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

Questions on Small Group Summaries

Below is a selection of questions to get us all started on our attempt to derive a consensus position on the human half-life of PFOA, whether as a single value or as a range. We should all feel free to comment on these questions, add additional questions, and in general discuss what we see as difficulties in the resolution of the PFOA half-life.

1. Question: Several studies have subtracted out the background exposure from reference populations in an attempt to estimate a more accurate half-life in the contaminated population. However, not all of these studies have recognized the potential for ongoing exposure to the contaminated population. For example, Olsen et al. (2007) studied retired workers whose exposure after retirement was assumed to be that of the reference population, but whose household exposures were otherwise not monitored. It is well known that workers bring home contamination and that this often permeates household dust.

   How should this potential unmonitored contamination be addressed from such studies?

   Comment: This is fully explained in Russell et al. (2015), and he actually provides a background-corrected half-life for Olsen et al. (2007) as one of his examples. Even when data is lacking on background/continuing exposures, the intrinsic half-life can still be calculated from the study data by using this approach.

   Comment: Apologies for not making the description in the initial paragraph more clear. Some studies, and perhaps all studies of contaminated populations, may have had PFOA exposures that are in addition to the reference population. For example, in the case of Olsen et al. (2007), the worker population may have had PFOA exposure from household dust brought home from their working environment, which would not be expected in the reference population. Subtracting out the reference population background in this instance, as Russell et al. (2015) did, would miss this potential additional exposure and the resulting half-life from Olsen et al. (2007) would be inflated. That this continuing exposure in Olsen et al. (2007) is likely occurring is implied by Emmett et al. (2006) in question 2 below and from the fact that the estimated half-life from Olsen et al. (2007) is greater by about 50% of the value from contaminated communities such as Thompson et al. (2010) where contaminated household dust from worker exposure is less likely.

   Comment: Sorry, I was apparently not clear enough as well. My point was that it is possible to estimate both the intrinsic half-life and the background concentration at the same time using the equation form Russell et al. 2015):

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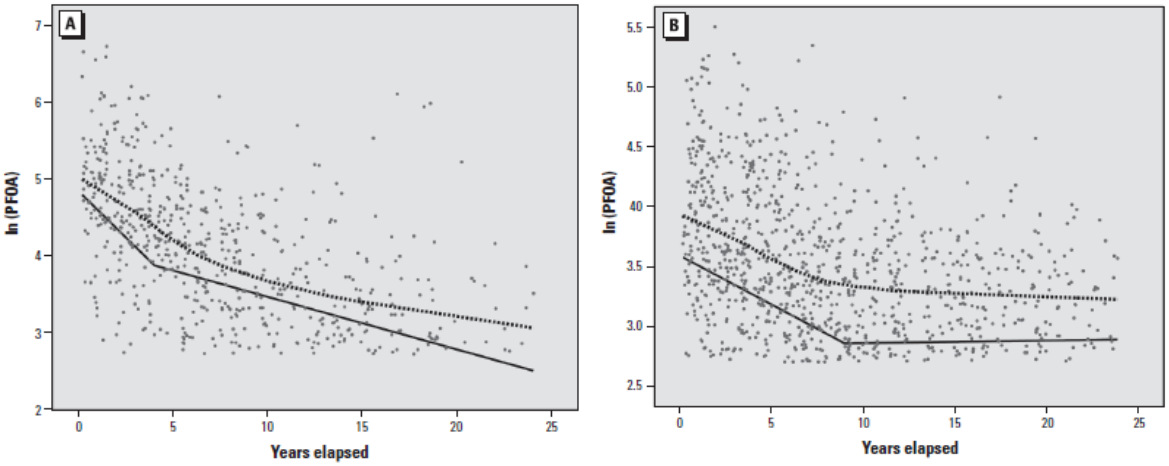
$$C(t) = C_{ss1} + (C_{ss0} - C_{ss1})e^{-k_e t}$$

Jerry Campbell has applied this approach to re-estimate the t1/2 for the data in Seals et al. 2011. Seals et al. 2011 used a two-segment linear spline approach to estimated PFOA half-lives for former Little Hocking residents (A) of 2.9 years (for specimens collected < 4 years since leaving the water district) and 10.1 years (for specimens collected > 4 years since leaving the water district). They also estimated a half-life for former Lubeck residents (B) of 8.5 years (for specimens collected <9 years since leaving the water district).



Jerry re-estimated both the intrinsic clearance (Ke) and the residual (continuing) exposure (R), using the following equation:

C(t) = (C0*e-kt) + (R/(Ke*Vd)) * (1-e-kt)

He was able to fit both the Little Hocking and Lubeck datasets with a single value of t1/2 = 3.56 yrs.

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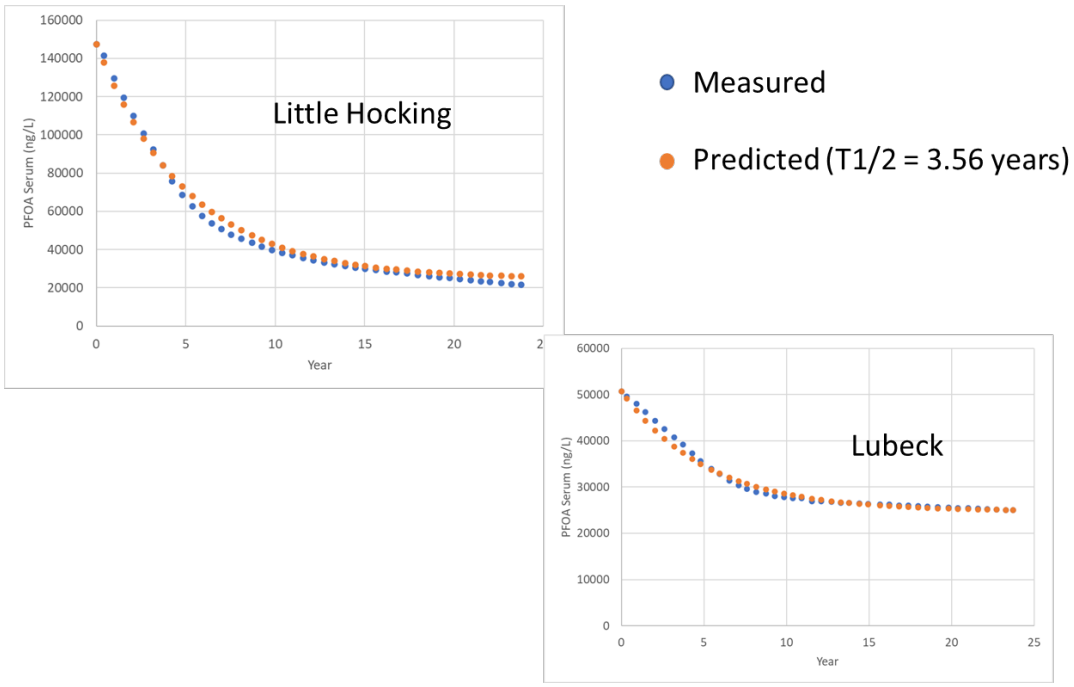

Comment: Perhaps I am misreading the Russell et al. (2015 study, but their equation appears to assume that after the principle exposure in the contaminated population is stopped, then all other exposure in the contaminated population stops except for background exposure, correct? The resulting upward bias in half-life estimate is then dependent on how far above the serum concentrations of the exposed population are in relation to the reference population. It is an important first step to use the Russell et al. (2015) equation in this way to subtract out the background exposure in the reference population of these various human observational studies. However, unknown or unmonitored exposures in the contaminated population will result in half-life estimates that are inflated, the extent to which can be approximated in Bartell's (2012) Figure 1.

The use of the Seal et al. (2011) population appears to be an example of this problem where drinking bottled water or growing ones own vegetables is associated with higher PFOA serum concentrations (their Table 1, page 121). This suggests a source of PFOA that is not from contaminated water. Seals et al. (2011) also state:

> "Differences in serum clearance rate between low- and high-exposure water districts suggest a possible concentration-dependent or time-dependent clearance process or inadequate adjustment for background exposures." (page 119)

And elsewhere:

> "The second major limitation [of their paper] is the implied assumption that exposure was uniform within a water district, both between individuals and over time, which we know to be false." (page 124)

Discussion at the previous meeting of our small groups suggested "Up to 26% bias in the half life was possible in studies with low serum PFOA levels due to unmeasured PFOA exposures, and an argument could be made for a 20% reduction in the average half life because of this problem." If we were not able to ascertain PFOA exposures in other media from some of these studies, would a generic reduction in the stated half-life be a reasonable approach?

Comment: The potential effect of unmeasured PFOA exposures would be too study-specific to support a generic reduction in the estimated half-life. The analysis of the Seals study by Jerry Campbell (described above) should be applied to any study where unmeasured PFOA exposures are a concern. If the data are not available to perform this analysis, the study may not be suitable for estimating the PFOA half-life.

2. Question: Emmett et al. (2006) shows significant exposures from the consumption of homegrown vegetables and local meat that affects serum PFOA concentration (**see attached Figure 1**). They state:

> "Our results thus lead us to question whether the serum PFOA half-life in the general community is as long as that published for the small retired worker group."

Bartell et al. (2010) also show that consumption of homegrown vegetables affects PFOA half-life, from an estimated value of 2.3 years from water only consumption to a lower value 2.1 years when considering both water and homegrown vegetable consumption.

How can such information from these two studies, and other studies whose populations likely include folks that eat homegrown produce, be worked into our ongoing evaluation?

Comment: As long as the analysis is performed as recommended by Russell et al. (2015), the level of continuing exposure in food will not affect the intrinsic half-life estimate. However, studies where the blood concentrations in the drinking-water-exposed population are not far above the blood concentrations in a no-drinking-water-exposed population should be viewed with skepticism because of uncertainty associated with such a comparison. The most informative studies are those where the exposure associated with the initial (steady-state) blood concentration in an "exposed" population is much greater than the range of expected "background" exposures or terminal steady-state exposures. A statistical evaluation of the

confidence interval for the intrinsic half-life estimated with the equation from Russell et al. (2015) should help to evaluate study uncertainty.

Comment: The Russell et al. (2015) analysis will work as long as the level of continuing exposure in foods is the same between the exposed and reference populations. However, if the exposed community uses contaminated water for gardens, for example, their intake of PFOA from homegrown foods will be in excess of the reference community after background is subtracted, and then the resulting half-lives estimated from the contaminated population will be inflated. This is what Bartell et al. (2010) state and what data from Emmett et al. (2006) also show to be occurring.

An ideal data set would include a population with a well-characterized and known exposure and a reference population that can be well matched. A good example of this is Xu et al. (2020) where contamination is limited to drinking water at work, thus avoiding the transfer of PFOA to the home by dust exposure, and the reference and contaminated populations are closely matched. The problems with using this study are its small population and short follow up time. In contrast, some of the other contaminated populations have higher exposures and larger populations. However, the general problems with these studies is they may have had PFOA exposures that were different from the reference population and not monitored, and if so, estimates of PFOA half lives are inflated even after background is subtracted.

Comment: If it is considered likely that the background exposures in the exposed population are different from those in a reference population, then that reference population should not be used. If it is not possible to estimate the background exposures in the exposed population and it is likely that the background exposure is not far below the contamination level, then the study is simply not useful.

Comment: This comment is very reasonable. Many of the existing human observational studies are likely not useful, since PFOA exposures in the contaminated population are likely occurring, such as through household dust or home-grown vegetables, that are not otherwise occurring in the reference population. That is not to say that these observational studies were poorly done, especially since the extent of PFOA contamination of various environmental media were not well understood until more recently. But using such studies without the caveat mentioned in the comment directly above, will likely lead to erroneous results. This is evident in the diversity of PFOA half-lives estimated as summarized in Table 2 of Dourson and Gadagbui (2021, page 6).

3. Question: Figure 1 in Bartell (2012, **see attached Figure 2**) shows that unaccounted PFOA exposure of only about 8 % is enough to overestimate the PFOA half-life by twice its

actually value, if the time between serum measurements is about 5 half-lives, or otherwise near steady state. Other combinations of unaccounted exposures and time measurements are also shown in Figure 2 that is taken from Bartell (2012).

How might information from Figure 2 be used to adjust PFOA half-life estimates among the various studies that we reviewed that otherwise did not account for other possible exposures?

Comment: As long as the analysis is performed as recommended by Russell et al. (2015), the level of continuing exposure from other sources will not affect the intrinsic half-life estimate.

Comment: Again, the Russell et al. (2015) analysis will work as long as the level of continuing exposure is the same between the exposed and reference populations. In the case of Olsen et al. (2007), for example, no attempt was made to monitor exposures to these workers from homegrown gardens, household dust, or other sources of exposure that may have been higher than the general population to which the background exposure is being compared. Thus, subtracting out the background exposure using the analysis by Russell et al. (2015), while appropriate, will miss these other, unmonitored exposures, and the resulting PFOA half-life will be inflated.

Comment: As discussed in an earlier comment, Russell et al. (2015) does not only discuss subtracting background, he also provides an equation for estimating residual exposures.

Comment: Perhaps we can talk further about how residual exposures from unmonitored sources are estimated? Bartell (2012) gives us some insight into this problem of unmonitored exposures. How might his Figure 2 (of this text) help us (or not) with understanding potential unmonitored exposure in several of these human observational studies?

Comment: The analysis of the Seals study by Jerry Campbell (described above) should be applied to any study where unmeasured PFOA exposures are a concern. If the data are not available to perform this analysis, the study may not be suitable for estimating the PFOA half-life.

4. Question: An ideal study to gauge the PFOA half-life might be a population whose exposure is well known and high enough to be well above known background exposures, thereby avoiding this complication, but with serum PFOA levels that are still below the renal resorption limit of about 12–24 uMoles (5 to 10 ug/ml) (*ARA*, 2021) and thereby including renal resorption into the estimate of PFOA half-live. One such population exists: the low single dose of 50 mg/kg-day of PFOA in three patients from the Elcombe et al. (2013) study.

How might information from this small group of humans be used to inform a PFOA half-life, either as a single value or as a range?

Comment: There are not enough subjects and these cancer patients are not sufficiently representative of the general population.

Comment: Agreed that the number of cancer patients is small, but this appears to be the only group of humans with a well-studied PFOA clearance that is at or lower than the renal resorption limit of 5 to 10 ug/L. This latter point is important since it means that PFOA's elimination in this small group of humans is not likely being affected by the saturation of renal resorption, which is the expectation in all of the other human observational studies. In contrast, the rest of the patients in Elcombe et al. (2013) all had higher doses that resulted in PFOA serum levels well above the limit of renal resorption. Half-lives estimated from these higher dosed groups of humans, while valuable, have this additional uncertainty.

Comment: On the contrary, the Elcombe study is the only one that is affected by the saturation of renal resorption. All of the other human observational studies are in the low-concentration region where renal clearance is linear. The dose-response for renal resorption is a Michaelis-Menten curve, and the nonlinearity begins well below the saturation point.

Comment: Agree that all patients with doses higher than the single, low dose of 50 mg had serum levels that were above the saturation of renal resorption, thus leading to quicker elimination. However, the 3 low, single dose patients exhibited a biphasic elimination. The first phase was above saturation leading to a quick elimination half-life of ~6 hours; the second phase was below this saturation leading to a much longer half-life of ~200 days (see Dourson and Gadagbui, 2021, Figure 4B and 4D, page 9). It is this low, single dose group that is below saturation which might be useful for investigating a terminal half-life.

Comment: I would recommend two or three doses, an order of magnitude apart, with the highest one similar to the low dose in Elcombe, followed up for at least a year.

Comment: Also agree that a clearance study in humans given these low doses of PFOA, similar to the low dose in Elcombe et al. (2013) and lower would be helpful. Depending on the half-life, one may not need to go for a year, however. For example, the low dose cohort in the Elcombe et al. (2013) study (n=3) was below the limit of renal resorption and shows an apparent half-life that is only ~200 days. However, the idea of two lower doses makes sense, since this may uncover a third elimination phase rather than the two that are evident from the Elcombe et al. (2013) data (see Dourson and Gadagbui, 2021, Figure 4D).

5. Question: The volume of distribution (Vd) is an important aspect of estimating half-life as shown in the following equation:

   Half-life (days) = 0.693 x Vd (liters/kg bw) ÷ Clearance (liters/kg bw/day)

   But since kinetic extrapolation of experimental animal data to humans is on the basis of clearance rather than half-life, this equation is rearranged to be:

   Clearance (liters/kg bw/day) = 0.693 x Vd (liters/kg bw) ÷ Half-life (days)

   Here it can be seen that a larger Vd is associated with a larger chemical clearance, which is associated with greater protection if all other parameters remaining the same.

   Current estimates of human Vd for PFOA are based on either experimental animals, generally primates, with values of 0.14 L/kg bw (referenced in Group 3 summary), or on humans with values of 0.17 L/kg bw by Thompson et al. (2010) who only consider water consumption. Higher values of Vd can be based on the human clinical study of Elcombe et al. (2013), either as 0.175 L/kg bw (Group 3 estimate) or as up to 0.22 L/kg bw as shown in the **attached Figure 3**, which is an enhanced version of the Appendix published by Dourson and Gadagbui (2021).

   DeSilva et al. (2020) state that drinking water "has been estimated to contribute *up to* 75% of exposures near contaminated sites." This means that studies of contaminated populations, such as that done by Thompson et al. (2010), might include up 25% of unmonitored PFOA exposures. If true in the case of Thompson et al. (2010), then their estimated Vd would be lower than appropriate. For example, using equation 2c of Thompson et al. (2010, page 391) and assuming that 25% of serum PFOA concentration is due to unmonitored exposures, the resulting Vd value from Thompson et al. (2010) is 0.23 L/kg. This value approximates one estimate from the data of Elcombe et al. (2013) of 0.22 L/kg bw.

   How might all of this information be used to extrapolate data from experimental animals to humans?

   Comment: Only the ratio of the volumes of distribution in the experimental animal and the human effects the risk assessment, and the available data support a ratio of one. Estimates of Vd in the rodent are in the range of 0.1-0.2, while the best estimates for monkey and human are 0.14 (Andersen et al. 2006) and 0.175 (Campbell et al. 2021) [the latter study based on Elcombe et al. (2013)], respectively. Using a higher Vd in human than in the experimental animal would result in a less conservative risk value and would need to be supported by much stronger data than this.

Comment: The estimate of Vd we have obtained from the Elcombe et al. (2013) study varied depending on the presumed time of steady state as shown in Figure 3. A value of 0.22 L/kg bw is found after steady state is presumed to be 2.3 years. Lower values of Vd are found at shorter times at steady state. An excel spreadsheet is included showing the calculations of these various values of Vd.

Additional insights are welcome.

Comment: The Vd of 0.175 obtained by the MCMC analysis of the Elcombe study is consistent with the EPA 2016 value. I don't feel that the Elcombe study data is strong enough by itself to supersede that value. I believe that a new study would be needed to support any such conclusions.

Comment: Would be very interested in how this Vd from the MCMC analysis was estimated, especially since many of the Elcombe et al. (2013) patients were well above the renal resorption limit. Is this something that is ready to be shared?

6. Question: Notes from our September 7/8 meeting raised several additional points that may need further discussion. Specifically, "Rat and mouse clearance is based on much higher doses than that expected in humans. If rats or mice clear PFOA in a biphasic way as humans do, as demonstrated in the Elcombe et al. (2013) study, then a biphasic elimination in rats or mice might be expected. If so, are we comparing toxicokinetic parameters at the same phases between the experimental animal of choice and humans?"
   - For example, the mouse kinetic study study of Lou et al. (2009) was used in part by EPA (2016) in its determination of the PFOA health advisory. Doses in this mouse study were 1 and 10 mg/kg-day, well above the human observational studies.
   - So here is the specific question: Does anyone know of kinetics in mice or rats at low doses, specifically those comparable to humans in the observational studies?

   Comment: In order to grapple with question #6 on our developing Q&A text (see: https://toxicologyexcellenceforrisk.app.box.com/file/872242854662), I recently reviewed the supplemental files of Macon et al. (2011) where concentrations of PFOA were followed up to 80 days post birth. I plotted the PFOA serum values after day 14 in female mice, since this represented the high concentration from breast feeding and females had the more complete data than males. Relevant files are attached.

   The excretion of PFOA in this group mice appears to be biphasic with longer half-lives after smaller concentrations, similar perhaps to humans as demonstrated in the Elcombe et al.

(2013) study analyzed by Dourson and Gadagbui (2021). Although this evaluation is imprecise, if correct, it would lend credence to the suggestion that the kinetics between the experimental animal of choice should be matched to the human in the relevant dose range of interest, which is the basis of question #6. That is, comparing the elimination of PFOA at higher serum concentrations in experimental animals, should not automatically be compared with the elimination of PFOA in humans at lower serum concentrations. Thoughts?

We will post the workup of the Nilsson et al. (2010) publication and supporting files and rough estimate of PFOA half life on a small group (n = 3) mentioned in the previous note on our *ARA* website. As before, comments on this posting are most welcome.

Comment: The correct half-lives to use, whether for the EPA Data-Derived Extrapolation Factor (DDEF) for animal to human differences in toxicokinetics (EF_{AK}) or for the IPCS Chemical-Specific Adjustment Factor (CSAF) for animal to human differences in toxicokinetics (AK_{UF}), are the half-lives for the relevant exposures in each species. That is, the animal half-life should be appropriate for the exposures used in the toxicology studies and the human half-life should be appropriate for the exposures of concern in the human. The TK adjustment is therefore not usually calculated using the half-lives at the same exposure concentration in the two species. A good example of the correct way to perform the TK adjustment is provided in the EPA Health Effects Support Document for PFOA (EPA 822-R-16-003, May 2016). (Note that the TK adjustment is actually performed using the clearance, which depends on both the half-life and the volume of distribution.)

Comment: My question about this is that the mice are neonates and are growing during the time that their serum concentrations and body burdens are being followed. Growth leads to larger Vd, and since they are not getting any new PFOA, this dilutes the body burden, leading to lower serum concentrations even without elimination. So the serum concentrations would be affected by growth as well as by excretion. The burdens are apparently adjusted to body weight, but if the GFR (plus any other clearance process) does not stay proportional to the increasing Vd, there could be an effect on clearance that is an artifact of the dilution of body burden (same % removed per pass through the kidneys but a lower fraction of Vd processed per day). I don't have enough info to gauge this, but it should be worked through.

On the larger question, the initial quick drop in serum concentrations in the Elcombe data was apparently well modeled as a consequence of saturation of re-uptake at high concentrations, and this is thought not to apply to the mice. Also, the timescale of the apparent change in clearance seems faster in Elcombe than in the mice, so I wonder if the two biphasic phenomena are comparable. My initial question on this was wondering if the Elcombe data showed some short-term process that also might apply to rodents — my

speculation was that perhaps the initial binding was slow enough that an initial bolus might get partly excreted before becoming fully "systemic" (bound and resistant to clearance) — and a similar phenomenon might happen in rodents, such that short-term experiments might show only this fast initial phase and not a slower eventual one that might be more comparable to what is seen in humans. To the extent that the "systemic" incorporation is mostly the immediate re-uptake in the kidneys, this precludes the picture of faster initial elimination because uptake elsewhere in the body has not yet fully happened. This suggests that it really is the saturation in humans that leads to the phenomenon in Elcombe.

I don't think we have much good evidence of a longer-term biphasic elimination in humans. A lot of the slower long-tail elimination seems to be readily explained by the problem of ongoing exposure. On the question of "correction " for such ongoing exposure, I agree that the best solution is to use studies with high enough exposure to overwhelm any such effect (but not so high as to engender saturation of re-uptake). Any correction needs to make some kind of assumptions or estimates about the ongoing exposure — that it is the same for a comparison population that didn't have the big initial exposure, or that it is unrelated to the initial exposure (and not, e.g., eating vegetables that were also contaminated by the same event as the eaters), or that the ongoing exposure is constant. I was struck that several studies of general "control" populations also showed drops in PFOA serum concentrations over time, suggesting that "background" exposures may be decreasing over the years in a way that might need to be considered in making corrections.

Comment: I agree with -----'s comments. In particular, ----- is correct that concentration dilution due to growth is an important confounder for estimating excretion from neonatal blood concentrations over time, so a strictly empirical analysis is unhelpful. There are PBPK models of PFOA exposure during pregnancy and lactation in rat (Loccisano et al. 2011) and human (Loccisano et al. 2013), but I'm not aware of one for mice. However, a good example of the correct way to estimate the correct animal half-life for use in the TK adjustment is provided in the EPA Health Effects Support Document for PFOA (EPA 822-R-16-003, May 2016).

Comment: Thanks for these additional thoughts. Thus, the Macon data will not be helpful, unless of course the critical effect is judged to be in young animals where the kinetics of Macon is then more appropriate (but not when the critical effect is judged to be *in utero*, where the dam is the dosed subject). If the critical effect is judged to be in young animals, we will definitely need to look at the Loccisano et al work, since we do not have similar data in humans.

Comment: So my initial take home message from your nice note is that comparing PFOA excretion in neonatal experimental animals with adult humans would not be a good idea since

the growth in the experimental animal dilutes the PFOA exposure, thus giving the impression of a shorter half life in experimental animals than otherwise appropriate. Makes sense. And yes, the Elcombe et al. data appear to be biphasic, for which the data in the experimental animals of Macon et al. were only mildly suggestive. Whether or not the 3 low dose patients in Elcombe et al. are representative of the longer term elimination in humans is open to debate perhaps, but they were at or lower than the presumed range of the renal resorption limit of 12–24 uMoles based on Harvey's estimated renal transporter Km of 5 μg/ml.

The work up of the Nilsson et al study in ski waxers might fit your idea of a high concentration that is reasonably unaffected by background. Fortunately, measurements of PFOA in these technicians were well below the range of the potential renal resorption limit of 5 μg/ml. What did you think of these data (attached).

7. ------- and I recently reviewed the Nilsson et al. (2010) publication and supporting files and worked up a rough estimate of PFOA half life on a small group (n = 3). We will post this on our working files for comments, but of course, please feel free to comments on this email. [All of these human half lives for PFOA are less than 1 year; **See attached Figure 4**]

8. I had the occasion to re-read the paper by Zhang et al. (2013—attached) who reported on clearance values of several PFAS by using paired urine and serum values. Using clearance values then enabled the authors to estimate various half-lives of PFAS. Unfortunately, I was unable to replicate the half life findings for PFOA from the information on clearances found in their Table 2 using the standard equation: Half-life = 0.693 x Volume of distribution ÷ Clearance. So I started a conversation with the lead author, which is found in the series of emails below my sign off (you may need to read them from bottom to top).

   The synopsis appears to be that the distribution of clearances is skewed in this population studied by Zhang et al. (2013), such that the estimation of the half-life based on arithmetic average clearance value for PFOA will not match the arithmetic value determined from individual findings. And importantly, that the geometric mean clearance value is a better indicator of central tendency in this population. My estimate of PFOA half-life for the total population of 86 individuals in this study is 1.3 years, found by averaging the geometric mean of the clearance value for young females (n = 20) and all other individuals (n = 66). Dr. Zhang's comments suggests that this half-life of 1.3 years is likely an upper limit,

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Begin forwarded message: [Note, this is an email stream with the oldest emails at the bottom]

From: Yifeng Zhang <yzhang6@ualberta.ca>

Subject: Re: Zhang et al. 2013

Date: November 8, 2021 at 8:24:45 PM EST

To: Michael Dourson <dourson@tera.org>

Cc: 祝凌燕 <zhuly@nankai.edu.cn>, Bernard Gadagbui <gadagbui@tera.org>

Dear Michael,

We cannot give a "real" GM of half-life for PFOA based on our study. We just considered renal excretion for all groups, and menstrual excretion for young females. We have no data for sweat excretion, fecal excretion, etc. Thus we said the estimations are upper limits.

I am glad to help you if you think I will be helpful in the future. Please let me know if you have any questions.
Best wishes,

Yifeng

On Nov 8, 2021, at 6:23 AM, Michael Dourson <dourson@tera.org> wrote:

Dear Yifeng

This is most helpful. My estimates of half-lives based on group GM are close to yours based on the average of individual GM, thereby suggesting that half-lives estimated in other human observational studies might be better based on the GM rather than the arithmetic average. My estimate of PFOA half-life for your total population of 86 individuals is 1.3 yr, found by averaging the GM for young females (n = 20) and all other individuals (n = 66).

You make a statement in your paper (page 10624) that biological half-life estimates should be considered as upper limit estimates of the biological half-life. Do

you have a sense of how much lower the “real” GM half life of PFOA might be based on your study?

I am also working with an international group on this question (see: https://tera.org/Alliance%20for%20Risk/Projects/pfoahumanhalflife.html). You should feel free to join this effort. Also, if you do not mind, I would like to forward our correspondence to this group.

Please advise.

非常感谢您
Michael

---*Those who have the privilege to know, have the duty to act. Albert Einstein*

——

On Nov 7, 2021, at 10:16 PM, Yifeng Zhang <yzhang6@ualberta.ca> wrote:

Thank you Michael.

First, for the young female group, "considering that menstrual clearance is an important clearance pathway for PFAAs in young females, menstrual clearance was estimated and added to renal clearance for calculation of CLtotal in young females, using the same rate estimated by Harada et al.28 for Japanese women (0.029 mL/day/kg)." But values of CLrenal are estimated as CLtotal for the other groups.

Second, we should not directly use the arithmetic mean values of CLrenal in table 2 to calculate and obtain the arithmetic mean values of HL in table 3. For example, if I use 50 individual CLrenal values to calculate the HL, I will obtain 50 values for HL. The data in Table 3 are mean values of the "50 HLs".

Third, a Canadian scientist has taken a test for this confusion in 2014, and you will see his results in the attached file. Here is his response.

> "Thank you for getting back to me so quickly.
>
> I knew I must be missing something so I generated some 'fake' PFAA renal clearance data in Excel and played around with the statistics. One of the 'fake' data sets is normally distributed (or pretty close to it), the other is more skewed

(see attachment - note that the normal distribution generator sometimes produces negative clearance values, if so just get it to re-generate numbers). For the skewed data, the arithmetic means are quite different if using individual renal clearance to calculate individual half-lives & then calculating arithmetic mean HL vs. using mean renal clearance to get mean HL. For the 'normally distributed' data set, the two approaches yield more consistent approaches for arithmetic means. Summary stats based on geometric means (and not surprisingly min, max and median) are the same for both the skewed and normally-distributed fake data (i.e. are not sensitive to calculation approach)

Anyway, I agree that Yifeng's approach is appropriate & have no further concerns with Table 2 and 3. If anyone else out there gets confused as I did, you have the answer handy. The real issue is the 'bias' in using arithmetic means to describe the central tendency of skewed data (or log-normally distributed data). Or put another way, one has to be the aware of the potential for confusion/apparent discrepancies when comparing indicators of central tendency that may be biased and/or have very different underlying distributions. This is not a criticism of your paper -- you did a great job presenting & discussing different indicators of central tendency in your paper so it's not a problem. Other data out there are less transparent. Just something for me to remember for the future!"

I hope you can figure it out now. Please let me know if you have any other questions.

Best wishes,

Yifeng

———

On Sun, Nov 7, 2021 at 7:34 PM Michael Dourson <dourson@tera.org> wrote:

Yifeng

I used your equation 2 from your page10621. So for example the mean n-PFOA half life for the young female group is found by:

T 1/2 = 0.693 x Vd ÷ CL (total)
T 1/2 = 0.693 x 170 mL/kg (from page 10621) ÷ 0.29 mL/day/kg (from Table 2)
T 1/2 = 406 days (1.1 year)

I calculated the other values found in my email below in the same way. Sorry to be such a bother. I am sure that it is something very simple.

Cheers!

Michael

---*Those who have the privilege to know, have the duty to act. Albert Einstein*

____

On Nov 7, 2021, at 7:52 PM, Yifeng Zhang <yzhang6@ualberta.ca> wrote:

Hi Michael,

You are not the first person to ask me this question. I guess you directly calculate the HL with the data in the table 2. That is not suitable. If you cannot figure it out, could you show me how you calculate it and obtain the results below?

For me, I used the original data from individual sample to calculate the HL, and then show the average means, GM and median values of HL in the table 3.

Cheers,

Yifeng

____

On Nov 7, 2021, at 12:52 PM, Michael Dourson <dourson@tera.org> wrote:

Dear Yifeng

I very much appreciate your quick response and did not appreciate the large differences in clearance until you pointed these out. Thank you. I also have a question on how you got the half-lives in Table 3 from the clearances in Table 2 by using equation 2 in your paper. For example, I calculate the half-lives for n-PFOA below. Perhaps I did something wrong?

n-PFOA

young females (n = 20)

• mean = 1.1 yr

• g-mean = 2.2 yr

others (n = 66)

• mean = 0.4 yr

• g-mean = 1.2 yr

overall average (n = 86)

• mean = 0.6 yr

• g-mean = 1.4 yr

干杯！

Michael
Toxicology Excellence For Risk Assessment: A 501c3 environmental science NGO

—*Public outreach and education see: http://tera.org/Global/Outreach/index.html.*

——

On Nov 7, 2021, at 1:30 PM, Yifeng Zhang <yzhang6@ualberta.ca> wrote:

Hi Michael,

We are very excited that you read our paper so carefully.

To keep the original information, we used individual renal clearance data to estimate the half-life, and then calculated the mean value half-life data. We should note that the range of the renal clearance data for each person is very large (I think that is the point). Take n-PFOA for an example, the range is near 3 orders of magnitude (See Figure2). Thus, it is not suitable to use the mean value of renal clearance to estimate the half-life simply. If you check the median data for n-PFOA (Table 2), you will find the renal clearance for young females (0.14+0.03, menstruation) is similar with male and older female group

(0.18). Then, the median of HL in Table 3 for n-PFOA in females is 2.0 year, which is also comparable with all males and older females group (1.8 year). For the mean value, the HL of n-PFOA is lower for young females, but for the median value, the HL of n-PFOA is higher for young females.

We believe it is better to use the individual data to estimate the HL than only use one mean value. Because that will keep more original information, and on the other hand, the results are also comparable to the half-life data published.

If you have any questions, please do not hesitate to contact me.

Have a great day!

Yifeng

http://orcid.org/0000-0002-6454-4918

——

On Sat, Nov 6, 2021 at 7:48 PM 祝凌燕 <zhuly@nankai.edu.cn> wrote:

-------- 转发邮件信息 --------

发件人：Michael Dourson <dourson@tera.org>

发送日期：2021-11-07 02:40:27

收件人："zhuly@nankai.edu.cn" <zhuly@nankai.edu.cn>

主题：Your 2013 study

Dear Dr. Zhu

I am having difficulty replicating the half-live estimates for PFOA and for sum of PFOA in your table 3 of the attached 2013 publication with Dr. Zhang, when compared with the information on clearance found in your table 2. Any help with this would be appreciated.

Sincerely,
Michael L. Dourson, Ph.D., DABT, FATS, FSRA
President

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

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Comment: Thank you for sharing your email correspondence with Dr. Yifeng Zhang. The discussion of how the data was used and the inherent difficulties posed by individual variation in half-life estimates was very illuminating.

Comment: Thanks ---, turns out that this study is much better than I thought at first reading. They approached the estimation of half life through a clearance study using paired urine an serum levels, something that I thought would be difficult to do. Although they had to assume a volume of distribution, their estimates of half-life are lower than other studies, which rely on estimates of ongoing exposure, and nearly all of these authors note that not all sources of exposure were likely monitored. According to the Zhang, their estimated half lives may be higher than appropriate since not all excretion pathways were monitored. If true, then the half life for PFOA in their study is well within the range found in the Elcombe et al. and Xu et al. studies that ------- and I summarized in our recent paper.

Comment: ----- is not an outlier. I agree that a summary of the issues is required so that any recommended PFOA half-life, or range of applicable PFOA half-lives, might be appropriately applied to subject populations.

INTERACTIVE AND OVERLAPPING EMAIL DISCUSSION

Comment: I know the purpose was to come to consensus on a particular choice and to identify a sound basis to choose the PFOA half-life, but I think the actual process showed

that there are a number of inescapable issues of interpretation, and that no particular study is immune to all the challenges. Elucidating the nature of the challenges and the reasons why no single study manages to avoid them all is an important part of the contribution of the group. The contributing documents — the sub-group summaries and the discussions that got recorded on the website — show these discussions pretty well. My worry is that the present Revised Summary drops a lot of that discussion and seems to suggest that, despite the difficulties, clear choices are there to be made.

I think that the problem of isomers with different half-lives is a big one, and though it is helpful that two studies allow looking at linear PFOA in particular, most do not and their results are biased to some degree by examining the properties of mixtures that may vary among study populations and over timescales of observation. Even if we rely on the two studies examining linear PFOA alone, those studies have their own issues (small populations with representativeness problems, incomplete accounting of clearance in Zhang). (Indeed, we haven't even clearly stated that the aim is a half-life for linear PFOA alone and not one that would apply to branched isomers or to mixtures.)

Similarly, the ongoing exposure issue plagues many studies, biasing toward longer half-life to different degrees depending on the particulars, and the means to adjust for this vary among studies and are themselves uncertain and entailing assumptions about constancy and uniformity of the ongoing exposures. A blanket 25% correction, not discussed in terms of how it might under- or overestimate the needed adjustment from study to study, seems to suggest that the problem was solved. The role of non-urinary clearance has been demonstrated, but its importance varies among populations and makes any general application of a half-life estimate be skewed for sub-populations that have different non-urinary excretion routes or rates.

I'd be happier with a summary that carries through more of the identification and discussion of these issues — one that acknowledges that any single consensus finding represents a feeling that some approximate agreement can be found across different studies that individually are biased in somewhat different directions and for different kinds of reasons. Approximate (but only approximate) adjustments suggest that a value that is not unduly skewed by these study-by-study interpretation challenges can be made, but there is the remaining issue of interpreting that consensus finding when applying it to various sub-populations that are expected to have somewhat different values and to exposures that are unresolved mixtures of isomers.

In short, this has not been a process of simply weeding out the "bad" studies and finding the few "good" ones that can be taken at face value to give a "correct answer." Shouldn't a summary document make sure that this context is clear to any eventual users?

I'm sorry to raise fundamental questions at a late date. Perhaps I'm an outlier, or perhaps I haven't understood the role of this Summary in the larger process of producing the effort's output. It does get at where the center of opinion lies, but I think the context of interpretation challenges is important to communicate.

Comment: Your comments are always welcome, and at any time. Honestly, what you wrote came across to me as part of a well-wrought discussion of a potential paper. But at the very least we should add this to the developing summary.

As to the aim of our collaboration, I am pretty sure that it was on the straight chain PFOA, since this is on which regulatory agencies focus. This also makes sense since the branch-chain isomers are excreted more quickly, and so focusing on the straight chain is protective of human health. However, your thought, and those of others including Norm who first raised it in our joint conference call, is that few studies looked at difference in isomers, and so this is a general problem with most studies. As to non-urinary excretion routes, our group is working on some references that may give us a sense of this. A proportion of urinary to non-urinary excretion routes would be necessary for any credible adjustment of the Zhang et al. (2013) PFOA half-life, but at least we know the direction of the adjustment—the half-life from Zhang et al. (2013) has to be lower. As to the various and different populations, I think that all of us would agree that this is often an issue. In this case however, we would need multiple studies like Zhang et al. (2013) in different populations to make these distinctions. The current variety of studies nearly all estimate the half-life from an exposure viewpoint, and if some exposures are missed, then the half life is inflated. Not surprisingly, half-lives vary among these studies enormously, most likely due to missed exposures as you indicate. Finally, I do not feel that we have been picking good and bad studies. Our overall objective was to determine the PFOA half-life with the greatest confidence given the variety of half-lives among different populations. This variety in half-lives is not likely to be greatly due to differences in populations, in my opinion, because PFOA is not generally metabolized. Rather these difference in half-lives appear to be due to different unmonitored exposures. Heck, we did not have a clear sense of PFOA exposures, or at least I did not, until the international SETAC meeting in 2019. So no study prior to this should be faulted for missing exposures, or considered to be bad.

Hope this helps. If you do not mind, can I add your thoughts below to a discussion section? Or perhaps we can turn the developing summary into a brief communication for publication?

Comment: I think this is coming along nicely. I request that a decision be made by COB on Monday, November 22 as to the need to meet again by phone prior to releasing the document for comment to our greater group of colleagues. I think this should provide sufficient time for a thoughtful review of the information.

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Comment: I've made some comments in the document. I think we all need to talk before you send this anywhere.

Comment: Your comments, as usual, are spot on. All changes have been incorporated into the attached revised text and comments have responses. A clean version is also attached. If all of us are more or less satisfied with this revision, then I do not see the need to meet again by phone prior to releasing this for comment to our greater group of colleagues. But what do others think?

Comment: To all, please find attached a revised draft summary. It has been tweaked to reflect text changes due to the removal of ----- and -----'s unpublished work, and a revision to Table 1 to reflect what the authors' show on what we think of two important issues, specifically whether unmonitored exposures were addressed and whether PFOA isomers were studied. Both of these issues would affect the estimated PFOA half -lives in the various studies. We should all carefully review this table to make sure we agree with its content. Also included is a second table that calls out 3 of these studies, with adjustments as needed, for unmonitored exposures and unmonitored elimination.

It would be good if we could release a version of this draft summary to our greater group of interested colleagues sometime next week. In the mean time, our group will continue to investigate the unmonitored elimination question for the Zhang et al. (2013) study, cobble together some of our email correspondence into the Q&A text on our private website, and perhaps draft a short communication paper with all of us as authors to describe our process.

As always, thoughts and suggestions are welcome. We would be happy to set up a zoom call if needed for further discussion.

Comment: I'd add breastfeeding as a major elimination pathway for women as well.

Comment: -----'s comments on other elimination routes is helpful. And we shouldn't forget that various blood losses also reduce body burden: menstrual blood and blood donation, primarily. And some body burden is lost to the mother in childbirth (though inherited by the newborn). How such factors are appropriately considered in the use of half-life estimates in further risk assessment calculations could be debated, but the factors are there.

Comment: Very helpful. We will tract these items down and try to work out a reasonable and scientifically supportable adjustment to the Zhang half-life as appropriate.

Comment: I have several thoughts regarding other routes of PFOA elimination loss.

Firstly, the ability of cholestyramine to facilitate the loss of PFAS from the gut, by interrupting enterohepatic circulation (Genius et al 2010 and 2013, Maddaloni 2017 [M6331], and Ducatman et al 2021), suggests that certain dietary components may play a significant role in fecal elimination of PFAS. Certain dietary may play a similar role in PFAS elimination. To my knowledge, the specific loss of PFOA resulting from the inclusion of specific dietary components has not been studied.

Secondly, the loss of PFAS in sweat was studied by Genius et al (2013) [Attached as G4311]. He collected urine and sweat samples from 20 individuals (male and female) and analyzed for PFAS. Four of the 20 subjects had PFHxS level in serum that exceeded the 95th percentile of the NHANES study referenced (2012). The same 4 subjects also had PFOS and PFOA serum levels exceeding the 90th and 50th percentile of the same NHANES population, respectively. While Genius et al. was able to detect several PCB congeners in sweat, he did not detect any of the 7 targeted PFAS compounds (i.e., PFHxS, PFOS, PFOA, PFNA, PFDA, PFUA or PFTA). The authors concluded that " ... *induced perspiration through sauna or exercise does not seem to hasten the clearance of these three common PFCs from the human body via perspiration*."

Finally, it seems that PFAS may be lost (eliminated) through hair (Alves et al 2015).

I hope that this information is helpful.

Comment:

On Nov 17, 2021, at 7:54 AM, Michael Dourson > > > wrote:

> Dear Dr. Zhang
>
> So based on the email below, what kind of adjustment to your GM half life might be appropriate for the unmonitored PFOA excretion in your study please?
>
> Cheers!
>
> Michael Dourson
>
> Toxicology Excellence For Risk Assessment: A 501c3 environmental science NGO
>
> **From:**"Michael L. Dourson" > > >
> **Subject:Re: Revised Summary**
> **Date:**November 17, 2021 at 11:28:08 AM EST

To: Yifeng Zhang > > >

On Nov 17, 2021, at 11:06 AM, Yifeng Zhang > > > wrote:

Hi Michael,

In my opinion, adjustment with a factor for the HLs should be more reasonable than without adjustment. The next question is do you have references to support the factor 0.8? Why it is not 0.9 or 0.7?

In addition, can I share all your discussions as well as your draft with my former supervisor Dr Jonathan Martin, who is the corresponding author of the paper Zhang et al 2013? Jon is a famous scientist in the PFAS field. He is currently a professor at Stockholm University. I guess he may have some good comments for your draft. However, as I know, he is usually super busy, so I can't guarantee he have time to help you.

Best wishes,

Yifeng

Yifeng

Thanks for your quick response. We have used an 0.8 factor as a rough guess. We do not have any information to back it up other than your statement that not all elimination pathways were measured in your study. Perhaps we can investigate the proportion of PFOA eliminated in the bile and or sweat and hair. What do you think? However, we would also be happy with your estimate of what this adjustment might be.

You should feel free to share this information with whomever you wish. This international collaboration is open to all interested investigators.

Cheers!
Michael
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Comment: Based on the latest exchange of emails and our previous discussions, it appears that the unpublished studies/analysis should probably be removed from our summary

table. This leaves us with 3 studies, none of which have overt issues with unmonitored exposures and all of which address the issue of PFOA isomers directly, albeit in different ways.

The most recent of these three studies is by Dourson and Gadagbui (2021), who give a range in the PFOA half-life of 0.5 to 1.5 years. Their lower value is based on an analysis of the 3 single, low-dose patients in the clinical study by Elcombe et al. (2013). This latter study has the advantage of a high enough PFOA dose to be well above background and yet still below the saturation point for kidney resorption, and is not impacted by differences in PFOA isomers, since straight-chain PFOA was administered as the drug. These patients were also followed weekly for PFOA levels. But the analysis of this study by Dourson and Gadagbui (2021) suffers from a small number (n = 3) with a limited follow up time (6 weeks). Also, an unpublished analysis of all patients in the Elcombe et al. (2013) study yielded a higher half-life estimate. Some would also argue that the individuals in the Elcombe et al. (2013) study were ill and therefore not necessarily a good representation of the normal population, but this argument is mollified by an unpublished analysis of 3 healthy individuals described in Nilsson et al. (2010) that yields a similar half-life of 0.6 years.

The next most recent of these three studies is by Xu et al. (2020), who give a PFOA half-life of 1.48 years, after subtracting out background. The population here is exposed to only one source of PFOA, exposures were below the presumed renal resorption limit, and fewer subjects allowed a more careful study. More importantly, background exposures were subtracted out giving a more accurate PFOA half-life. But this study also had a limited number of subjects (n=17), follow up was briefer than other observational studies (~6 months), and the starting serum levels were less that <10-fold of general background suggesting that any unmonitored PFOA exposures would have more impact on inflating the stated half-life. Also, although PFOA isomer analysis was part of this study, it was not immediately obvious that the given PFOA half-life was for straight-chain PFOA, or whether it included isomers that might be expected to be eliminated more quickly. A follow up with these authors would be appropriate.

The least recent of these three studies is by Zhang et al. (2013), who give a PFOA geometric mean half-life of 1.3 years. This analysis is based on a clearance study using paired urine an serum levels in 86 individuals, which obviate issues with background exposures that are common to all other human observational studies. Nor is follow up time an issue with a clearance study. The authors also conducted an analysis of PFOA isomers and give different half-lives accordingly. This obviates the problem with isomer analysis that is not done in nearly all other observational studies. However, the authors state that their estimated half lives should be considered as upper limits, since not all excretion pathways were

monitored. A follow up with these authors to gauge the appropriate adjustment for this issue would be helpful.

Of these three studies, the one that seems to have the least problems, and therefore one that might give us an accurate PFOA half-life, or at least one with the greatest confidence, is that by Zhang et al. (2013).

The revised table is attached. What do we all think?

Comment: As ----- mentioned, the Elcombe study should be used with the latest modeling, which is yet to be published. But it could support a more generally-based finding by showing consistency with it in a study that did not mix isomers.

Our subgroup tended to favor using an estimate that is compatible with several of the more reliable studies, rather than picking one. But to me, the isomer question is big enough that using Zhang to anchor that approach is a good idea.

Comment: I reread your email after I sent out my response to -----. You are correct, the Zhang et al. (2013) study has an advantage over perhaps all of the other human observational studies in that it shows the half-lives of different isomers, and importantly for our international collaboration, the half-life of straight-chain PFOA directly. The Elcombe et al. (2013) study also appears to have this advantage since it administered only straight-chain, or n-PFOA.

Others' thoughts?

Comment: Another good thing about Zhang is that they looked at each PFOA isomer separately, and they found substantially faster clearance (shorter half-life) for branched isomers vs linear PFOA. As you and they noted, the estimates are somewhat dependent on the assumptions about volume of distribution and GFR, but these don't seem unreasonable or subject to too much error. As you note, it assumes that the urine is the only clearance route, and we know that there are others, especially menstrual blood but also some other possibilities, so the actual overall half-life is likely somewhat shorter than Zhang's results suggest (as they themselves note)

I think the isomer question is one that really needs some dealing with. As some of my earlier comments noted, when several isomers are present, the observed overall half-life for unspecified "PFOA" is shorter than the actual one for the predominant linear isomer, and the balance among isomers changes over time (as the faster-cleared ones become a smaller fraction of remaining body burden). This could be another reason for the longer half-life

observed in longer studies (separate from the real issue of ongoing exposure biasing the result). We haven't delved into the question of differences in toxicity among the isomers, but that introduces a further complication in any use of a single compromise half-life for all isomers.

Comment: Just to throw another monkey wrench into this conversation, normal fatty acids are linear, so not only are the branched-chain PFOA isomers likely to have lower affinity for the fatty acid transporters, they may also have different toxicity and even a different mode of action than the linear PFAS. The USEPA recently proposed a chronic RfD for GenX of 80 ng/kg/day (compared to 200 ng/kg/d for PFOA), based on single-cell hepatocellular necrosis in female mice. Relevant to this conversation, GenX is a branched-chain PFAS, and EPA says that the single cell necrosis is not related to PPAR activation. If this is borne out, the PFAS mixture questions could become similar to PCBs (different MOAs for coplanar vs. non-planar).

I think this issue is complicated enough that it we should just point it out and not try to solve it.

Comment: Although the draft RfD/MCLG document was released only last week for PFOA (and subject to change), the RfD is at 0.0015 ng/kg-day and based on a human study (decreased serum anti-tetanus antibody concentration in children). For PFOS, it is 0.0079 ng/kg-day for a similar endpoint (diphtheria vaccine).

Comment: Most federal agencies have historically focused on linear chain PFAS compounds in their analytical analyses. This is rapidly changing, however, since the CDC regularly analyzes for both linear and branched chain PFAS in the blood of the general population (NHANES) – a metric of PFAS exposure in the general population. The Department of Defense (DoD) is in the process of up-dating serum analyses (firefighters) to include branched and linear chain isomers for certain PFAS (for some PFAS the branched chain isomers can represent a significant fraction of the total. For PFOS, branched chain isomers can account for up to 30% of the total mixture of PFOS). Others in DoD have pioneered and remain connected to interagency efforts to harmonize federal government analytical analyses to include both branched and linear chains of selected PFAS in a wide variety of media.

----- brings up an interesting issue … Branched isomers are generally more easily eliminated from human serum than linear chained isomers. As far as I am aware, the reason for this difference in excretion has not be satisfactorily determined, but may reflect different avidity for serum protein (more free PFAS in serum) and decreased avidity for organic anon transport (OAT) proteins mediating kidney reabsorption (more urinary loss). One question of interest in this regard may be … How are health outcomes influenced by PFAS interactions

with receptors, clearance, and non-specific effects associated with membrane fluidity? And what role might branched isomers play in the development of these health outcomes?

Regarding: "As to the aim of our collaboration, I am pretty sure that it was on the straight chain PFOA, since this is on which regulatory agencies focus", it is the reality that standard analytical methods that are being used to characterize the nature and extent of PFOA contamination at sites across the nation and consequently to develop exposure data for risk assessments require analysts to quantify PFOA by specifically integrating branched and linear isomers together. Thus, what's reported as "PFOA" in typical site investigations actually represents the sum total of branch AND linear, which biases PFOA exposure estimates high. It's a disconnect. This was a main discussion topic in our subgroup.

Comment: We might not want to include adjustments for gestation and lactation except in discussion because these are specific to some women and only during a small window of their lives. It would not include a large chunk of women or men.

The same could go for the 20% adjustment. I feel that we are adding uncertainties for no clear benefit.

Comment: I do appreciate -----'s suggestion of including a broader discussion of the issues that really makes this gathering fruitful and helpful.

Comment: I agree with ----- .

Comment: Attached is a revised summary of our findings to share with our greater group of colleagues later this week. It is slightly different than before in an attempt to make it a wee bit more "stand alone." I have also maintained the 0.8 adjustment to the Zhang et al. half-life as a placeholder pending the outcome of our brief literature review on PFOA elimination routes.

What has become apparent from our last set of interesting and productive email exchanges is the need to capture the various nuances in this area arising from our collaboration, and because of this I proposed to draft a short communication by the mid next week for all of us to review and improve. Of course, volunteers to assist in this drafting would be welcome!

In the mean time, please look this summary over and suggest changes by Wednesday. If are fortunate enough to gain some comments from our greater group of colleagues in the next several weeks, we can incorporate their thoughts into our developing short communication.

Comment:

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1. Goeden et al suggest a 5.2% serum to breast milk transfer rate with a range of 2.5% and 12%.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6760606/pdf/41370_2018_Article_110.pdf

- The authors' model suggests that breastfeeding contributes much more to the infant's serum than formula (assuming same water used for drinking and formula)

2. I see that Harvey et al have published on the topic.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3502013/pdf/nihms-403084.pdf .

- The modeled dip in maternal plasma PFOA is large following lactation (Figure 3).

3. Gestation and lactation will affect females. Males do not have as many elimination routes. So, it depends where the half-life is used, in combination with which study, and for what purpose.

Comment: Although the draft RfD/MCLG document was released only last week for PFOA (and subject to change), the RfD is at 0.0015 ng/kg-day and based on a human study (decreased serum anti-tetanus antibody concentration in children). For PFOS, it is 0.0079 ng/kg-day for a similar endpoint (diphtheria vaccine).

Comment: Thanks for this information. Part of EPA's draft judgment, no doubt, is based on an estimate of the human PFOA half-life, with which our international collaboration can help. I have not seen EPA's assessment, but had the chance to briefly look at the European Food Safety Authority (EFSA) value that was also based on decreased serum anti-tetanus antibody concentration in children. The critical study appears to Abraham et al. (2020) which is a human observational study. The critical information appears to be found in Table 2 of this paper, replicated below in a screen shot. Notice any problems? Spoiler alert, PCBs are also known to affect the immune system. See for example: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4290093/.

Comment: We might not want to include adjustments for gestation and lactation except in discussion because these are specific to some women and only during a small window of their lives. It would not include a large chunk of women or men.

The same could go for the 20% adjustment. I feel that we are adding uncertainties for no clear benefit.

I do appreciate Lorenz's suggestion of including a broader discussion of the issues that really makes this gathering fruitful and helpful.

Comment: So if we do not make adjustments to garner one or more specific values, then we are left with a discussion of a likely range, correct? The Xu et al. (2020) half life of 1.48 years would go down with any potential unmonitored exposures; the average Zhang et al. (2013) half-life value of 1.3 years would go down based on the authors' acknowledgement of unmonitored elimination; and the Dourson and Gadagbui (2020) half life of 0.5 years based on the clinical study of Elcombe et al. (2013) or 0.6 years based on the work of Nilsson et al. (2010) would go up based on the good work of ----.

Does this define the range? Or does someone want to propose something else?

What do others thing about developing a range versus one or more specific values? Of course, we do could easily do both.

Comment: I think the tables speak for themselves as they are. While I would give precedence to the Zhang and Xu studies, we should not give the impression of a precision that is not supported.

Comment: Such a range is also consistent with the imprecision that is associated with uncertainties in our Table 2 studies, and even more so in our Table 1 studies that did not address unmonitored exposures or PFOA isomers.

Others' thoughts?

Comment: I'd like to see a range since a single value implies that one can pin down a number with more precision than we think can be had. A suggested single number would be OK if needed, as long as the range is right there to emphasize that alternative reasonable bases give somewhat varying answers.

Comment: It is reasonable to select a range based on Table 1 (0.5-3.5 years). We might consider removing Table 2 and have it in discussion text. I'm not sure I want to marginalize the other studies. By Having Table 2, we are marginalizing them.

Comment: All of this is reasonable discussion and we should give others in our international collaboration a chance to consider these comments over the next several days and then weigh in as appropriate. Why do we not take the balance of this week to consider our options before we go out to our greater group of colleagues?

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The options as I see them are several and the ones I list below are in no way exclusive of others. We can:

- Select a single study to represent our best judgment of the PFOA half life; a study such as Zhang et al. (2013) might be an appropriate choice since as a clearance study its half life does not depend on monitoring exposures as every other study except Elcombe et al. (2013) does. Nor is this study complicated with unknown PFOA isomers since it measures the serum levels of PFOA isomers directly. Furthermore, elimination pathways that were not monitored by the authors are researchable as several of our various emails have indicated.
- 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. This might also be reasonable since two of the studies do not have the problem of unknown PFOA isomers (Elcombe et al., 2013 and Zhang et al. 2020), and two or possibly three of them do not have a problem with unmonitored exposures.
- 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. This has the advantage of being inclusive and reflecting of previous attempts to solve this vexing problem, but many of these studies included unmonitored exposures as acknowledge by the authors and potential mixtures of isomers which are not acknowledged. One of us has stated that this adds an unreducible amount of uncertainty to the upper part of the half-life range.

Comment: I align with the position put forth by ----- on the importance of including a range of half-life values range than reliance on a single value.

Comment: We are to the point in our international collaboration that we may be able to make a consensus judgment based on the various discussions and emails among our individual and combined groups since this summer. Of course, new information may also be coming around, but this does not change the fact that we need to let our greater group of colleagues know about our ongoing effort.

How about the following approach to reaching this possible consensus?* First, look over the three options below and, if possible, chose a preferred one along with reasons for your choice. It may also be helpful to the rest of us for you to indicate an option that you could live with, but of course not preferred, and, if appropriate, to select an option that you could *not* live with. If you wish to propose a different option, please send it around for all of us to consider. Finally, you should feel free to pass on selecting any options.

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 our summary 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 our summary Table 1.

I also proposed that each of us send our choice of option to ----- with a carbon copy to -----. ----- has agreed to collate our responses by the end of this week and will keep all responses confidential. This will allow anyone of us to perhaps "speak" more freely than the usual back and forth emails might allow. Afterwards, we can all look at the collation and see if it changes our individual choices. If so, we can proceed with an additional round of emails to ----- and -----=, with the expected potential consensus by around mid December. It would be nice to end up with a unanimous consensus, but it would be entirely reasonable to have some diversity in our thinking. After all, this is where most of our colleagues currently are.

If this sounds reasonable to you, please send your responses to ----- and ----- by Wednesday of this week.

Comment: Here is a summary of the 6 responses that ----- and ----- have received to date. Option 2 is preferred by 5 of the 6.

	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)	5	1		Five favored option 2. One stipulated without a single value; another said with Table 1 included to document studies considered
3 (larger group)	0	2	2	

----- and ----- also think option 2 makes best sense.

Two stated rationales for preferring option 2 were:

- Different subpopulations probably have different elimination half-lives
- The studies in Table 2 have been selected as those with the fewest issues affecting interpretation of a half-life

Other recommendations noted by respondents included:

- Do not including an explicit "exposure or elimination adjustment" (as was drafted into Table 2) as there is little basis for this, but rather discuss it in the text as food for thought.
- Present all the studies that were evaluated to show all data considered.

We can update this summary table if others want to send preferences, but so far it looks like option 2 is the (strong) majority choice.

Comment: Thanks, ----- ! I received one more vote for option two this morning.

Comment: Ok, this means we have 5+ ----- + ----- +1 for option 2, correct? The one person voting for option 1 could live with option 2, so this means we have a consensus, but it is not unanimous. I will write this up in the draft summary, but please let me know if I am missing something.

Comment: Right!

Comment: Any comments or suggestions on our summary? If we have no comments or suggestions, it would be appropriate to say that we have a consensus, correct? We should plan to send this out this week.

Comment: The summary looks great! I made a few small changes to the text.

Comment: I have no comments or suggestions. It all sounds reasonable to me based on our discussions and emails.

Comment: I've just made some edits in both of the tables to clarify the description of the published study (Dourson and Gadagbui 2021) and document the estimation of the Km for saturation of reabsorption. Apart from that, it looks fine to me.

Comment: I agree with this consensus. I don't mean to derail this process, but perhaps a follow-up could be a meta-analysis that looks at the studies we've isolated. I took the liberty to do a very rough attempt using these studies.

The main issues are not having data from some of the studies, and having to assume the distribution of half-lives are normal even though they're probably log-normal. This could be solved by tracking down the data but I haven't attempting getting that from the study authors yet.

The other issue is that because it has the studies without background correction, the final range is bit higher than the ~1.5 years if the background is subtracted. There's not really a solution for this unless all the studies have the backgrounds corrected. I've also used the all-isomer PFOA half-lives since so few studies provide n-PFOA numbers.

Nonetheless, its still interesting to me that the studies in the meta-analysis are not heterogeneous, so a fixed summary effect can be used instead of a random-effects model. That indicates that essentially the studies are measuring the same value, but with low precision and there are not categorical differences between studies.

I'm happy to discuss further if there is interest.

Comment: Yes, I think that the international group came up with a good consensus. And I also agree with you that a meta-analysis would be fun and productive. Our group would relish the opportunity to follow up with authors for the individual data to determine distributions, and estimating backgrounds or potentially unmonitored exposures. It would also be really nice to get another clearance study, like Zhang et al. (2013) for confirmation.

Comment: Several of us have offered comments on the draft summary. All comments have been accepted. Please find attached the intended final summary, which I will send around to our greater group of interested colleagues tomorrow at about noon (Washington DC time). Please feel free to suggest any additional changes.

I will focus next on developing a short communication for journal publication, and submitting our work for a "hot topic" session at the upcoming Society of Toxicology in March of 2022. See https://toxchange.toxicology.org/blogs/michael-aschner1/2021/12/02/call-for-hot-topic-session-proposals-for-the-2022?CommunityKey=fc369e8b-e268-48fa-b276-8edd4ab68fb2&tab=community-home-blogs&utm_source=SOT%20Website&utm_medium=Referrels&utm_campaign=ToXchange . Comments or thoughts on this submission would be very welcome.

Comment: My comments and suggested edits are attached. Nothing major, just a few clarifying edits. I think the document reads well and does a good job capturing the nuances of the group's thoughtful evaluations and discussions.

Please let me know if you have any questions.

Final Comment:

On Dec 10, 2021, at 12:02 PM, Michael Dourson <dourson@tera.org> wrote:

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

Dear Colleagues [133 receipients]

As previously mentioned, scientists associated with this international collaboration continued discussions via a web-based chat function, the results of which are summarized in the attached document.

We will be placing a summary of our discussions next week at: https://tera.org/Alliance%20for%20Risk/Projects/pfoahumanhalflife.html), and plan to follow this up with submission to both a journal and a "hot topic" session at the upcoming Society of Toxicology in March of 2022.

We invite your thoughts and comments on any of this material.

On behalf of the Advisory Committee,

Sincerely,

Michael Dourson

PFOA 1/2 Life Advisory Committee:

- Harvey Clewell, Ramboll
- 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 (CRC CARE)
- Nitin Verma, Chitkara University

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Alliance for Risk Assessment (*ARA*):
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Figure 1. Data from Emmett et al. (2006)

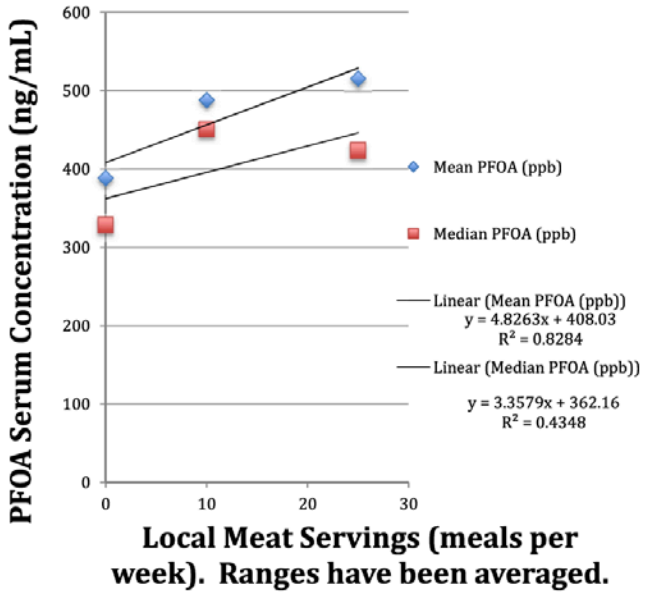

Fig. 2. PFOA concentration versus local meat; data from Emmett et al. (2006).

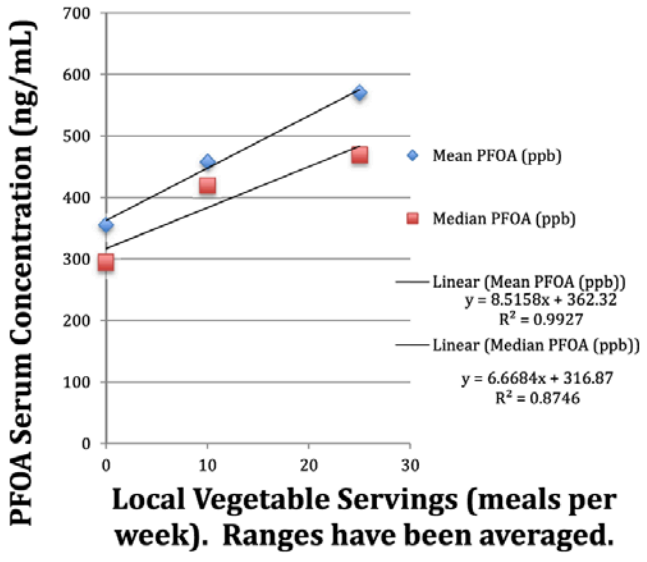

Fig. 3. PFOA concentration versus local vegetables; data from Emmett et al. (2006).

Figure 2. Which is Figure 1 of Bartell (2012) and associated text

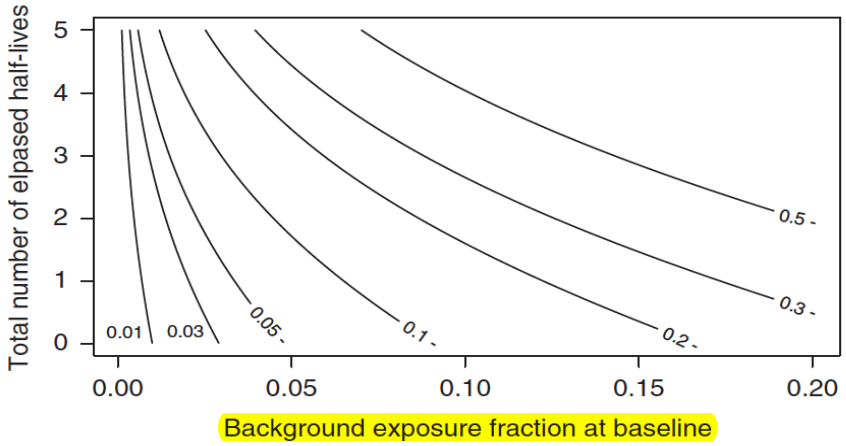

Figure 1. Approximate bias in log concentration regression half-life estimates in the presence of background exposures. Contours show the bias as a fraction of the true half-life, depending on the ratio of background initial to biomarker concentration (f) and the number of elapsed half-lives between the two time points (m).

In this special case of evenly spaced samples, the amount of bias introduced into the half-life estimate by log concentration regression in the presence of background exposures, written as a fraction of the true half-life, is

$$E\left(\frac{\hat{t}_{1/2}-t_{1/2}}{t_{1/2}}\right)=kE\left(\frac{1}{\hat{k}}\right)-1\approx\frac{\ln(2)\frac{\Delta t}{t_{1/2}}n(n-1)(n+1)/12}{\sum_{i=1}^{n}\left(\frac{n+1}{2}-i\right)\ln\left[f+(1-f)2^{-\frac{\Delta t}{t_{1/2}}(i-1)}\right]}-1 \quad (8)$$

Equation (8) provides the half-life bias fraction for evenly spaced samples, and is accurate at large sample sizes or when the error terms are relatively small (see Appendix).

Notably, the bias fraction for evenly spaced samples shown in Eq. (8) is a function of only three distinct quantities: f, n, and $\frac{\Delta t}{t_{1/2}}$. Recall that f is the ratio of the background serum concentration to the baseline serum concentration, n is the number of measurements, and $\frac{\Delta t}{t_{1/2}}$ is the length of time between any two adjacent measurements, in terms of the number of half-lives. Let m be the total number of "elapsed half-lives" across all n measurements; thus $m=\sum_{i=1}^{n-1}\frac{\Delta t}{t_{1/2}}=\frac{\Delta t}{t_{1/2}}(n-1)$

Alliance for Risk Assessment (*ARA*):
The Conundrum of the PFOA Human Half-life
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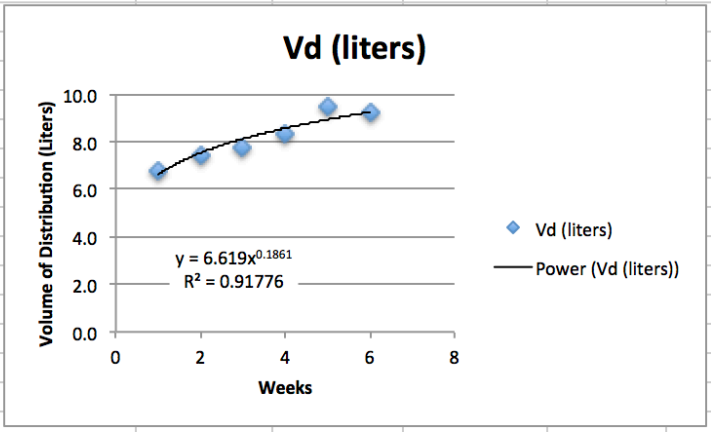
Figure 3. Enhanced Volume of Distribution from Dourson and Gadagbui, 2021, Appendix

Elcombe et al. (2013)
42 patients

Week	Vd (liters)
1	6.8
2	7.5
3	7.8
4	8.3
5	9.5
6	9.3



Linear Regression			Vd	>>>>	linear regression not biologically plausible
Extrapolated Vd at 250 d 1/2 life			25.9		
Extrapolated Vd at 1.5 yr 1/2 life			49.2		
Power Regression			Vd		
Extrapolated Vd at 190 d 1/2 life			12.2		
Extrapolated Vd at 1.0 yr 1/2 life			13.8		
Extrapolated Vd at 1.5 yr 1/2 life			14.9		
Extrapolated Vd at 2.3 yr 1/2 life			16.1		
			v		
v	<<<<<	<<<<<	<<<<<		
v					
Vd L/kg	1/2 life	Clearance	Alter/EPA		
0.17	2.3 yr	0.00014	-	EPA 2016 position	
0.16	0.52 yr	0.00060	4.2	power for 190 days (0.52 year)	
0.18	1.0 yr	0.00035	2.5	power for 365 days (1 year)	
0.20	1.5 yr	0.00025	1.8	power for 548 days years (1.5 years)	
0.22	2.3 yr	0.00018	1.3	power for 840 days years (2.3 years)	
^					
^					
^					

mean 75 kg bw for the Elcombe et al. patients as per Convertino et al. (2019)

Figure 4. Analysis of Nilsson et al. (2010) ski waxers.

Analysis of Nilsson et al., 2010

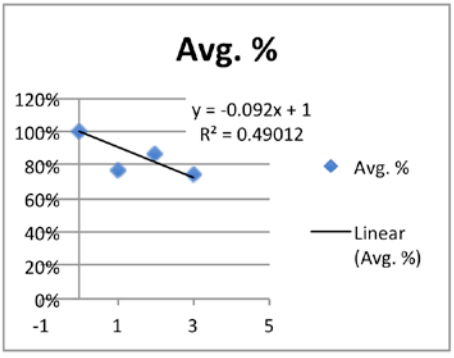
Data from supplemental Table S2; note Figure 2d of the paper has information from Techician 8 misplaced.

Note: Bk = background; De = decrease

	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			May	23.1		
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			
	Month	PFOA (ng/ml)	%De	% De-Bk
Pre-exposure	Sep	474		
Exposure	Dec	528		
Exposure	Jan	-		
Exposure	Feb	535		
Exposure	Mar	-		
Post-exposure	Apr	501		
Post-exposure	May	520		
Post-exposure	Jun	471	9%	107%
Post-exposure	Jul	468	10%	113%
Post-exposure	Aug	-		

Months after high level	%De with Bck. Avg. %	%De without Bck. & tech 8 Avg. %	
0	100%	100%	
1	86%	77%	
2	90%	86%	
3	84%	74%	
>>>>	>>>>	>>>>	>>>>



Without background subtracted out		
half-life =	11	months unforced data; r2 = 0.66
half-life =	8.5	months when intercept is forced to 100%; r2 = 0.57
With background subtracted out		
half-life =	7.2	months unforced data; r2 = 0.59
half-life =	5.4	months when intercept is forced to 100%; r2 = 0.49