The Conundrum of the PFOA Human Half-life, An International Collaboration

By

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Disclaimers

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Abstract

The Steering Committee of the Alliance for Risk Assessment (*ARA*) opened a call for scientists interested in resolving what appeared to be a conundrum in estimating of the half-life of perfluorooctanoate (PFOA) in humans. An Advisory Committee was formed from nominations received and a subsequent invitation led to the development of three small independent working groups to review appropriate information and attempt a resolution. Initial findings were shared among these groups and a conclusion developed from the ensuing discussions.

Many human observational studies have estimated the PFOA half-life. Most of these studies note the likely occurrence of unmonitored PFOA exposures, which could *inflate* values of the estimated PFOA half-life. Also, few of these studies estimated the half-life of PFOA isomers, the branched chains of which likely have shorter half-lives. This could *deflate* values of the estimated linear PFOA half-life. Fortunately, several studies informed both of these potential problems. The majority opinion of this international collaboration is that the studies striking the best balance in addressing some of these uncertainties indicate the likely central tendency of the human PFOA half-life is less than 2 years. The single best value appears to be the geometric mean (GM) of 1.3 years (Zhang et al., 2013; Table 3), based on a GM = 1.7 years in young females (n = 20) and GM = 1.2 years in males of all ages and older females (n = 66). However, a combined median value from Zhang et al. (2013) of 1.8 years also adds value to this range of central tendency. While the Collaboration found this study to be the least encumbered with unmonitored PFOA exposures and branched isomers, more studies of similar design would be valuable. Also valuable would be clarification around background exposures in other existing studies in case adjustments to half-life estimates are attempted.

Introduction

Estimated safe doses for PFOA vary by several hundred-fold among government organizations (Dourson et al., 2019; Mikkonen et al., 2020; Drinking Water Inspectorate, 2021). This wide range is due to differences in both the judgment of PFOA's critical effect and its elimination in experimental animal versus humans or among humans. In particular, elimination half-life estimates of PFOA in humans have been made in numerous observational studies and are found to vary from a low of 1.2 years to a high of 14.9 years (Dourson and Gadagbui, 2021). This elimination, when compared with daily excretion in experimental animals or the amount of PFOA in the animal's body over time [measured as the Area-Under-the-Curve (AUC)], leads to adjustments to the experimental animal No Observed Adverse Effect Level (NOAEL) or Benchmark Dose (BMD) point of departure to determine difference safe doses.

Most authors of human observational studies in which half-life estimates are rendered have stated that unmonitored PFOA exposures might exist in their studies, and that the corresponding estimates of half-life may therefore be inflated. Russell et al. (2015) and Bartell (2012) give theoretical underpinnings for this inflation and show how accounting properly for unmonitored exposures results in smaller half-life estimates. For example, Bartell (2012) estimated that unmonitored background exposures that contribute 20% of the total exposure will greatly reduce estimated half-life if more than two half-lives pass between the sampling time points. Bartell (2012) provided a figure that can be used to adjust half-life estimates based on other estimated background exposures and time between sampling points. A clinical study by Elcombe et al. (2013)[1] that tested PFOA as a chemotherapeutic agent has also been used to determine a PFOA half-life of 0.5 year in a small subset (n=3) of the whole exposed patient cohort (n=42) (Dourson and Gadagbui, 2021). While helpful because of the clinical nature of this study, this range adds to the disparity in estimated half-life values.

This disparity was recognized by the Steering Committee of the Alliance for Risk Assessment (*ARA*)[2] as a problem that might be resolvable via collaboration of interested scientists, similar to other, seemingly intractable, problems that cross multiple jurisdictions. An example of the latter includes the development of a workshop series to showcase research case studies in response to the 2009 National Academy of Sciences publication entitled Science and Decisions (see: https://tera.org/Alliance%20for%20Risk/ARA_Dose-Response.htm). *ARA* endorsed an international collaboration to meet and develop this brief communication which explores reasons for the large range in values of the human PFOA half-life, and ways to reconcile these differences, if possible.

[1] Elcombe et al. (2013) administered PFOA to 42 adult humans, both male and female, in a phase 1, range-finding, clinical trial for cancer chemotherapy. Doses were given once weekly as an oral tablet from 50 to 1200 mg for up to 6 weeks. Blood concentrations of PFOA over 6 weeks were closely monitored. After the 6-week period, nine patients continued the therapy. Adequate kidney and liver function and physical integrity of the gastrointestinal tract were important criteria for acceptance of patients into the trial. No overt toxicity was observed. The daily mg/kg-day doses were estimated by Dourson et al. (2019) as 0.1 to 2.3 mg/kg-day and approximated exposures in the experimental animal studies that caused toxicity.

[2] See: https://tera.org/Alliance%20for%20Risk/ARA_Steering_Committee.htm

Methods

The Steering Committee of the Alliance for Risk Assessment (*ARA*) solicited nominations from interested scientists and managers in the early spring of 2021 to form an advisory committee that would shepherd the project entitled "The Conundrum of the PFOA Half-life" through to a potential resolution.[3] After reviewing nominations, the following scientists were selected by the Steering Committee as members of the Advisory Committee:

- Harvey Clewell, Ramboll
- Tony Cox, Cox Associates
- Michael Dourson, Toxicology Excellence for Risk Assessment
- Shannon Ethridge, International Association of Plumbing and Mechanical Officials
- Ali Hamade, Oregon Health Authority
- Ravi Naidu, CRC CARE
- Nitin Verma, Chitkara University

The Advisory Committee next assembled a list of relevant publications on PFOA human half-life and opened a call for interested scientists in the late spring of 2021 to participate in an international collaboration to investigate this issue. After nominations from scientists interested in this collaboration were reviewed, the following scientists were selected and arranged into three independent groups, assuring that various sectors were represented in each group:

- Jerry Campbell, Ramboll
- Harvey Clewell, Ramboll
- Norman Forsberg, Arcadis U.S., Inc.
- Bernard Gadagbui, Toxicology Excellence for Risk Assessment
- Ali Hamade, Oregon Health Authority
- Ravi Naidu, CRC CARE
- Nathan Pechacek, Ecolab
- Tiago Severo Peixe, State University of Londrina, Parana, Brazil
- Robyn Prueitt, Gradient
- Andrew Prussia, Agency for Toxic Substances and Disease Registry
- Mahesh Rachamalla, University of Saskatchewan
- Lorenz Rhomberg, Gradient
- James Smith, Navy and Marine Corps Public Health Center
- Nitin Verma, Chitkara University

The charge to the Small Groups was determined by the Advisory Committee to be as follows:

- Select studies from the list of studies found at https://tera.org/Alliance%20for%20Risk/Projects/pfoahumanhalflife.html for further review

[3] See: https://tera.org/Alliance%20for%20Risk/Projects/pfoahumanhalflife.html

and explain why certain studies were excluded. The small groups were free to add studies as appropriate and explain why they were added.

- Develop a Small Group consensus on PFOA half-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. Small Groups were free to add critical issues as appropriate.
- No inter-group discussions are allowed as to avoid premature closure.
- The deadline was August 31st, 2021 for this first round of review.
- First intergroup international discussion was held on September 7/8, 2021.
- A second round of reviews occurred through an interactive web-based discussion during October and early November of 2021.
- A position was developed and shared with the international community in December 2021 and is shown in the following results.

Results

Table 1 summarizes studies and or analyses of studies that were considered by the Small Groups to be of some use. Initial findings for two of three Small Groups did not consider any one study as sufficient for determining the PFOA half-life but selected a subset of better studies. The third Small Group considered Xu et al. (2020) to be more credible due to the reduced likelihood of unmonitored PFOA exposures. Initial findings were summarized in brief reports that are available at https://tera.org/Alliance%20for%20Risk/Projects/pfoahumanhalflife.html.

During the course of the Collaboration most studies were judged to include unmonitored PFOA exposures, with the exception perhaps of the clinical study by Elcombe et al. (2013), where doses were sufficiently high so as to preclude conflation with unmonitored exposures. For studies with lower serum PFOA levels, up to ~25% bias in the half-life was considered possible due to these unmonitored PFOA exposures based on the work of DeSilva et al. (2020) who stated that drinking water "has been estimated to contribute *up to* 75% of exposures near contaminated sites." The Collaboration thought an argument could be made for a 20% reduction in the average half-life in studies that otherwise mentioned or alluded to unmonitored PFOA exposures, but also recognized that this adjustment would be study-dependent. Further to this point, Russell et al. (2015) and Bartell (2012) found that estimates of PFOA half-lives that include unmonitored PFOA exposures are inflated, although the magnitude is difficult to determine without additional evaluation of individual studies. For example, Bartell (2012) found the three studies they evaluated to include a bias ranging from 2.7% to 26% when compared with background exposures, although not all exposures may have been monitored. However, the study by Zhang et al. (2013) was found by the Collaboration to be insignificantly encumbered by unmonitored PFOA exposures, since its estimated half-lives were based on estimates of renal clearance from men and women of the general Chinese population (aged 20 years to 88 years) with no known point source of exposure to PFOA.

An issue also arose on whether reported PFOA half-lives were specific to the straight chain isomer of PFOA, represented measurement and summation of mixtures of several PFOA

isomers, or accounted for exposure to PFOA precursors. Benskin et al. (2009) and De Silva et al. (2009) reported faster elimination rates and shorter half-lives for branched isomers of PFOA compared to linear PFOA in rats gavaged with an electrochemically fluorinated PFOA standard. Beesoon et al. (2015) provided a mechanistic explanation for the faster elimination rate of branched isomers of PFOA that was related to dissociation constants (K_d) of linear and branched PFOA isomers with human serum albumin. Beesoon et al. (2015) showed that K_ds were three to four-fold higher for individual branched isomers compared to linear PFOA and that branched isomers were less protein bound than linear PFOA in experiments that evaluated a technical mixture of PFOA. However, the analytical methods employed to analyze PFOA in blood have not used consistent quantification procedures and few studies reporting serum elimination rates in human populations have distinguished between PFOA isomers in their analytical methods (Bartell et al. 2010, Gomis et al. 2016, Li et al. 2018). An exception to this is the study by Zhang et al. (2013) that analyzed and determined elimination rates for branched and linear PFOA isomers. Since branched PFOA isomers were seen to be eliminated more quickly (see Zhang et al., 2013, Table 3), this would lower the overall PFOA half-life in situations where PFOA included a substantial percentage of branched isomers.[4] Exposure to PFOA precursors might also artificially inflate half-life estimates for PFOA. The Collaboration considered this to be a critical issue for human health risk assessment, where risk-based criteria and/or standards for PFOA are often calculated using a single human PFOA half-life estimate (for which the profile of PFOA isomers is not commonly reported), but applied to samples quantified using analytical methods that sum isomers to report a single PFOA value[5].

The Collaboration discovered after a more careful reading of studies in Table 1 that this mixture issue was poorly addressed in almost all studies, with the exception of Zhang et al. (2013). In particular, Zhang et al. (2013) monitored branched isomers of PFOA and estimated their half-lives. This study showed little variation between the estimated half-life of the linear isomer and that of the sum of all PFOA isomers including the linear isomer due principally to the small proportion of branched isomers in the mixture. Specifically, a geometric mean PFOA half-life of 1.3 years was evident for both along with a median PFOA half-life of approximately 1.8 years for both. However, the geometric mean and median half-lives of the 4*m*- and 5*m*-PFOA branched

[4] From EPA Method 533: "A quantitative standard for PFOA is currently available only for the linear isomer; however, a technical grade standard (Sect. 3.22) is available for PFOA that contains the linear and branched isomers (Wellington Labs, Cat. No. T-PFOA, or equivalent). This product or a similar technical-grade PFOA standard must be used to identify the retention times of the branched and linear PFOA isomers. However, the linear-only PFOA standard must be used for quantitation until a quantitative PFOA standard containing the branched and linear isomers becomes commercially available."

[5] From the U.S. Department of Defense and Department of Energy's (2019) Quality Systems Manual (QSM) for Environmental Laboratories: "Standards containing both branched and linear isomers must be used when commercially available. PFAS method analytes may consist of both branched and linear isomers, but quantitative standards that contain the linear and branched isomers do not exist for all method analytes. For PFAS that do not have a quantitative branched and linear standard, identify the branched isomers by analyzing a qualitative standard that includes both linear and branched isomers and determine retention times, transitions and transition ion ratios. **Quantitate samples by integrating the total response (i.e., accounting for peaks that are identified as linear and branched isomers) and relying on the initial calibration that uses the linear isomer quantitative standard** [emphasis added]."

isomers were commonly 40 to 70% lower than the linear isomer (Zhang et al. 2013). Uncertainties due to lack of isomer characterization were present in the estimated PFOA half-lives in many of the other studies. Similarly designed studies as Zhang et al. (2013) could shed more light on the range of half-lives for PFOA isomers, both straight and branched. The Collaboration did not uncover any additional hypotheses beyond those reported by Beesoon et al. (2015) that would account for the quicker half-lives of branched isomers when compared with the straight chain. However, it was recognized that this information would be of great use in human health risk assessment given the reports of differential biological and environmental transport and fate properties between linear and branched PFOA (Benskin et al. 2009; De Silva et al. 2009; Schulz et al. 2020).

Studies from Table 1 considered by the Collaboration to have the least amount of uncertainty with unmonitored PFOA exposures and isomer accountability are shown in Table 2. The first study by Elcombe et al. (2013) was used by Dourson and Gadagbui (2021) to estimate a half-life of 0.5 years based on 3 individuals who were monitored extensively over 6 weeks in this clinical trial of PFOA given as a chemotherapeutic drug. This study had the advantage of a dose high enough to avoid problems with unmonitored PFOA exposures and avoided branched-chain PFOA isomers since the administered PFOA was straight chain. The half-life in this study was also determined from PFOA serum concentrations that were at or lower than the estimated human renal resorption limit of Km of 4 µg/ml. Saturation of resorption is only likely to occur at plasma concentrations above 10 µMoles/L, based on an estimated renal transporter Km of 4 µg/ml from an analysis of Elcombe et al. (2013) by Campbell et al. (2016). The Elcombe et al. (2013) study had the disadvantages that only a very small number of individuals (n=3) had a dose that was not expected to saturate renal resorption. An estimate of PFOA half-life including all 42 patients might shed more light from this unique study. A potential additional problem with using this study for estimating a PFOA half-life is its relatively short duration of 6 weeks.[6]

The second study by Xu et al. (2020) showed a half-life geometric mean of ~1.5 years based on a human observational study of 17 individuals monitored frequently over 5 months from a likely single source of PFOA exposure. This study had the advantage of minimal additional sources of PFOA exposure, some measurement of PFOA branch isomers, and an estimate of background exposures from which a lower, and more appropriate half-life could be determined. This study had the disadvantage of a small number of individuals and a rather short follow up time, but certainly both were better than that found in Elcombe et al. (2013). Also, although this study measured branched PFOA isomers, they were not clearly distinguished in the estimated PFOA half-life.

The third study by Zhang et al. (2013) determined the PFOA half-life from estimates of renal clearance from 86 men and women of the general Chinese population (aged 20 to 88 years) with no known point source of exposure to PFOA. Specifically, the half-life geometric mean was estimated at 1.7 years in young females (n = 20) and 1.2 years in males of all ages and older

[6] Some might posit that the individuals in this study were sick so that the elimination measured in these individuals may not relate to the general population, but clinical measures in study individuals demonstrated normal liver and kidney function (personal communication between Geary Olsen and James Smith, 2021).

females (n = 66). The combined geometric mean was 1.3 years. Median values of half-life were 2.0 years in young females and 1.8 years in males of all ages and older females, or 1.8 years when combined. Arithmetic mean values were not reliable since the clearance values formed a skewed right distribution. This study had the advantage of a half-life unencumbered by the problem of unmonitored PFOA exposures, since clearance from the blood integrates all sources of exposure. Also, PFOA isomers were individually quantified and separate estimates of isomer half-lives were given. This study had the disadvantage that not all sources of elimination from the body were accounted for, leading the authors to suggest that the half-lives determined were likely upper limits.

After extensive email discussions,[7] the Collaboration then considered three options. Each scientist was asked to consider choosing a preferred option along with reasons for the choice. Scientists 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:

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

Scientists' choices were sent to two members of the Advisory Committee in a confidential manner and responses were collated as shown in Table 3. Option 1 was preferred by the majority of scientists although several of those voting for option 1 could also live with option 2. A smaller number of scientists preferred option 2, with several of them also able to live with option 1. Option 3 was preferred by two scientists, with one able to live with this choice, judging that the choice of only one study (as in option 1), or even of a few studies (as in option 2), was not sufficiently supportable at this point in the investigation.

During the course of this Collaboration three additional items were discussed. First, the question of the appropriate averaging value for the PFOA half-life arose. Several studies give the half-life as the geometric mean, the arithmetic mean, or the median value. Zhang et al. (2013) showed that arithmetic mean half-lives based on arithmetic mean clearances did not match arithmetic mean half-lives based on individual clearances. In contrast, 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 individual clearances and corresponding half-lives were found to be skewed right (Zhang et al., 2013; *ARA*, 2021). Based on this finding, the Collaboration considered the geometric mean to be superior to the arithmetic mean, and that the medians can add value to this range of central tendency.

[7] A summary of these email discussions can be found at: https://tera.org/Alliance%20for%20Risk/Projects/PFOA%20Groups/ARA_2021_Questions_%20Discussion_on_SG Summaries_Fall%20_of_2021.pdf

Second, the estimation of the volume of distribution was discussed. In some studies, the volume of distribution was based on measured PFOA exposures in humans, but such estimations would be inappropriately low if unmonitored sources of exposure are occurring. Other studies or analyses estimated the volume of distribution from a small population of humans in a clinical trial where PFOA was used as a cancer chemotherapeutic drug and in subjects in whom the kinetics of PFOA may or may not represent that expected in the general population (Elcombe et al., 2013). Other investigators selected a volume of distribution from either a small group of monkeys (n = 3) by Butenhoff et al. (2004) or from other experimental animals. Selecting one value for the volume of distribution from this assortment of values is challenging given these different approaches. However, a value of around 0.18 Liters/kg body weight was considered by the Collaboration to approximate the likely value in humans.

Finally, some studies showed indications of the potential range for inter-individual variability in PFOA clearance. In particular, instances of blood loss and replacement appeared to lead to faster elimination, as the lost blood removes part of the PFOA body burden and is replaced by blood without added burden. This includes menstrual blood loss and episodes of blood donation. Pregnancy and breastfeeding may also diminish body burden, although that burden is transferred to the fetus and infant, respectively. Observations of somewhat faster elimination among reproductive-age women in some studies appeared to be explicable by menstrual and childbirth loss. The possible role of nutritional differences among people, perhaps through an effect on fatty acid uptake, was also suggested in some studies but has not been clearly characterized. The Collaboration encourages additional research in this area.

Discussion

This Collaboration was an attempt to bridge the rather large differences in estimated PFOA half-lives, ranging from 1.2 to 14.9 years, shown by a number of investigators (e.g., Dourson and Gadagbui, 2021). The *ARA* Steering Committee invited a wide participation in the deliberations and discussions by an active list of over 100 international colleagues from government, industry, academia and consulting, whom received periodic summary emails, and several social media postings to over 4000 individuals. The effort lasted the better part of 6 months and included scientists from various sectors and countries.

The Collaboration's majority opinion is that the study with the least encumbrances to determine the PFOA half-life is that of Zhang et al. (2013) with a geometric mean value of 1.3 years as in Option 1 of Table 3. Eight members preferred this option and two members could live with it. Four participants preferred Option 2 of Table 3 with a half-life range of central tendency of between 0.5 and 1.5 years and six participants could live with that option. It is possible that the lower part of this range of central tendency might increase with the close monitoring of additional individuals. It is also possible that the upper part of this range might decrease if additional information is provided on possible unmonitored exposures or elimination. Regardless, this range of central tendency not exceeding 2 years is a challenge to the ongoing convention that the half-life is in multiple years. Finally, two scientists opined for Option 3 of

Table 3 and one could live with this choice, suggesting that while the fewer studies of Options 1 and 2 minimized uncertainties from background exposures and branched isomers, these studies also had limitations in terms of cohort size and or representation of various populations; thus, other studies as in Option 3 are useful for highlighting the inter-individual variability in the half-life estimate among members of the different cohorts.

Perhaps most important, in the course of this Collaboration, two uncertainties in the conventional thinking that the PFOA half-life is in multiple years became more clear, specifically:

- The uncertainty in the amount of unmonitored PFOA exposures, including precursors, expressed by nearly all authors in most studies, and
- The uncertainty in PFOA half-life estimates due to the unknown proportion of branched-chain isomers versus straight chain in the measured PFOA exposures.

The first uncertainty will inflate PFOA half-life estimates, the extent of which could be determined by estimating the percent of unmonitored PFOA exposures when compared with total PFOA exposure and using the time between measurements to determine a downward adjustment to the PFOA half-life as per Bartell (2012). That this first uncertainty is likely occurring is evident in recent deliberations by the U.S. Environmental Protection Agency (2021) where the contribution of PFOA from water sources in communities that do not have considerable water contamination could be around 10% overall.[8]

The second uncertainty deflates PFOA half-live estimates due to the fact that branched isomers of PFOA are eliminated more quickly than PFOA's straight-chain, the extent of which would be determined by estimating the percent of branched PFOA isomers when compared with total PFOA (see Zhang et al., 2013 for an example of this determination). Although these two uncertainties work in opposite directions, the extent of these changes together is not knowable in most of these studies without additional investigation of the PFOA mixture of interest.

Among the studies reviewed by the Collaboration, the study that is least encumbered by uncertainties from background exposures and PFOA isomers appears to be that of Zhang et al. (2013). The investigators estimated renal clearance values of several PFAS, including PFOA and several of its branched isomers, by using paired urine and serum measurements. The use of paired measurements in this way does not depend on determining sources of PFOA in the environment, since the blood serum concentration integrates all exposures. Thus, uncertainty in potential unmonitored PFOA sources is minimal in this study. However, clearance values in this study depended on determining total PFOA excreted, which the authors acknowledged was not

[8] Specifically, EPA (2021) cites Hu et al. (2019), East et al. (2021), and Gebbink et al. (2015) providing evidence that drinking water only accounts for about 10 % of the total PFOA exposures at both low- and high-exposure scenarios, with house dust and diet being the primary sources. For example, the results below are from Gebbink et al. (2015):

- Low-exposure scenario: diet (~50%) > air (~25%) > dust (~15%) **> water (~10%)**;
- Intermediate-exposure scenario: diet (~45%) > dust (~35%) > **water (~10%)** ≈ air (~10%);
- High-exposure scenario: dust (~65%) > diet (~20%) > **water (10%)** > air (~5%).

done, which led them to suggest that their stated half-life values were upper limits.[9] Research should continue to determine the proportion of PFOA that is excreted in human urine versus other routes of human elimination, such as feces, hair, sweat, bile, menstruation, and breast-feeding. This might enable a change to the half-life proposed by Zhang et al. (2013).

The two other studies in Table 2 also avoid these two uncertainties to some extent, although both of thems also have some uncertainties. The clinical study by Elcombe et al. (2013) yields a lower half-life of ~0.5 years as determined by Dourson and Gadagbui (2021) based on three, low, single dose patients. However, a similar analysis of 3 healthy individuals from the study of Nilsson et al. (2010) shows a similar half-life, ~0.5 years, after exposure ceased and the background PFOA exposure is subtracted, as shown in Appendix Figure 1.

The second study in Table 2, Xu et al. (2020), yields a geometric mean half-life of 1.5 years based on 17 individuals with longer follow up time than the Elcombe et al. (2013) study, and likely single dominant source of exposure similar to this latter study. Xu et al. (2020) also subtract background exposures, which ends up lowering their unadjusted half-life significantly, from 1.77 to 1.48 years.

A good number of studies reviewed by the Collaboration (Table 1) are well-conducted and adjust for background exposures and other sources of bias. They might extend the range of central tendency of half-lives identified in the minimally encumbered studies. However, there remain data that are not presented or are unknown relating to background exposures and branched PFOA isomers. 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 potentially unmonitored exposures and branched-chain isomers. This area of research may also benefit from additional clearance studies, like Zhang et al. (2013), for confirmation.

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[9] Vanden Heuvel et al. (1991) reported differences in fecal excretion between female and male rats and that the extent to which humans eliminate PFOA in urine versus feces is not known. If there is significant fecal excretion of PFOA in the human, the intrinsic PFOA half-life would actually be shorter than that estimated on the basis of renal clearance, as in Zhang et al. (2013).

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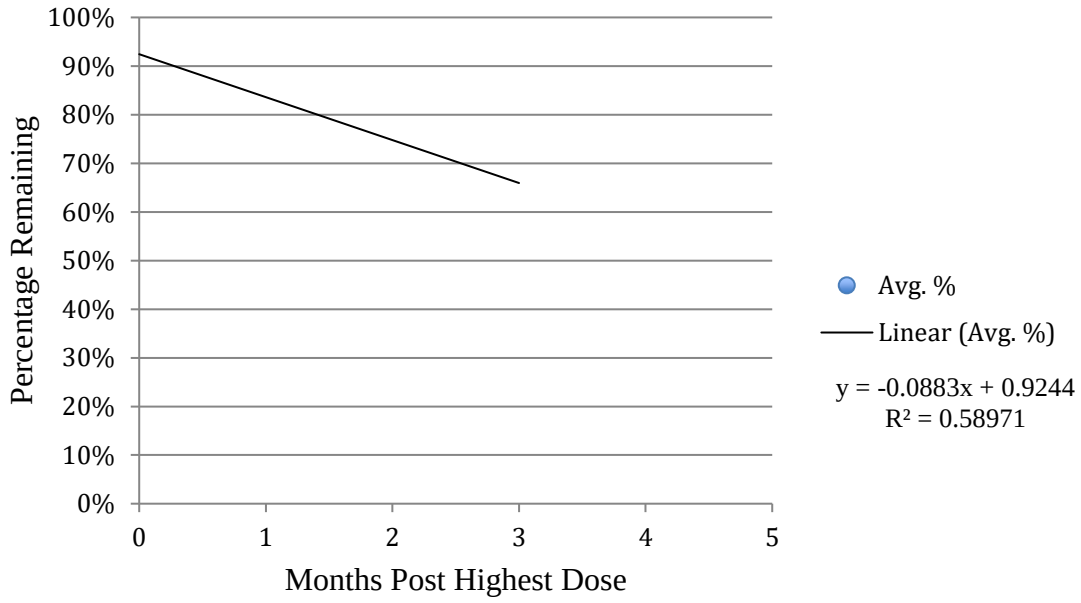
Appendix

Appendix Figure 1. Average remaining PFOA over time; background subtracted out and last two data points of technician 8 removed (data on next page).



Without background subtracted out			
half-life =	33	months	unforced data; r2 = 0.27
half-life =	16	months	when intercept is forced to 100%; r2 = 0.16
With background subtracted out			
half-life	**5.7**	**months**	**, unforced data; r2 = 0.59**
half-life =	4.2	months	when intercept is forced to 100%; r2 = 0.47

Data for Appendix Figure 1

Analysis of Nilsson et al., 2010

Data from supplemental Table S2; note Figure 2d of the paper has information from Techician 8 misplaced.

Note: Bk = background; De = decrease from high month

	Technician 1				Technician 2			
Condition	Month	PFOA (ng/ml)	%De	% De-Bk	Month	PFOA (ng/ml)	% De.	% De-Bk
Pre-exposure	Sep	4.80			Sep	8.54		
Exposure	Dec	6.28			Dec	10.1		
Exposure	Jan	12.4			Jan	14.2		
Exposure	Feb	14.3			Feb	15.0		
Exposure	Mar	16.8			Mar	19.9		
Post-exposure	Apr	-			Apr	21.9		
Post-exposure	May	20.1	<<< high month		May	23.1	<<< high month	
Post-exposure	Jun	16.8	16%	22%	Jun	19.6	15%	24%
Post-exposure	Jul	-			Jul	21.0	9%	14%
Post-exposure	Aug	-			Aug	19.3	16%	26%

	Technician 8				%De from Pre with Bck.	%De from Pre without Bck.	
	Month	PFOA (ng/ml)	%De	% De-Bk	Months after high	Avg. %	Avg. %
Pre-exposure	Sep	474					
Exposure	Dec	528			0	100%	100%
Exposure	Jan	-			1	84%	77%
Exposure	Feb	535	<<< high month		2	92%	65%
Exposure	Mar	-			3	90%	75%
Post-exposure	Apr	501	6%	56%	4	88%	-7% *
Post-exposure	May	520	3%	25%	5	87%	-13% *
Post-exposure	Jun	471	12%	107%			
Post-exposure	Jul	468	13%	113%	* 2nd set of values at 4 & 5 months not plotted		
Post-exposure	Aug	-					

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	No, during off duty assumed background exposures only	No, isomers were combined in analysis
Elcombe et al. (2013)	AM 0.5	• Based on a new analysis of data from Elcombe et al. (2013) by Dourson and Gadagbui (2021) for 3 cancer patients • Patients received a single dose of PFOA with 6 weeks of follow up with serum levels likely to be below level of saturation of renal resorption [b]	Not needed based on high dose given	Not applicable, dosing was with linear isomer

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 = 1.77 (+background) GM = 1.48 (-background)	• Alternate exposures were unlikely. • Small population (n = 17) and short follow up (5 months) • Exposures not greatly above background.	No, assumed only background exposures from the referent population	Not clear from description
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, assumed only background exposures from the referent population	No, all isomers were combined
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, modeling conducted on biomonitoring data	No distinction was made among isomers

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, during off duty assumed background exposures only	No mention was made of isomers
Zhang et al. (2013) General population: healthy volunteers in China N=86	AM = 2.3 GM = 1.7 Median = 2.0 Range (0.2-5.3) (young females, n = 20) AM = 2.8 GM = 1.2 Median = 1.8 Range (0.1-16) (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, separate analysis done on straight and branched chains

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, assumed that "ongoing PFOA exposures only contribute negligible amounts"	Not mentioned
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.	Mentioned as possible but not monitored	Analysis done but separate half-lives not estimated

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

b) Saturation of resorption is likely to occur at plasma concentrations above 10 µMoles/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)

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
Elcombe et al. (2013)	AM 0.5	• Based on a new analysis of data from Elcombe et al. (2013) by Dourson and Gadagbui (2021) for 3 cancer patients • Patients received a single dose of PFOA with a 6 week follow up with serum levels likely to be below level of saturation of renal resorption	• 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) Airport employees in Sweden exposed to PFAS through airport's waterworks	GM = 1.5	• 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.

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 Median = 2.0 (young females, n = 20) GM = 1.2 Median = 1.8 (all males and older females, n = 66) **Central tendency** GM = 1.3 Median = 1.8	• 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

Table 3. Results from Consensus Polling of the International Group

Option	Preferred	Can live with	Cannot live with	Comments
1 (single study)	8	2	1	Zhang et al., 2013
2 (small group of studies)	4*	6	1	As in Table 2. *One vote with a special emphasis on Zhang et al., 2013
3 (larger group of studies)	2	1	2	As in Table 1.