

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

Harvey Clewell
Ramboll

What Drove the Creation of This Collaboration?

- Many government agencies and other expert groups have estimated tolerable daily doses of perfluorooctanoate (PFOA) that they believed would be protective of human health.
- These evaluations were based on a review of many of the same studies (whether of human, laboratory animal, or both), and all noted various uncertainties in existing knowledge with regard to PFOA and its risks to human health.
- Nonetheless, the values of these various estimates of a “safe” exposure to PFOA vary widely, with some disagreeing by as much as 100,000-fold.
- Such a large discrepancy invites scrutiny and explanation, in order to properly inform the public and drive future efforts to reduce uncertainty in the estimated risk.

Steps in the Assessment

- 1) Evaluate the evidence regarding potential Modes of Action (MOAs) for the various reported effects of PFOA and determine whether there is useful MOA information that could contribute to the determination of whether a particular endpoint should be considered a critical effect.
- 2) Select the critical study(s) for each of the critical effect(s).
- 3) Determine the appropriate extrapolation method and uncertainty factors to estimate Human Equivalent Doses (HEDs) for each critical effect.

Review of Evidence for PFOA Modes of Action (MOAs)

- PFOA can be mistaken by the body to be an essential fatty acid; however, PFOA is resistant to endogenous fatty acid metabolism.
- Potential modes of action associated with this mimicry include:
 - Disruption of lipid homeostasis by PFOA, particularly in the liver
 - These liver effects of PFOA have been shown to involve activation of multiple, related nuclear receptors, including PPAR α , PPAR γ , CAR, FXR, LXR, and PXR
 - The activation of these receptors in both rodents and humans occurs at concentrations on the order of 10 – 100 $\mu\text{g/mL}$
 - Misincorporation of PFOA in lipid membranes, resulting in dysfunction
 - In vitro exposure of human peripheral blood mononuclear cells to 1, 10, or 100 μM showed clear effects on immune cells only at the highest concentration (41 $\mu\text{g/mL}$).

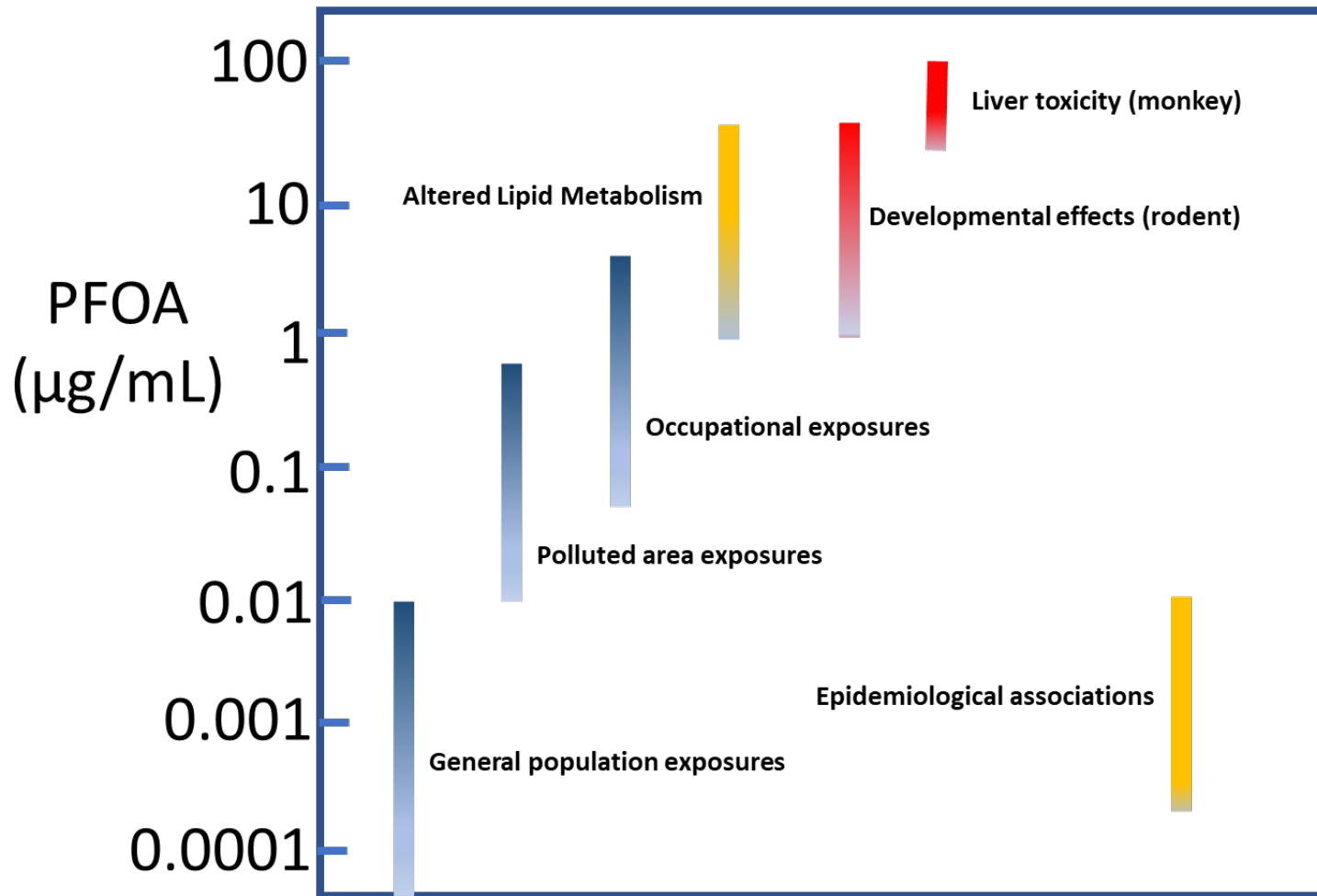
Implications of a PFOA Mode of Action Involving Disruption of Lipid Homeostasis

- In the dose range where animal studies are conducted, observations of liver toxicity and delayed development may reflect the disruption by PFOA of normal lipid processing, which has been observed at similar doses.
- However, while in mice, rats and humans, there is a core response leading to upregulation of fatty acid processing; in the mouse and rat, but not the human, there is a secondary pathway, controlled by PPAR α , that makes the cells more responsive to proliferation.
 - Therefore, the relevance of rodent data for some endpoints (e.g., cancer) is more uncertain.

The Critical Issue in Disparate Evaluations of PFOA Toxicity

- Until recently, critical effects for PFOA have been based on animal studies (primarily developmental studies) in rodents.
- Some of these animal-study based toxicity values are now being revised based on the results of epidemiological studies for a variety of endpoints in human populations.
- Key uncertainties associated with the use of epidemiological studies:
 - Whether the observed associations are causal (rather than due to confounding)
 - Whether the observed effects in humans are clinically relevant (adverse)

Comparison of PFOA Serum Concentrations Associated with Reported Exposures and Effects in Humans and Animals



(adapted from Andersen et al. 2021a)

The doses at which toxicity is observed in animal studies result in blood concentrations at which disruption of lipid metabolism occurs.

If effects reported for exposures of the general population were causal, it would be expected that more significant effects would be observed at occupational exposure levels, but they have not.

Blood levels of PFOA (and other PFAS) in the general population are orders of magnitude lower than those that disrupt lipid metabolism.

Epidemiological Associations of PFOA

- The most sensitive effects reported in epidemiological studies (when groups with higher exposures are compared to groups with lower exposures) are related to biomarkers (increases in total cholesterol and LDL cholesterol, increases in liver enzymes, and decreases in antibodies between groups) and decreased birth weight, for which the clinical relevance is uncertain.
- *What are the expected consequences of these differences?*
 - Increased risk of cardiovascular diseases - **negative or no associations**
 - Increased risk of liver diseases - **few studies of liver disease, no consistent associations**
 - Increased risk of infections or increased duration or frequency of infections - **mixed evidence**
 - Increased risk of low birth weight (<2500 g) - **no consistent associations**

Implications of PFOA Structural Similarity to Fatty Acids for Interpreting Epidemiological Studies

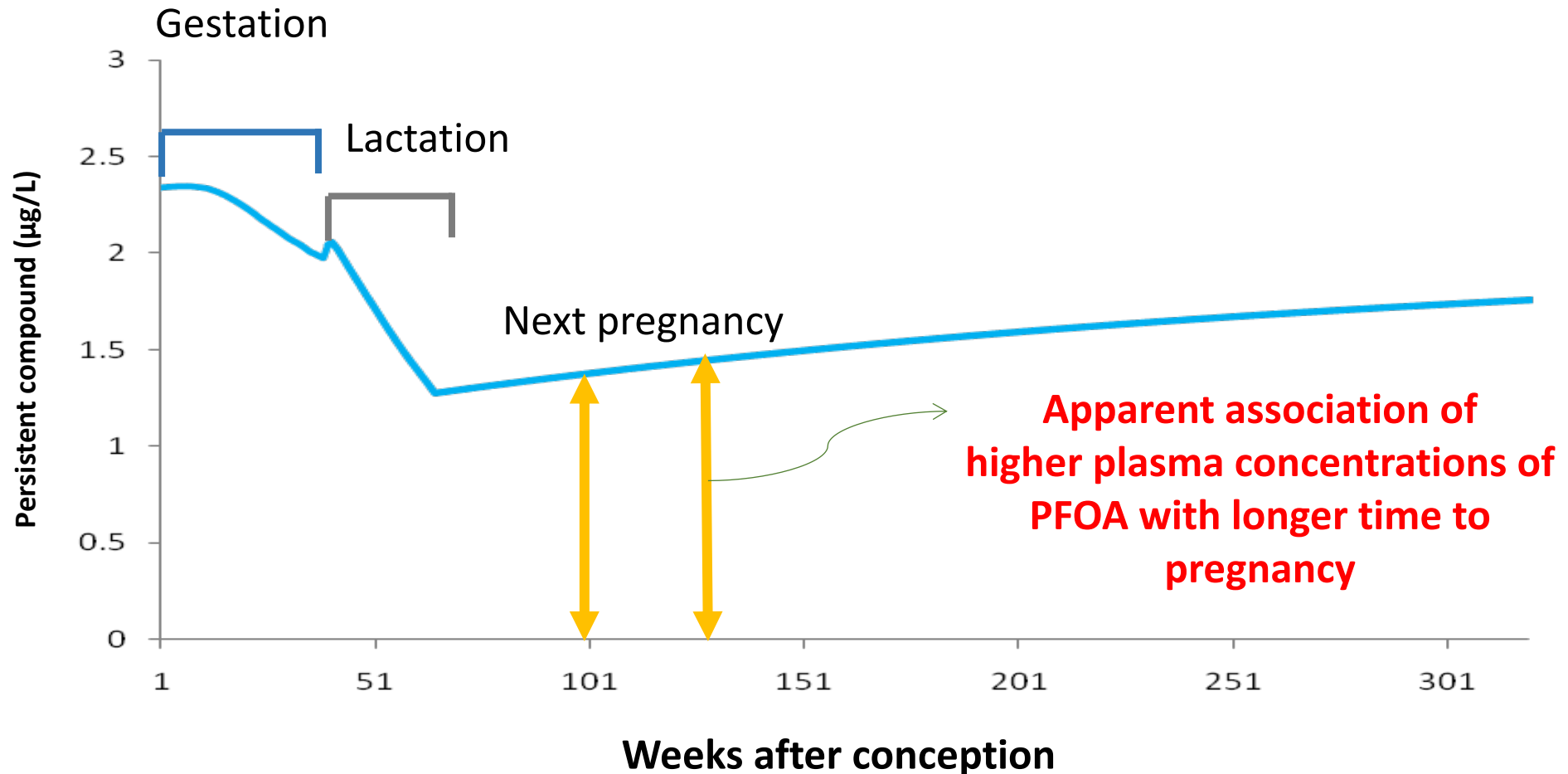
- The structural similarity of PFOA to endogenous fatty acids may underlie many of the associations of PFOA with various effects that have been reported in human epidemiology studies:
 - At human exposure levels, evidence suggests that inter-individual differences in lipid metabolism related to cholesterol homeostasis may affect PFOA pharmacokinetics, resulting in an apparent association.
 - “Common intestinal reabsorption of bile salts and PFASs, and uptake into the liver via shared membrane transport pathways is a possible mechanism of confounding since interindividual variability in reabsorption could lead to a positive association between serum levels of PFASs and cholesterol, the latter being affected by reabsorption of bile acids.” (EFSA 2020)

Epidemiological Associations Reported for PFOA

- In addition to cardiovascular effects, epidemiological studies have reported associations of PFOA with various developmental outcomes in human populations, including longer time to next pregnancy, early menarche / late menopause, and decreased birthweight.
 - However, there is evidence that these associations may also be confounded by pharmacokinetic bias, i.e., variations in the health biomarkers being evaluated are driven by underlying biological processes that also affect PFOA toxicokinetics.

Example of Reverse Causality

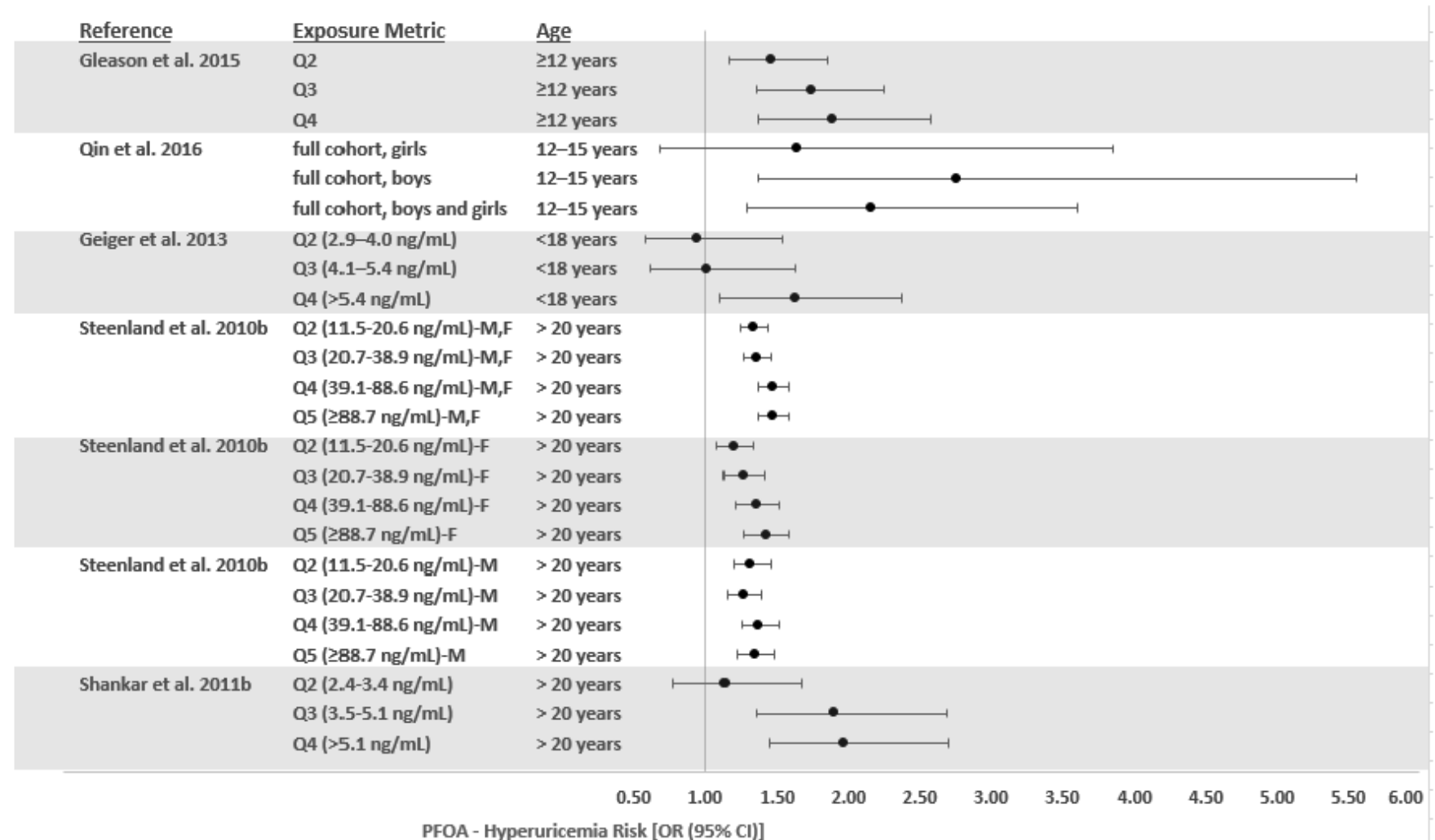
Effect of Childbirth on Maternal PFOA Blood Concentration



Example of an apparent association due confounding by a common underlying process

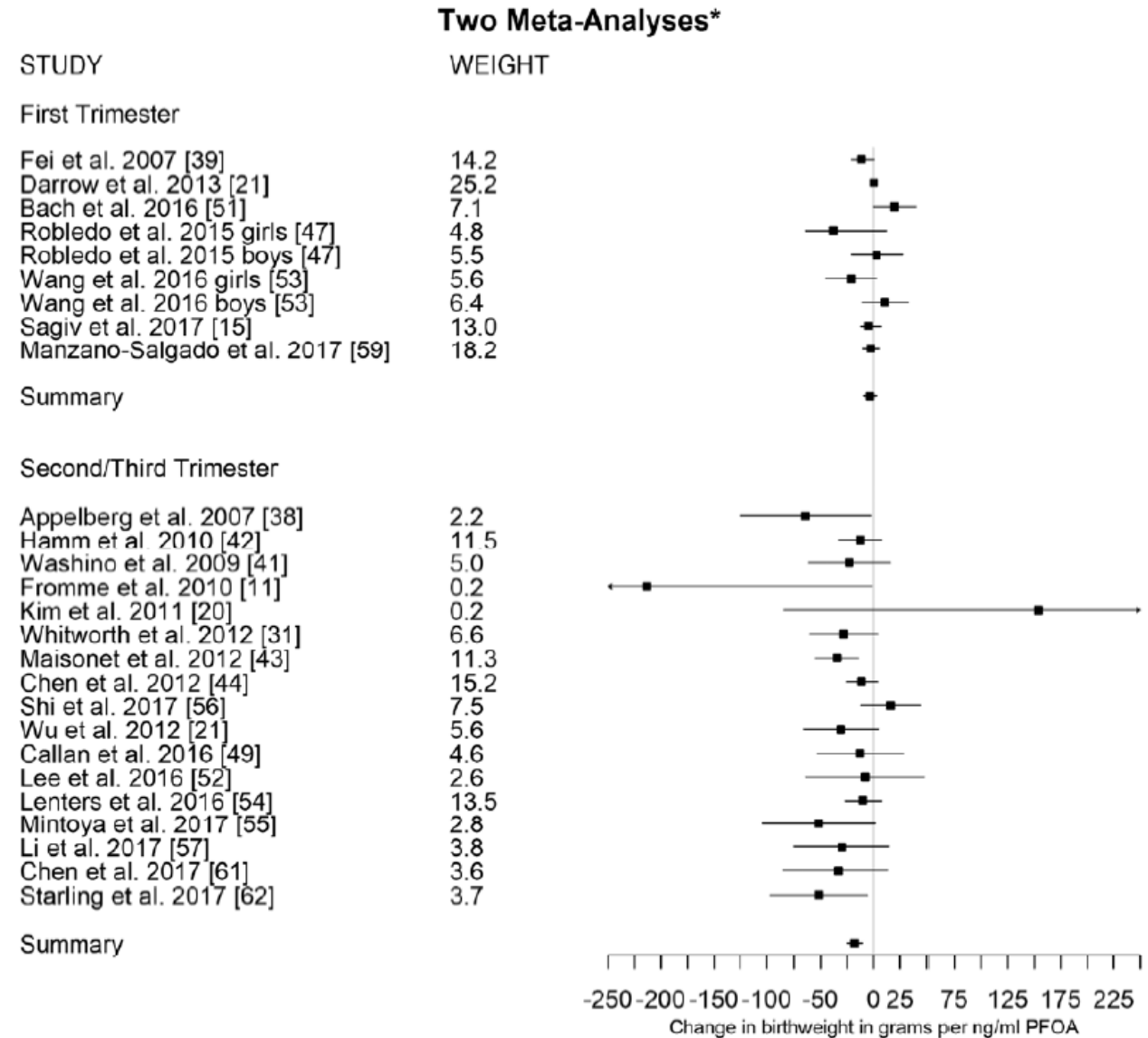
- Uric Acid and PFOA are both substrates for the Urate renal transporter
- Decreased activity of the Urate transporter leads to increased Uric Acid concentrations in the blood (Hyperuricemia)
- Decreased activity of the Urate transporter also leads to higher PFOA concentrations in the blood

Figure 2-17. Risk of Hyperuricemia Relative to PFOA Levels (Presented as Adjusted Odds Ratios)



PFOA and decreased birth weight

- Decreased renal clearance during pregnancy is associated with lower birth weight.
- Decreased renal clearance is also associated with higher PFOA concentrations
- Women with decreased filtration during pregnancy are more likely to give birth to infants with lower birth weights and are also more likely to have higher concentrations of PFOA during the third trimester of pregnancy, both due to the altered filtration rate.



Evaluation of the Epidemiological Data on Immunotoxicity

- There is currently no plausible MOA to link PFOA with the observed changes in antibody response at such low concentrations (> 10 ng/mL).
- Biomarkers should not be relied upon as a surrogate for an adverse effect without a MOA that ties them to a critical effect.
 - In the case of perchlorate, the use of changes in biomarkers (T4, TSH) as a surrogate for potential developmental effects was supported by a well-defined MOA involving inhibition of thyroid iodine uptake.
- It is unclear whether small decreases in antibody response to vaccines are clinically significant
- While observed associations should prompt additional investigation of potential immunosuppressive effects of PFOA, the current serum concentration/antibody level data were not deemed suitable for developing a safe dose.

Impact of PFOA Clearance on Animal-Based Toxicity Values

- Clearance of environmental chemicals from the body is generally slower in the human than in rodents
- Because of this difference, the Human Equivalent Dose (HED) is usually lower than the animal point of departure by about a factor of 7 (from rats) to 12 (from mice).
- However, the half-life for elimination of PFOA in rodents is on the order of **days**, while in the human it is on the order of **years**
- In the case of PFOA, the HEDs are therefore on the order of 100- to 500-fold lower than the animal dose.

The long human half-life of most PFAS appears to result from active reabsorption in the kidney at low concentrations

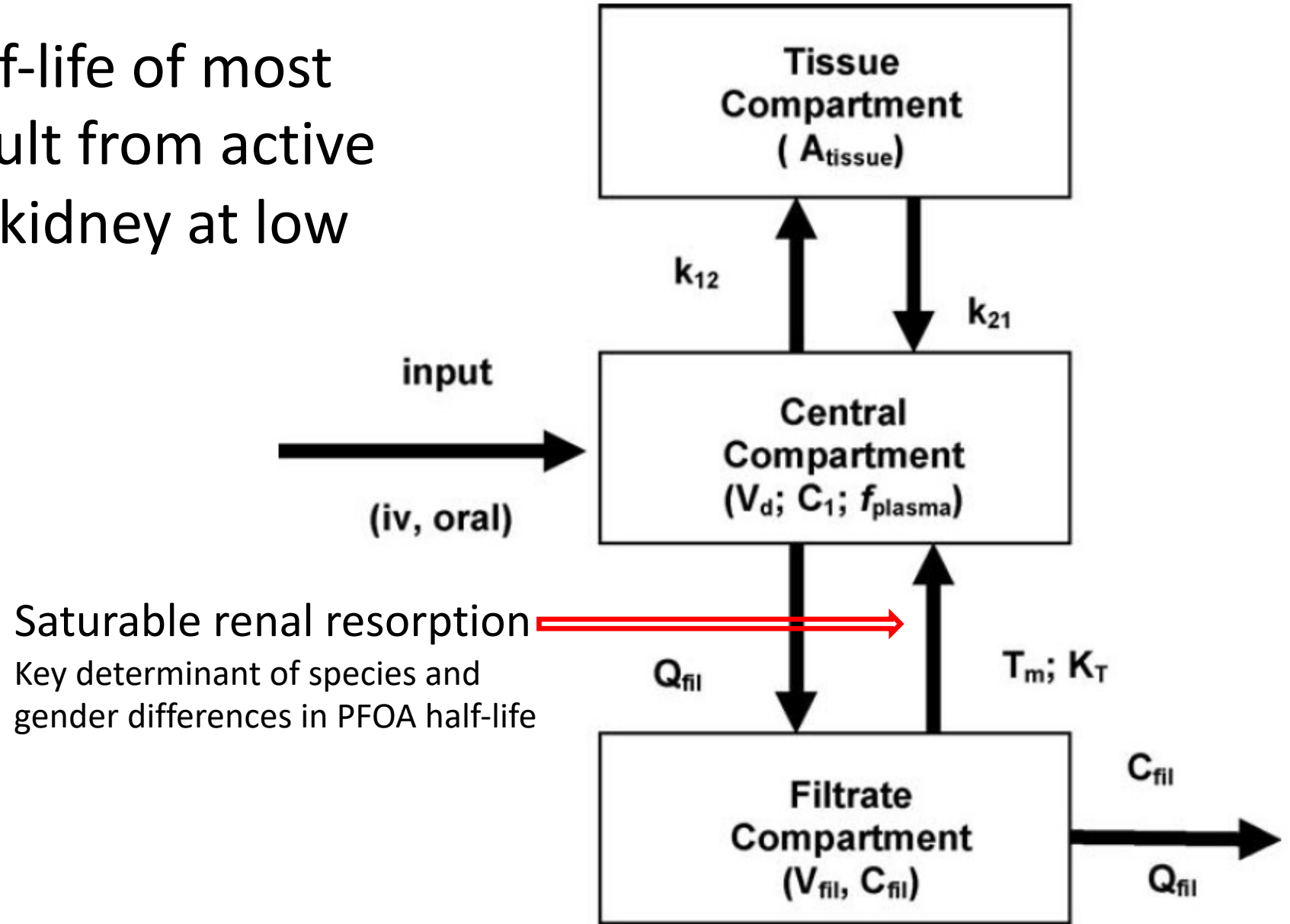


Fig. 1. A schematic for a physiologically-motivated renal resorption pharmacokinetic model. (Andersen et al. 2006)

Findings from an International Collaboration on the PFOA Human Half-life

- Unfunded project under the Alliance for Risk Assessment
 - Website:
<https://tera.org/Alliance%20for%20Risk/Projects/pfoahumanhalflife.html>
 - Publication:
Campbell et al 2022. Regul Toxicol Pharmacol.
doi: 10.1016/j.yrtph.2022.105185.
- Conclusions:
 - The central tendency of the human PFOA half-life is likely less than 2 years
 - The single best half-life value appears to be the geometric mean of 1.3 years from Zhang et al. (2013)
 - This value is supported by a geometric mean of 1.5 years from Zu et al. (2020)
 - The half-lives derived from these two studies are considered to be more accurate than the value of 3.8 years used by USEPA (2021)

Selected Critical Studies for PFOA

Study	POD µg/mL	Basis of POD
Butenhoff et al. (2002).	19	<u>Monkey</u> : Point of Departure = 19 ug/ml estimated by Green and Crouch (2019) based on a serum PFOA benchmark concentration (BMC) for increased liver weight
Lau et al. 2006	23	<u>Mouse</u> : Point of Departure = 1 mg/kg-day (23 µg/ml) NOAEL for dose-dependent growth deficits for gestation days 1-17
Loveless et al. (2006)	4.35	<u>Mouse</u> : Point of Departure = 4.35 µg/ml based on a serum PFOA BMC estimated by New Jersey/New Hampshire (Post et al., 2021) for lipid parameters/relative liver weight in male mice
Abbott et al. (2007)	10.4	<u>Mouse</u> : Point of Departure = 0.3 mg/kg-day (10.4 ug/ml) NOAEL for neonatal survival
DeWitt et al. (2016)	0.94	<u>Mouse</u> : Point of Departure = 0.94 mg/kg-day (no serum values available) NOAEL for immune suppression

Calculation of Safe Dose Range for PFOA

Reference	AK _{UF}	AD _{UF}	HK _{UF} *	HD _{UF}	RfD μg/mL	RfD** μg/kg/day
Butenhoff et al. (2002).	1	2.5	8.4	3	0.25	0.06
Lau et al. 2006	1	2.5	8.4	3	0.30	0.07
Loveless et al. (2006)	1	2.5	8.4	3	0.058	0.01
Abbott et al. (2007)	1	2.5	8.4	3	0.14	0.03
DeWitt et al. (2016)	1	2.5	8.4	3	0.29	0.07

* Developed using 0.79 ml/day/kg arithmetic mean clearance of average group (Zhang et al., 2013, Table 2)
÷ 0.094 ml/day/kg arithmetic 95% lower bound clearance of sensitive group (Zhang et al., 2013, Table 2)

**Developed using geometric mean clearance (Zhang et al., 2013, Table 2) assuming steady state

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Participants in ARA Collaboration

- Lyle D. Burgoon, Raptor Pharm & Tox, Ltd, USA
- Harvey J. Clewell, Ramboll, USA
- Tony Cox, Cox Associates, USA
- Wolfgang Dekant, U. Würzburg (retired), DE
- Linda D. Dell, Ramboll, USA
- James A. Deyo, Environmental Protection Authority, NZ
- Michael L. Dourson, TERA, USA
- Bernard K. Gadagbui, TERA, USA
- Philip Goodrum, GSI, USA
- Laura C. Green, Green Toxicology LLC, USA
- K. Vijayavel, Cook Medical, USA
- Travis R. Kline, Geosyntec Consultants, USA
- Tamara House-Knight, GHD, USA
- Michael I. Luster, NIOSH (retired), USA
- Therese Manning, Environmental Risk Sciences Pty Ltd, AU
- Ravi Naidu, Contamination Assessment and Remediation of the Environment, University of Newcastle, AU
- Paul Nathanail, LQM, UK
- Frank Pagone, RHP Risk Management, USA
- Katie Richardson, Senversa, AU
- Tiago Severo-Peixe, State University of Londrina, BR
- Anurag Sharma, Nitte University, IN
- James S. Smith, US DoD, USA
- Nitin Verma, Chitkara University School of Pharmacy, Chitkara University Himachal Pradesh, IN
- Jackie Wright, Environmental Risk Sciences Pty Ltd, AU