Alliance for Risk Assessment (*ARA*):
The Conundrum of the PFOA Human Half-life

Summary of Findings

Advisory Committee:

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- Tony Cox, Cox and Associates
- Michael Dourson, Toxicology Excellence for Risk Assessment
- Shannon Ethridge, International Association of Plumbing and Mechanical Officials
- Ali Hamade, Oregon Health Authority
- Ravi Naidu, Cooperative Research Centre for Contamination Assessment and Remediation of the Environment
- Nitin Verma, Chitkara University

Members of the Three Small Groups:

- Jerry Campbell, Ramboll
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- Norman Forsberg, Arcadis
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Charge to the small groups:

- Select studies from the current list found at https://tera.org/Alliance%20for%20Risk/Projects/pfoahumanhalflife.html for further review and explain why certain studies were excluded. Feel free to add studies as appropriate and explain why they were added.
- Develop a small group consensus on PFOA 1/2 life, discussing critical issues, such as, volume of distribution, half-lives in different populations, and how uncertainty factors for experimental animal to human extrapolation and within human variability are affected. Groups are free to add critical issues as appropriate.
- No inter-group discussions are allowed as to avoid premature closure.

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- The deadline is August 31st for this first round of small group review (deadline was met).
- First intergroup discussion is to be held in September (discussion occurred on September 7/8).
- A second round of review is to be held through interactive web-based discussions during October and early November (discussions occurred on schedule).

The following points show some of the consensus findings from this international collaboration. In no particular order they are:

- Two of three small groups did not consider any one study sufficient for determining the PFOA half-life. The third small group considered Xu et al. (2020) to be more credible than other studies due to the apparent single dominant source of PFOA exposure. Collectively, studies and/or analyses of studies that were considered to be of some use are summarized in Table 1. Each of these studies has advantages and disadvantages.

- Almost all studies alluded to unmonitored PFOA exposures as noted in Table 1. All 3 small groups considered that up to ~25% bias in the half-life was possible in studies with low serum PFOA levels due to these unmonitored PFOA exposures, based on the work of DeSilva et al. (2020) who state that drinking water "has been estimated to contribute *up to* 75% of exposures near contaminated sites." This latter study suggests that as much as 25% of PFOA exposure might be coming from other sources. The consensus of all small groups was that an argument could be made for a 20% reduction in the average half-life in such studies because of this problem. However, the study by Zhang et al. (2013) was unencumbered by this problem, since its PFOA half-life was based on estimates of renal clearance from men and women of the general Chinese population (aged 20 to 88 years) with no known point source of exposure to PFOA.

- The geometric mean was considered to be a superior averaging metric than either arithmetic mean or median values base on the work of Zhang et al. (2013) where it was shown that arithmetic mean half-lives based on arithmetic mean clearances did not match arithmetic mean half-lives based on individual clearances. The estimation of geometric mean half-lives from either geometric mean clearance or individual geometric mean clearance did not differ to the same degree. This is because the distribution of half-lives was found to be skewed right in a graph of PFOA serum concentration versus time (Zhang et al., 2013; *ARA*, 2021).

- The issue of mixture of several PFOA isomers and precursors was poorly dealt with in almost all studies as also shown in Table 1, lending unreducible uncertainty to the estimated half-lives. For an exception of this, however, see the findings of Zhang et al. (2013), where isomers of PFOA were monitored and separate estimates of isomer half-lives were given; branched isomers had shorter half-lives than the straight chain isomer.

- The estimation of the volume of distribution in some studies is based on measured PFOA exposures, but such estimations will be inappropriately low if unmonitored sources of exposure are occurring. Other studies or analyses estimate the volume of distribution from a small population in a clinical trial where PFOA was used as a cancer chemotherapeutic drug and in whom the kinetics of PFOA may or may not reflect that expected in a normal population. Other investigators selected a volume of distribution from either a small group of monkeys (n = 3) or from other experimental animals. Selecting one value for the volume of distribution from this assortment of values is challenging given all of these different approaches. However, a value of around 0.18 Liters/kg body weight should approximate the likely appropriate value.

- Studies from Table 1 that were considered to have the fewest problems with unmonitored PFOA exposures and isomer accountability are shown in Table 2. Collectively these studies show a range in the straight-chain, PFOA half-life of 0.5 to 1.5 years. The lower limit of this range is based on 3 individuals who were monitored extensively over 6 weeks in a clinical trial of PFOA given as a chemotherapeutic drug (Elcombe et al, 2013). The upper part of this range is based on a human observational study of 17 individuals monitored frequently over 5 months from a likely single dominant source of PFOA exposure, but where isomers were not clearly distinguished (Xu et al., 2020). The mid part of this range is based on a PFOA clearance study, thus obviating any uncertainty in unmonitored exposures, and half-lives of PFOA isomers were individually estimated (Zhang et al. (2013).

- After extensive email discussions, the whole group then considered three options. Each group member was asked to consider choosing a preferred option along with reasons for the choice. Members were also encouraged to indicate an option that could be lived with, but of course not preferred, and, if appropriate, to select an option that could *not* be lived with. The development of other options was also solicited. Options considered were:

    1. Select a single study to represent your best judgment of the PFOA half-life.
    2. Select a range of the PFOA half-life from a small group of studies with or without a single value, such as what we show in Table 2.
    3. Select a range of the PFOA half-life from a larger group of studies with or without a single value, such as what we show in Table 1.

    Individual member choices were then sent to two senior members of the group in a confidential manner and responses were collated as shown in Table 3. Option 2 was

preferred by all responders except one, but this person stated that they could live with option 2. Thus, a consensus[1] was reached for the choice of option 2.

Additional efforts to extend this work might include a meta-analysis of selected studies after a follow up with authors for individual data to determine distributions, and estimating backgrounds or potentially unmonitored exposures. It would also be helpful to get another clearance study, like Zhang et al. (2013), for confirmation.

References:

Alliance for Risk Assessment (*ARA*). 2021. Beyond Science and Decisions Workshop XII. Meeting report available at: https://tera.org/Alliance%20for%20Risk/Workshop%20XII/Final%20Report.pdf.

Campbell, J., Allen, B., Olsen, G., Elcombe, C., Doyle, E., Evans, J., Clewell, H., 2016. Evaluation of the short-term clearance of perflourooctanoic acid (PFOA) in a clinical trial using a PBPK model and Markov chain Monte Carlo analysis. In: Poster at the Society of Toxicology Annual Meeting.

Bartell SM, Calafat AM, Lyu C, Kato K, Ryan PB, Steenland K. 2010. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ Health Perspect 118(2):222–228, PMID: 20123620, https://doi.org/10.1289/ehp.0901252.

Brede E, Wilhelm M, Göen T, Müller J, Rauchfuss K, Kraft M, et al. 2010. Two-year follow-up biomonitoring pilot study of residents' and controls' PFC plasma levels after PFOA reduction in public water system in Arnsberg, Germany. Int J Hyg Environ Health 213(3):217–223, PMID: 20488749, https://doi.org/10.1016/j.ijheh.2010.03.007.

De Silva, Amila O., James M. Armitage, Thomas A. Bruton, Clifton Dassuncao, Wendy Heiger-Bernays, Xindi C. Hu, Anna Kärrman, Barry Kelly, Carla Ng, Anna Robuck, Mei Sun, Thomas F. Webster, Elsie M. Sunderland. 2020. PFAS Exposure Pathways for Humans and Wildlife: A Synthesis of Current Knowledge and Key Gaps in Understanding. Environmental Toxicology and Chemistry: https://doi.org/10.1002/etc.4935.

[1] "Unanimous consensus" is defined here as all scientists are in agreement with the preferred option. "Consensus" is defined here as all scientists are in agreement with the preferred option, or can live with the preferred option of the majority.

Dourson, Michael and Bernard Gadagbui. 2021. The Dilemma of Perfluorooctanoate (PFOA) Human Half-life. Toxicology Excellence for Risk Assessment (TERA). Regulatory Toxicology and Pharmacology. 126 (2021) 105025.

Elcombe, C.R., Wolf, C.R., Westwood, A.L., 2013. US Patent Application Publication. Pub. No.: US 2013/0029928. Available at: https://patentimages.storage.googleapis.com/24/ee/73/f58267c7d70dde/WO2011101643A1.pdf.

Gomis MI, Vestergren R, MacLeod M, Mueller JF, Cousins IT. 2017. Historical human exposure to perfluoroalkyl acids in the United States and Australia reconstructed from biomonitoring data using population-based pharmacokinetic modelling. Environment International 108:92–102. http://dx.doi.org/10.1016/j.envint.2017.08.002

Gomis MI, Vestergren R, Nilsson H, Cousins IT. 2016. Contribution of Direct and Indirect Exposure to Human Serum Concentrations of Perfluorooctanoic Acid in an Occupationally Exposed Group of Ski Waxers. Environ Sci Technol. 50(13):7037-46.

Li Y, Fletcher T, Mucs D, Scott K, Lindh CH, Tallving P, et al. 2018. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup Environ Med 75(1):46–51, PMID: 29133598, https://doi.org/10.1136/oemed-2017-104651.

Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, et al. 2007. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect 115(9):1298–1305, PMID: 17805419, https://doi.org/10.1289/ehp.10009.

Xu Y, Fletcher T, Pineda D, Lindh CH, Nilsson C, Glynn A, Vogs C, Norström K, Lilja K, Jakobsson K, Li Y. 2020. Serum Half-Lives for Short- and Long-Chain Perfluoroalkyl Acids after Ceasing Exposure from Drinking Water Contaminated by Firefighting Foam. Environ Health Perspect. 28:7 CID: 077004 https://doi.org/10.1289/EHP6785

Zhang Y, Beesoon S, Zhu L, Martin JW. 2013. Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life. Environ Sci Technol 47(18):10619–10627, PMID: 23980546, https://doi.org/10.1021/es401905e.

Table 1. Selected Studies with PFOA half-life estimates.

Study population	Reported Half-life (years) [a]	Comments	Unmonitored Sources of PFOA Exposure Addressed?	PFOA Half-life Accounted for Isomers?
Dourson and Gadagbui (unpublished) Analysis of Nilsson et al. (2010)	AM = 0.9 (+background) AM = 0.6 (-background)	• Based on the finding from 3 ski-waxers presumably exposed to PFOA via inhalation of airborne particles and fumes • Modestly high serum levels but below presumed renal resorption limit [b] • Too few individuals for GM estimation	Maybe	No
Dourson and Gadagbui (2021)	AM = 0.5 to 1.5	• Lower part of range based on a new analysis of data from clinical study of Elcombe et al. (2013) for 3 cancer patients receiving a single dose of PFOA with 6 week follow up who had serum levels likely to be below saturation of renal resorption [b] • High end of range based on data from observational study of Xu et al., (2020); see below.	Elcombe: Not needed based on high dose given Xu et al. (2020): see below	Elcombe: Dosing was with linear isomer Xu et al. (2020): see below

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Study population	Reported Half-life (years) [a]	Comments	Unmonitored Sources of PFOA Exposure Addressed?	PFOA Half-life Accounted for Isomers?
Xu et al. (2020) Airport employees in Sweden exposed to PFAS through airport's waterworks	GM = 1.8 (+background) GM = 1.48 (-background)	• Alternate exposures were unlikely. • Small population (n = 17) and short follow up (5 months) • Exposures not greatly above background.	Maybe	Not clear
Li et al. (2018) Community: 106 Swedes in Ronneby, Sweden, exposed to PFAS through contaminated municipal drinking water: 2-year follow-up time	AM = 2.7	• Exposures in water, food, dust, air, and household products not monitored. • Study assumed exposure levels in the general population from all sources were negligible, but excluded outliers that suggested ongoing exposure greater than the background of the control population. • Geometric mean is likely smaller.	No	No
Gomis et al. (2017) Population-based cross- sectional biomonitoring data from USA (NHANES, 1999-2013) and Australia (2003-2011)	Men: AM = USA 2.4; Australia 2.1 Women: AM = USA 2.1; Australia 1.8	• Study noted that background human exposure was likely dominated historically by consumer products. • Geometric mean is likely smaller.	No	No

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Study population	Reported Half-life (years) [a]	Comments	Unmonitored Sources of PFOA Exposure Addressed?	PFOA Half-life Accounted for Isomers?
Gomis et al. (2016) Ski waxers: 4 male technicians occupationally exposed to airborne particles and fumes from hot ski wax; followed after marked reduction of occupational exposure	AM = 2.4	• Average reported as intrinsic (i.e., corrected for the ongoing background exposure from diet and drinks only. • Dermal exposure assumed negligible. • Geometric mean is likely smaller.	No	No
Zhang et al. (2013) General population: healthy volunteers in China N=86	AM = 2.3 GM = 1.7 (young females, n = 20) AM = 2.8 GM = 1.2 (all males and older females, n = 66)	• Study assumed volume of distribution of 170 mL/kg. • Discussion of background or ongoing exposures or exposures were not needed since half-lives were based on renal clearance. • Study notes that half-lives should be considered as upper limit estimates since not all elimination routes were studied.	Not needed since study was based on estimated renal clearance	Yes

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Study population	Reported Half-life (years) [a]	Comments	Unmonitored Sources of PFOA Exposure Addressed?	PFOA Half-life Accounted for Isomers?
Bartell et al. (2010) 200 Americans (172 public water drinkers and 28 bottled water drinkers)	Median = 2.3 (all) Median = 2.1 (group eating homegrown vegetables)	• Water systems remained contaminated with PFOA to some extent for days to weeks after filtration began. • Study indicates their mean half-life is heavily influenced by the 12- month serum PFOA measurements and should be viewed as a preliminary estimate. • Geometric mean is likely smaller.	No	No
Olsen et al. (2007) Occupational workers: 26 retired fluorochemical production workers	GM = 3.5	• Study noted that it is unlikely that the potential for non-occupational exposures substantially distorted the elimination. • Study discussed other sources of exposure, but none was monitored in households of participants.	No	No

a) AM = arithmetic mean; GM = geometric mean.

b) Saturation of resorption is likely to occur at plasma concentrations above 10 uMoles/L, based on an estimated renal transporter Km of 4 µg/ml from an analysis of this clinical study of Elcombe et al. (2013) (Campbell et al. 2016, *ARA*, 2021)

c)

Table 2. Studies selected with fewest issues of unmonitored sources of PFOA exposure, elimination, or isomer uncertainties.

Study population	Reported Half-life (years) [a]	Comments	Exposure, Isomer or Elimination Uncertainty
Dourson and Gadagbui (2021)	AM = 0.5 to 1.5	• Lower part of range based on new analysis of data from clinical study of Elcombe et al. (2013) for 3 cancer patients receiving a single dose of PFOA with 6 week follow up who had serum levels likely to be below saturation of renal resorption • Too few individuals for GM estimation • High end of range based on data from observational study of Xu et al., (2020); see below.	• High dose in Elcombe et al. (2013) obviates the need for monitoring of other PFOA exposures • Single isomer was studied in Elcombe et al. (2013), so no uncertainty exists with this issue Xu et al. (2020): see below
Xu et al. (2020) Airport employees in Sweden exposed to PFAS through airport's waterworks	GM = 1.48	• Alternate exposures were unlikely. • Small population (n =17) and 5-month follow up • Exposures not greatly above background.	• Other unmonitored exposures are possible, and if available would result in a lower intrinsic half-life. • Some uncertainty exists since branched PFOA isomers were studied in drinking water, but not reported in serum.

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Study population	Reported Half-life (years) [a]	Comments	Exposure, Isomer or Elimination Uncertainty
Zhang et al. (2013) General population: healthy volunteers in China N=86	GM = 1.7 (young females, n = 20) GM = 1.2 (all males and older females, n = 66) Average GM = 1.3	• Study assumed volume of distribution of 170 mL/kg. • Discussion of background or ongoing exposures or exposures were not needed since half-lives were based on renal clearance. • Study authors note that half-lives should be considered as upper limit estimates since not all elimination routes were studied.	• No uncertainty in unmonitored exposures since renal clearance studied • Unmonitored elimination by other routes was likely which, if measured would result in a lower half-life; • Multiple isomers were individually studied so no uncertainty exists with this issue

a) AM = arithmetic mean; GM = geometric mean.

Table 3. Results from Consensus Polling of the International Group

Option	Preferred	Can live with it	No	Comments
1 (single study)	1	2 (with Tables 1 and 2 and caveats)	2	One favored option 1 and recommended Zhang et al., 2013
2 (small group of studies)	8	1	0	As in Table 2. Eight favored option 2. One stipulated without a single value; another said with Table 1 included to document studies considered
3 (larger group of studies)	0	2	2	As in Table 1.