An International Collaboration to Determine the Safe Dose for Perfluorooctanoate (PFOA)

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Abstract

- Development of a safe PFOA dose has been going on since 2002 with values ranging from 4000 ng/kg-day to a now much lower, and still draft, value of 0.0015 ng/kg-day (USEPA, 2021).

- Drinking Water Inspectorate (2021), Health Canada (2018), the EFSA (2020), FSANZ (2017) and US ATSDR (2018) also have 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.

- The purpose of this presentation is to propose an international collaboration to resolve this extraordinary disparity.

The Primary Issue: Risk Characterizations Differ Widely: PFOA*

| Agency	EFSA (2020)	EPA (2021 draft)	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

What Makes PFOA So Different?

- PFOA (and PFOS) is mistaken by the body for a medium-length essential fatty acid, but it is resistant to metabolism.

- Therefore, PFOA can disrupt lipid homeostasis at sufficiently high concentrations in animal studies, and inter-individual differences in lipid homeostasis can also affect PFOA pharmacokinetics at low human exposures (Andersen et al. 2021).

- Due to its structural mimicry of essential fatty acids, active uptake of PFOA from the GI tract results in high oral bioavailability, and active resorption of PFOA excreted in the bile and urine limits clearance.

- Due to the complexity of the active control of PFOA pharmacokinetics associated with lipid homeostasis, it may be that human interindividual pharmacokinetic variability is significant
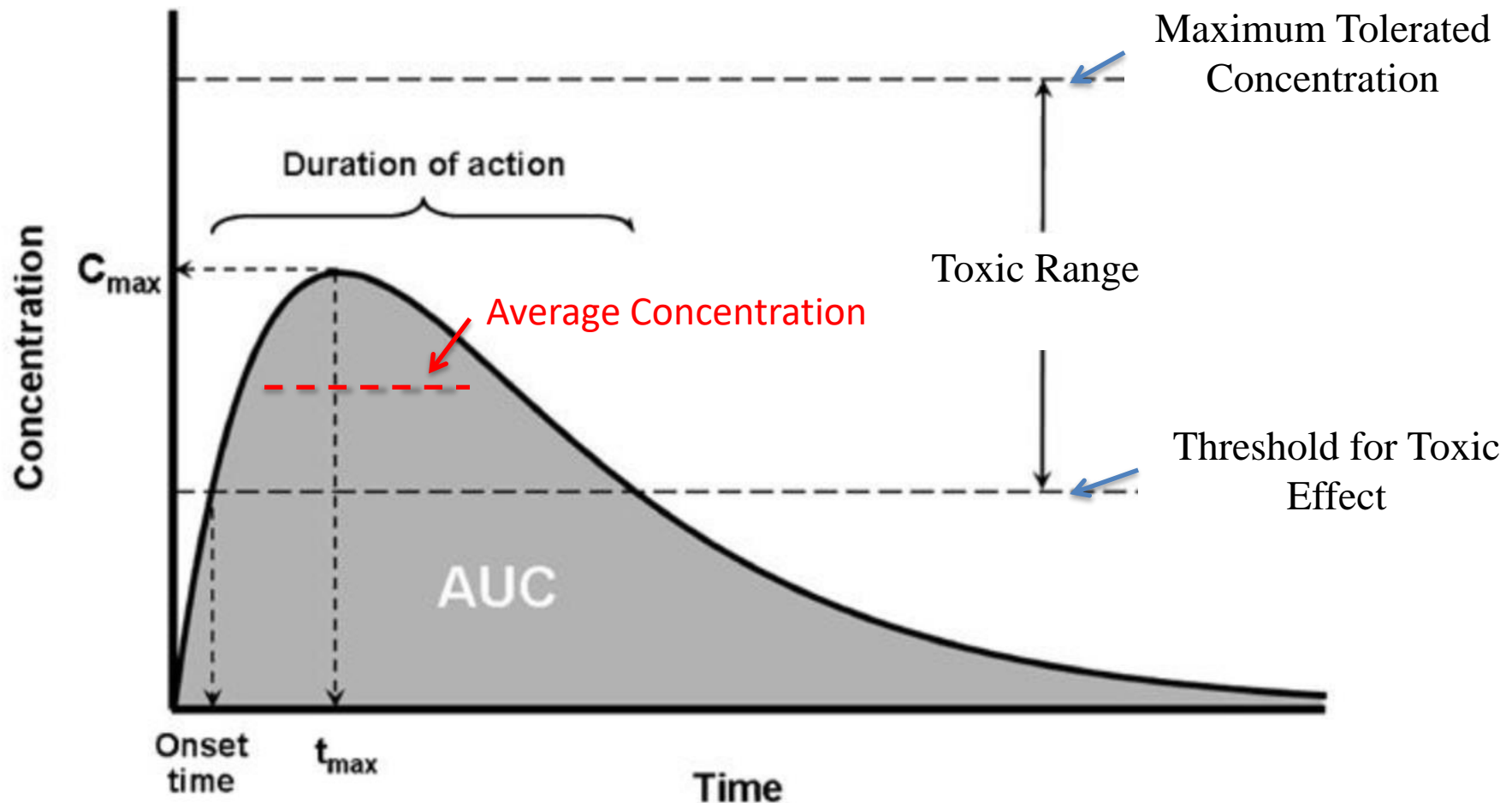
(Adapted from Harvey Clewell, 2022. Society of Toxicology Annual meeting)

Blood Concentrations Associated with Exposures & Effects in Humans & Animals

Box represents range of human Clinical study
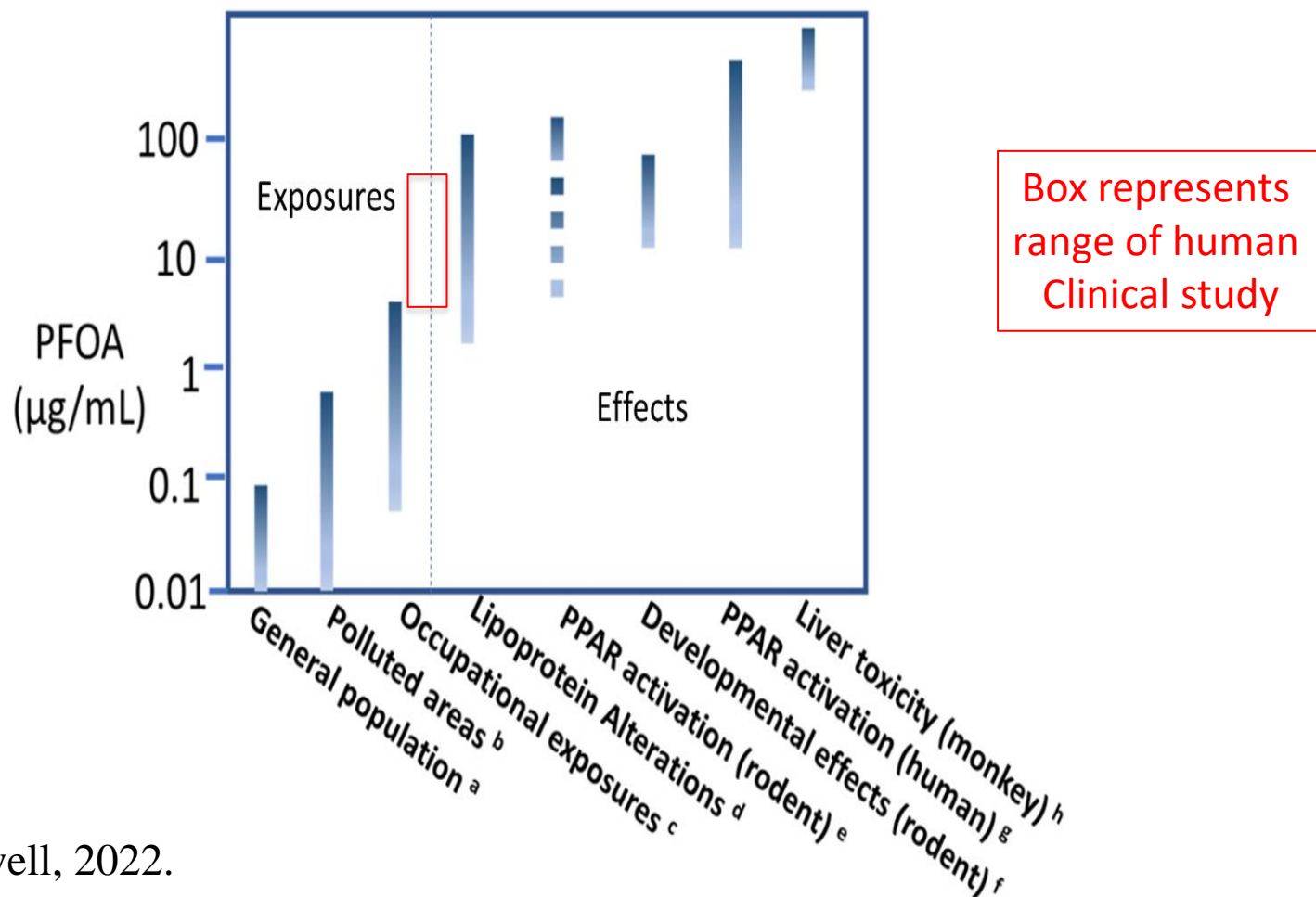
(Harvey Clewell, 2022.
Society of Toxicology Annual meeting,
citing Andersen et al. 2021)

Appropriate measure of dose? Depends on the critical effect: Area Under the Curve (AUC)... or Maximum Concentration (Cmax)…or Average Concentration?

Maximum Tolerated Concentration

Duration of action

C_{max}

Average Concentration

Toxic Range

Threshold for Toxic Effect

Concentration

AUC

Onset time

t_{max}

Time

Appropriate measure of dose?

Area under the Curve (AUC), or Maximum concentration (Cmax), or Average Concentration during an appropriate window
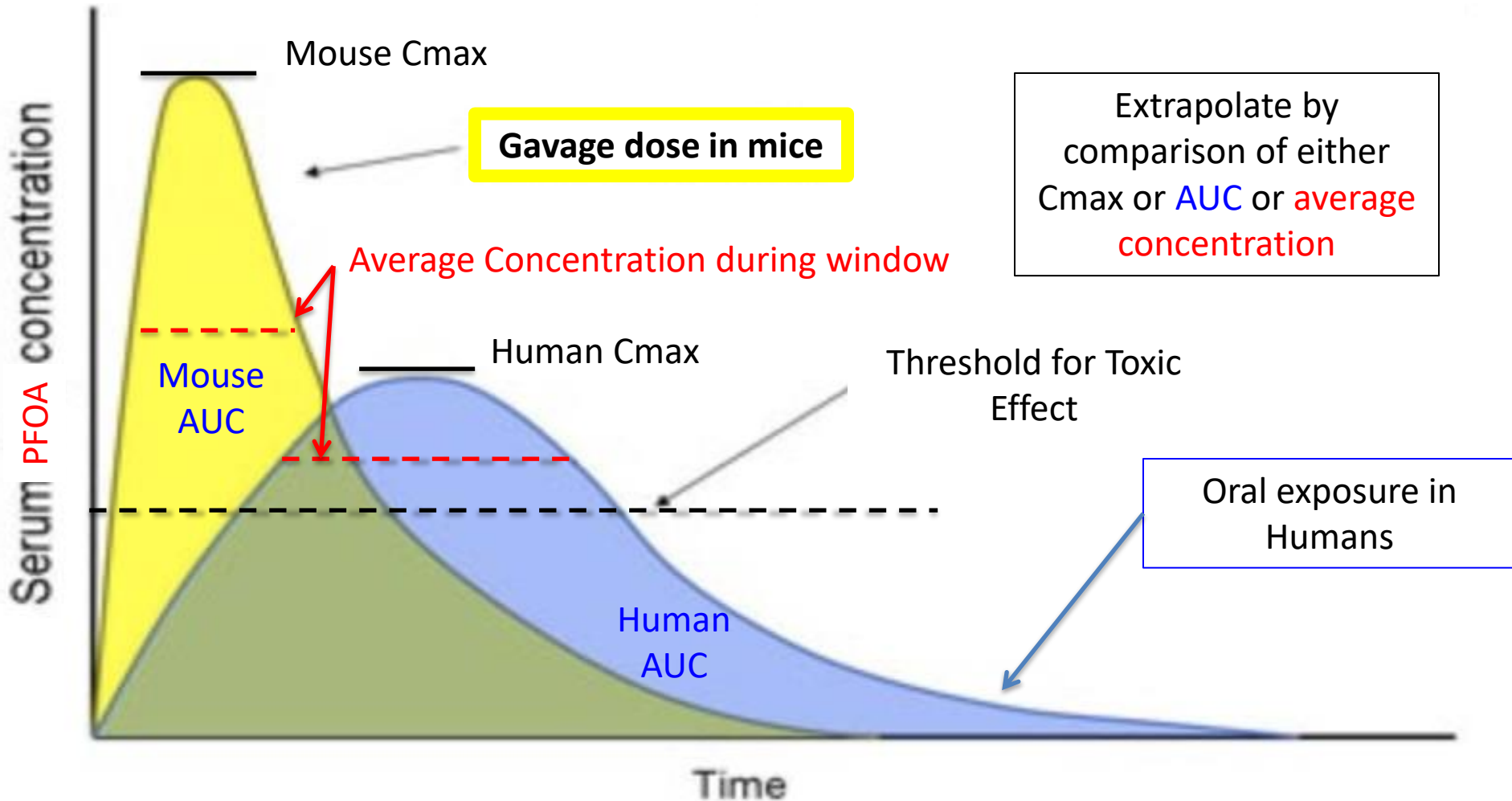
Is **Critical Effect** fetal? Consider Cmax or Average Concentration for
Chemical Specific Adjustment Factor (CSAF)

- Elcombe et al. (2013) reports that Cmax rises in 9 individuals after initial 6 weeks of continued weekly capsule exposure to approximate a steady state.

- A CSAF can be based on an estimate of this human exposure steady state by comparing to the shorter-term mouse exposure of 17 days that also has a steady state value.

- This DDEF value is ~14, i.e., 480 mg/L ÷ 35 mg/L ~14 (Dourson et al., 2019).*

*Paper of the year, Regulatory and Safety Evaluation Specialty Section, Society of Toxicology.

Elcombe et al. (2013) Clinical Study
Weekly doses in 9 patients.

Straight chain PFOA

Figure 78

CXR1002 Plasma Exposure Levels beyond the Initial 6-week Assessment Period
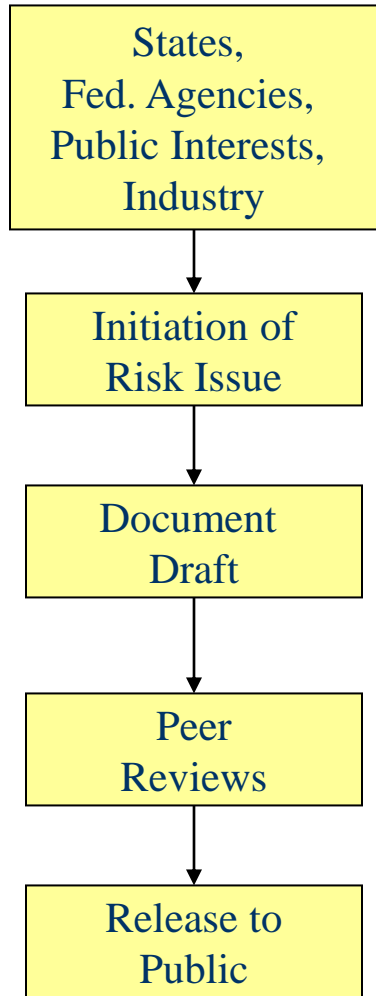

Doses in range
Of animal study

If **Critical Effect** is Liver or Immune, Consider Impact of Differing PFOA **AUC**s

- AUC or clearance of is typically slower in humans than rodents due to scaling of metabolism and excretion, resulting in differences in clearance on the order of a factor of 3-12.

- Clearance (liters/kg bw/day) = Volume of distribution (liters/kg bw) x ln2/Half-life (days).

- Since data indicates that Volume of distribution is similar across species, then interspecies CSAF is approximately the ratio of the half-lives.

- For example, if the half-life of PFOA in rodents is on the order 1-5 **days**, and the human half-life is 1.3 years (475 days), then the CSAF for PFOA could be 95 (i.e., 475 days/5days).
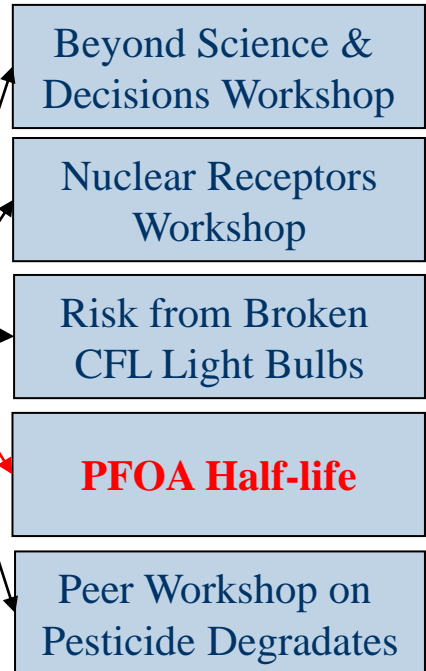
Conundrum of the PFOA Human ½ Life

- 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, USA
  - 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, USA
- Harvey Clewell, Ramboll, USA
- 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

![ARA - Alliance for Risk Assessment logo]

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

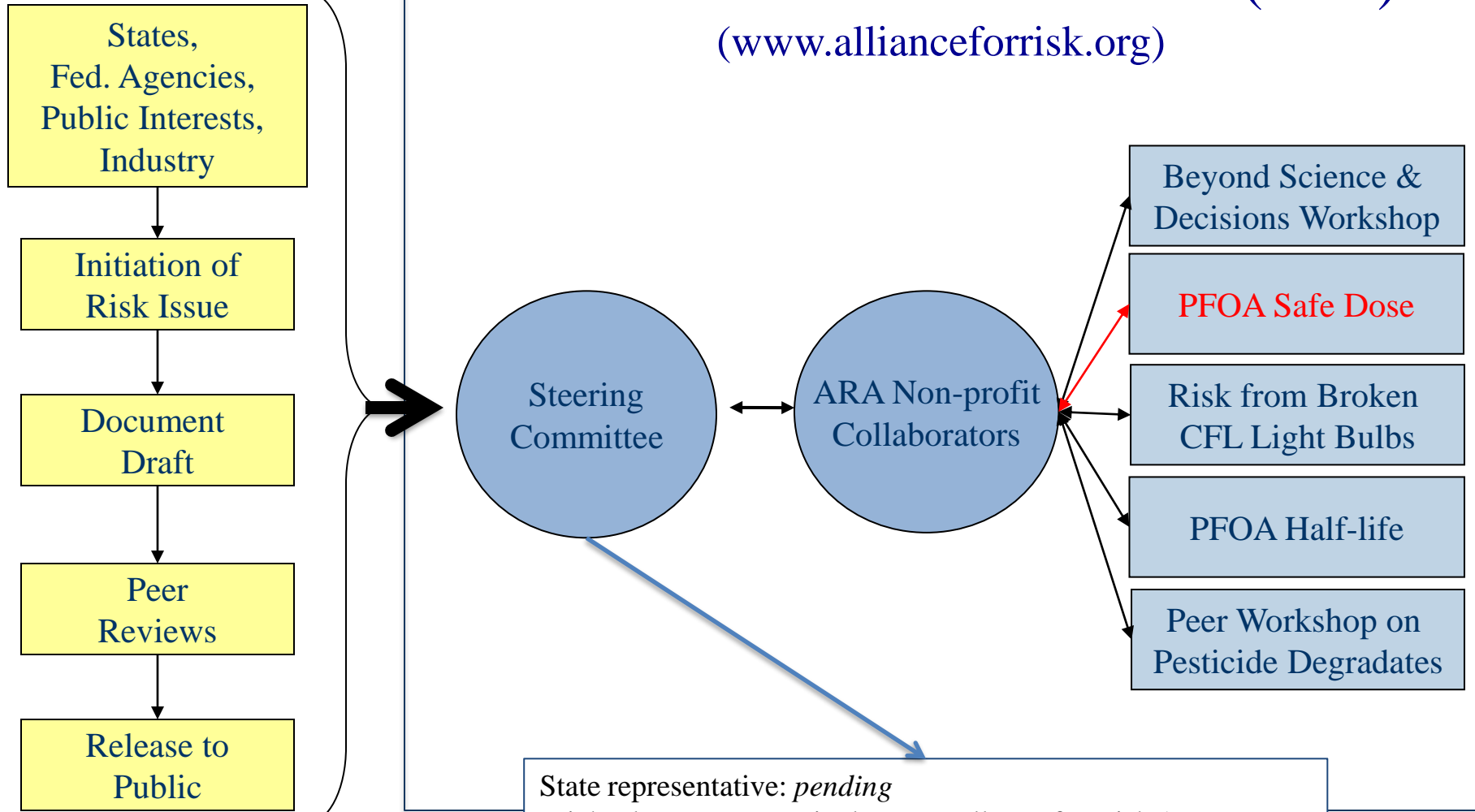| Study population	Half-life (years)	Comments	Uncertainty
Elcombe et al. (2013) Clinical trial (n = 3)	Arithmetic Mean (AM) 0.5	• Based on analysis of Elcombe et al. (2013) by Dourson and Gadagbui, 2020. • Patients received a single dose with 6 week follow up; serum levels <renal resorption.	• High dose 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.

Conclusions/Key findings

- The central tendency of the human PFOA half-life is likely less than 2 years.

- Zhang *et al.*, 2013 is the least encumbered 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 key issues.

- Recommendations:
  - More studies of similar design to Zhang et al., 2013
  - Clarification regarding background PFOA exposures of existing studies to enable potential adjustments to PFOA half-life estimates

Alliance for Risk Assessment (*ARA*)
(www.allianceforrisk.org)

States,
Fed. Agencies,
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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.

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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).

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What is Needed for Estimating A PFOA Safe Dose?

- <u>Needed</u>: A consensus on PFOA's critical effect, defined as the first adverse effect or its known, immediate precursor.

- <u>Needed</u>: Determine a point of departure in which reasonable confidence can be placed.

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

- *If* additional studies are done to estimate a half-life based on blood concentration decline, determine exposures from non-target media (e.g., house-hold dust).

Next Steps for Estimating a PFOA Safe Dose

Select an organization to manage the collaboration:

- The Steering Committee of the Alliance for Risk Assessment (*ARA*) is endorsing a call to develop an international collaboration on this topic. Decision to be announced at Adelaide on September 12, 2022.

Select an Advisory Committee to shepherd the effort:

- After announcement nominations solicited for advisory committee.

Committee to work with interested scientists/groups from around the world to form a consensus on PFOA safe dose or its range:

- The advisory committee will then open up the collaboration for all interested scientists and groups. Consensus positions will be developed as appropriate, or differences explained.

- Interested? Please email me at dourson@tera.org.

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.