Controversies in the Interpretation of PFAS and PFOA Toxicity-Chapter 1”

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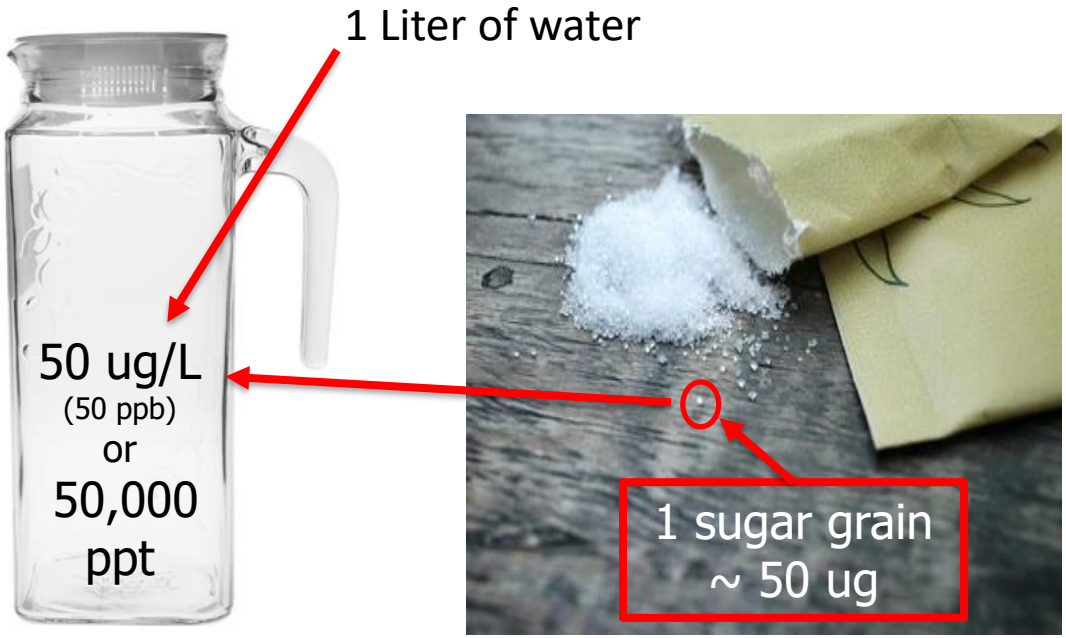
PFOA The "Forever" Chemical

- Perfluorooctanoate (PFOA) and its sulfonic acid (PFOS) are fatty acids. Our bodies think they can be used for energy---Not!
- Development of a safe PFOA dose has been going on since 2002 (e.g., *Dark Waters*) with values ranging from 4000 ng/kg-day to a now much lower, and recent, value of 0.0015 ng/kg-day (USEPA, 2021).
- Drinking Water Inspectorate (UK, 2021), Health Canada (2018), the EFSA (2020), FSANZ (2017) and US ATSDR (2018) also have PFOA safe doses; values differ by over 100,000-fold.
- One principal reason for disparity is improved underlying database; equally important is the complexity of data.

EPA Versus Other PFOA Health Advisories



	EPA (2023)	ATSDR	EPA (2016)	HC	Aus	CAAT
PFOA Advisory (ppt):	0.004	10	70	200	560	30,000

140,00-fold difference

Conundrum of the PFOA Human ½ Life

- Human PFOA half-lives differ significantly in human observational studies from 1.2 to 14.9 years (Dourson and Gadagbui, 2021).
- Alliance for Risk Assessment (*ARA*) Steering Committee initiated a collaboration in Spring of 2021 to explore these differences.
- Advisory Committee formed in Spring of 2021 by *ARA* Steering Committee
  - Harvey Clewell, Ramboll, Global
  - Tony Cox, Cox Associates, USA
  - Michael Dourson, TERA, USA
  - Shannon Ethridge, Internation. Assoc. of Plumb. & Mech. Officials, USA
  - Ali Hamade, Oregon Health Authority, USA
  - Ravi Naidu, CRC CARE, Australia
  - Nitin Verma, Chitkara University, India
- Work finished Spring of 2022 with paper by Campbell et al. (2022). See: https://www.tera.org/Alliance%20for%20Risk/Projects/pfoahumanhalflife.html

Stakeholder Process

States,
Fed. Agencies,
Public Interests,
Industry

Initiation of
Risk Issue

Document
Draft

Peer
Reviews

Release to
Public

Alliance for Risk Assessment (*ARA*)

(www.allianceforrisk.org)

Steering Committee

ARA Non-profit Collaborators

Beyond Science & Decisions Workshop

Nuclear Receptors Workshop

Risk from Broken CFL Light Bulbs

PFOA Half-life

Peer Workshop on Pesticide Degradates

Annette Dietz, Portland State University
Michael Dourson, TERA
Michael Honeycutt, TCEQ
Matthew McAtee, US Army
Moiz Mumtaz, ATSDR
Ralph Perona, Neptune & Company, Inc.

Half-Life Small Group Participants

- Jerry Campbell, Ramboll, Global
- Harvey Clewell, Ramboll, Global
- Norman Forsberg, Arcadis, USA
- Bernard Gadagbui, TERA, USA
- Tiago Severo Peixe, State University of Londrina, Parana, Brazil
- Ali Hamade, Oregon Health Authority, USA
- Ravi Naidu, CRC CARE, Australia
- Nathan Pechacek, Ecolabs, USA
- Robyn Prueitt, Gradient, USA
- Andrew Prussia, ATSDR, USA
- Mahesh Rachamalla, University of Saskatchewan, Canada
- Lorenz Rhomberg, Gradient, USA
- James Smith, Navy and Marine Corps Public Health Center, USA
- Nitin Verma, Chitkara University, India

Impacts of Identified Issues?

Selection of a subset of studies

Unmonitored PFOA in human observational studies could ***inflate*** values of estimated PFOA half-life.

- Half-lives biased high

PFOA half-life values based on branched chain isomers could ***deflate*** linear chain PFOA half-life.

- Half-lives biased low

Collaboration identified three studies with the fewest issues.

Studies Identified as Having the Fewest Issues for Unmonitored PFOA exposures and/or Isomer Uncertainties

Study population	Half-life (years)	Comments	Uncertainty
Elcombe et al. (2013) Clinical trial (n = 3)	Arithmetic Mean (AM) 0.5	• Based on analysis of Elcombe et al. (2013) by Dourson and Gadagbui, 2020. • Patients received a single dose with 6 week follow up; serum levels <renal resorption.	• High dose in Elcombe et al. (2013) obviates need to monitor other PFOA. • Single isomer studied. • If serum levels above saturation then this may raise half life.
Xu et al. (2020): Employees exposed via water (n = 17)	Geometric Mean (GM) 1.5	• Unlikely alternate exposures. • 5-month follow up. • Exposures not greatly above background.	• Other unmonitored exposures possible & may lower half-life. • Branched PFOA isomers were studied but not reported.
Zhang et al. (2013): Healthy Chinese volunteers (n = 86)	GM = 1.7 young females GM = 1.2 males and older females) **Central** GM = 1.3 Median = 1.8	• Discussion of background or ongoing exposure not needed since half-lives based on renal clearance. • Study authors note that half-lives should be considered as upper limits since not all elimination routes were studied.	• No uncertainty in exposures; based on renal clearance. • Unmonitored elimination by other routes was not studied. • Multiple isomers were studied.

Key findings/Conclusion

- The central tendency of the human PFOA half-life is likely less than 2 years.
- Zhang *et al*., 2013 is a clearance study; its single best value appears to be the geometric mean of 1.3 years, but authors consider this to be an upper limit.
- Unmonitored PFOA exposures and branched PFOA isomers identified as issues.
- **Conclusion**: PFOA is not as "forever" as some folks think.

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PFOA Half-life

Peer Workshop on Pesticide Degradates

State representative: *pending*
Michael Dourson, Toxicology Excellence for Risk Assessment
Wally Hayes, University of South Florida
Sabine Lange, Texas Commission on Environmental Quality
Matthew McAtee, US Army Public Health Center
Ralph Perona, Neptune & Company, Inc.

ARA™
ALLIANCE FOR RISK ASSESSMENT™

The Steering Committee of the Alliance for Risk Assessment (*ARA*)

Steps for Estimating a PFOA/PFOS Safe Dose

1. Select an organization to manage the collaboration: Done. TERA is managing this project; donations are tax-deductible.
2. Select an Advisory Committee to shepherd the effort: Done. A nine member international advisory committee has been formed.
3. Committee to work with interested scientists/groups from around the world to form a consensus on range of PFOA/PFOS safe dose: Ongoing. Consensus positions are currently being developed in several areas.

Advisory Committee on International Collaboration for Range of PFOA/S Safe Doses

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

Challenges for Estimating a PFOA Safe Dose

- Different agencies have focused on different critical effects as a basis of their safe dose, recent judgments include immune, hepatic, and developmental effects.

- Some agencies have focused on human observational studies (EFSA, EPA); others focused on definitive experimental animal work (Health Canada, FSANZ). Match the two when possible.

- Study modes of action/AOPs for effects of PFAS other than liver in rodents, particularly for effects, such as immuno-suppression & developmental toxicity (Fenton et al., 2020).

What is Needed for Estimating A PFOA Safe Dose?

- Needed: A consensus on PFOA's critical effect, defined as the first adverse effect or its known, immediate precursor, and its relevant mode of action.

- Needed: Determine a point of departure in which reasonable confidence can be placed to estimate the PFOA safe dose.

- Needed: Affirmation of the existing consensus on the PFOA human half-life, or at least additional urinary clearance studies like Zhang et al. (2013).

The Primary Issue: Risk Characterizations Differ Widely: PFOA*

Agency	**EFSA (2020)**	**EPA (2022)**	**Health Canada (2018)**	**FSANZ (2018)**
Study	Abraham (2020)	Grandjean et al., (2012)	Perkins et al. (2004)	Lau et al. (2006)
Critical Effect	Immune	Immune	Liver	Fetal
Human Dose (ng/kg-day)	17.5 ng/ml	0.015	521	4900
Uncertainty Factor	1	10	25	30
"Safe" Dose (ng/kg-day)	0.63	0.0015	21	160

Over 100,000-fold difference

* Adapted from Mikkonen et al., 2020

TERA
TOXICOLOGY EXCELLENCE FOR RISK ASSESSMENT

Mission is to support the protection of public health by:

- Developing, reviewing and communicating risk assessment values and analyses;
- Improving risk methods through research; and
- Educating risk assessors, managers, and the public on risk assessment issues

- TERA is a 501c3 nonprofit organization

- Research support for this presentation is from TERA's developmental reserve.

Extra Slides

The Four Stages of a Career

- Novice: learns the basics
- Practitioner: knows the basics and applies them dogmatically; does not know what to exclude
- Artisian: knows the basics and applies them judiciously; excludes obviously irrelevant material
- Expert: knows the basics and applies them with insight and wisdom; excludes all irrelevant material

Adapted from Persky and Robinson, 2017. Moving from Novice to Expertise and Its Implications for Instruction. Am J Pharm Educ. 2017 Nov; 81(9): 6065. doi: 10.5688/ajpe6065

A Problem with Risk Assessment?

- Risk documents: are extraordinarily large with oodles of information that is not relevant for a reasoned judgment
- Peer reviewers: are generally overwhelmed by the size of the risk document and as a result generally focus on a smaller area of knowledge.
- Peer review structure: needs 1/3 expertise in chemical, 1/3 expertise in critical effect and 1/3 expertise in risk assessment; few panels have this mix of expertise.
- Management Oversight: managers need to know risk assessment at least to the artisian level; otherwise they make mistakes in assignment and cannot see what are otherwise (to the expert) *non sequiturs*.

What Can Companies Do?

- **Own your assessment & get it peer reviewed!**
  - Why allow an assessment on a chemical of commercial importance by a group of practitioners…
  - And its peer review by a group that is poorly constructed?
- Within the limits of antitrust work collaboratively with colleagues; activist organizations already do this; *"hang together or hang separately"*
- Resist the temptation to stigmatize your competitors by allowing poor science to go un-addressed.