanding of, PFOS and similar chemicals; (ii) published reviews, and (iii) published and unpublished reports of bioassays and other studies, both experimental and observational. Consensus both within and across the groups was not a requirement, but was nonetheless often achieved. Given the wide range of personalities, scientific backgrounds, and habits of mind, this was perhaps surprising. In writing up our results, we relied on one or two of us to do the bulk of the drafting, and on many more of us to comment on, add to, and/or re-write parts of the manuscript-in-process. All authors signed off on the final, peer-reviewed, accepted, and now published manuscript (Dourson et al, 2025).

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?**

   The case study is a description of the results of applying the method described in the publication discussed, which is one method of achieving a virtual scientific consensus on a toxicological question of some significance.

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.**

   Our study method was used, successfully we believe, for a similar assessment for the PFAS, perfluorooctanoate (PFOA). Please see Burgoon et al. (2023).

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

   Strengths: constructive collaboration between and among health-scientists with different backgrounds, skill-sets, habits of mind, etc. We relied, when possible, on original laboratory reports in addition to published material. Weaknesses: entirely self-funded, so that those of us with many conflicting demands on our time and efforts could not always put in the time that might have been needed to dig deeper, as it were. Also, none of us were involved in undertaking the key bioassays upon which we came to rely.

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

Requires well-documented occupational or experimental epidemiological studies, together with laboratory animal studies and preferably *in-vivo* and *in-vitro* mode of action (MOA) studies. While the database on PFOS is now large, many of the studies are compromised by lack of knowledge of MOA, so they must be considered at best to provide potential leads only. Since all humans are currently exposed to PFOS, informative epidemiological studies would require very high-level exposures to provide reliably non-confounded results. Laboratory animal studies need to be in animals as resistant to PPARalpha-activation as are humans (in other words, guinea pigs, rather than rats and mice), and/or are otherwise likely to be reliable models for relative modes of action of PFOS.

Does your case study:

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

The object of the study was to determine a "safe" dose for humans, taking account of plausible dose-response relationships, down to doses relevant to current human exposures. Lacking MOA information, end-points of questionable relevance necessarily had to be used. Of course, this introduced considerable uncertainty.

B. Address human variability and sensitive populations?

Human pharmacokinetic variability was taken into account, and other variabilities, uncertainties, and sensitivities by means of safety factors.

C. Address background exposures or responses?

PFOS does not naturally occur, but is widely distributed in the environment so that background exposures are present throughout the entire human population. This was taken into account in evaluation of the epidemiological studies. Backgrounds exposures to the laboratory animals was present but negligible compared with deliberate dosing at higher levels.

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

The Mode of Action (MOA) for PFOS was considered. While some MOAs in laboratory animals could be determined, none in humans could be reliably identified.

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

The database for PFOS is extensive. It includes several long term laboratory animal studies but sufficient understanding of interpecies differences is inadequate to perform some types of extrapolations – so that safety factors were used. Multiple epidemiological studies are also available, but are primarly observational and environmental. Occupational surveys are small and provide no interpretable positive results.

F. Address uncertainty?

Uncertainties encountered in the PFOS database were addressed with traditional safety (uncertainty) factors. Data on the variability of excretion-rates in humans, and other parameters, allowed the development of chemical-specific adjustment factors.

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

No estimates of probabilities of response are developed, except for the high likelihood of no response within and below the estimated range of "safe" doses.

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

This consensus approach to developing safe doses is a practical implementation of standard, dose-response assessment methods (adjusted to account for interspecies-comparisons based on blood-serum concentrations, rather than delivered dose-rates). Nonetheless, political and public pressures being what they are, both in the U.S. and internationally, we think it unlikely that purely scientific answers to the problems posed by PFOS and countless other PFAS will prevail.

References

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