Work Group 3's Consensus on Issues Related to the Human Elimination Half-Life for PFOA

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Review of the Literature on PFOA Half-life and Volume of Distribution

PFOA is mistaken by the body as a medium-length essential fatty acid. Its primary difference from essential fatty acids is that it is resistant to metabolism. The pharmacokinetics of PFOA is primarily driven by its mimicry of an essential fatty acid. For example, active uptake from the GI tract results in high oral bioavailability, and active re-uptake of PFOA excreted in the bile limits fecal excretion. At the same time, high affinity renal resorption accounts for its long half-life in the human at environmental exposure levels, although women of child-bearing age have an additional clearance due to menstrual loss, episodic loss associated with transfer to the fetus, and lactation. Due to the complexity of the control of PFOA pharmacokinetics, it is likely that interindividual variability is significant.

A critical review of publications reporting a human half-life for PFOA identified five studies (Olsen et al. 2007, Bartell et al. 2010, Gomis et al. 2017, Li et al. 2018 and Xu et al. 2020) that, together, provide strong evidence for a PFOA half-life ranging from 1 year to 3.5 years (Table 1). The variation in reported half-lives likely results from study differences including the study design, the approach for considering "background" exposure (non-drinking water or residual exposures), nonlinear isomer content and PFOA-precursors, and, as suggested by the results of the Gomis et al. (2017) studies, variability across different populations. Therefore, attempting to derive a global probability distribution for the "intrinsic" half-life of PFOA by merging the various study results may not be appropriate. The observed three-fold variability in population PFOA half-life is less than the inter-individual variability expected for human pharmacokinetic parameters (Hattis et al. 1987).

Study	Plasma Concentrations (ng/mL)	$T_{1/2}$ (years)
Olsen et al. 2007	17 – 5100	3.5 / 3.0 [a.b]
Bartell et al. 2010	58 – 424	2.3 [a]
Gomis et al. 2017	1 – 50	2.4 (USA) 2.0 (Australia)
Li et al. 2018	~18	2.7
Xu et al. 2020	~117	1.77/1.48 [a]

[a] corrected for background
[b] Russell et al. 2015

To obtain an estimate of the intrinsic (true) half-life, it is necessary to correctly account for background exposures. Failing to properly account for continuing exposures can lead to half-life estimates that are artificially increased (Russell et al. 2015). For example, using a two-segment linear spline approach,

Seals et al. 2011 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 of (B) 8.5 years for specimens collected <9 years since leaving the water district. However, in an analysis of the same data using a statistical model that accounted for ongoing exposure, a time- and concentration-independent intrinsic half-life was estimated to be 2.3 years (Bartell et al. 2010).

The Campbell et al. (2016) Markov Chain Monte Carlo (MCMC) analysis of the Elcombe et al. (2013) clinical study has recently been updated and a manuscript is in preparation. The updated posterior distribution for the terminal half-life of PFOA in the clinical study (Figure 1) is consistent with the range suggested by the epidemiological studies (1 – 3.5 years) of environmental and occupational exposures.

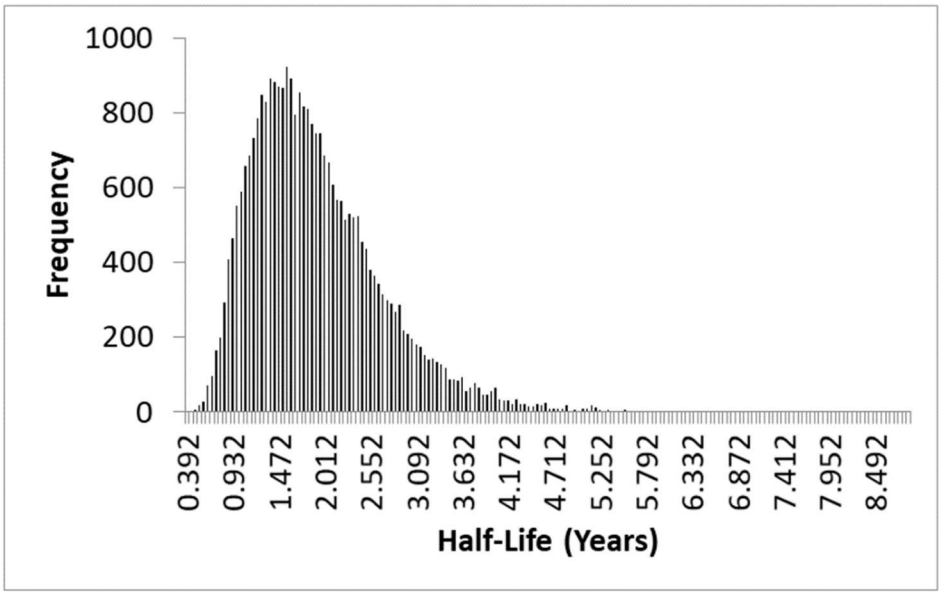

Figure 1. Histogram of the half-life distribution from the Markov chain Monte Carlo analysis of the Elcombe et al. (2013) clinical study

An analysis by Dourson and Gadagbui (2021) of the Elcombe et al. (2013) clinical study data found that the initial PFOA half-life is on the order of a few days. This short half-life is driven by the extremely high plasma PFOA concentrations (400 – 400,000 ng/mL) achieved in the clinical dosing, which exceeded the capacity for renal resorption, resulting in rapid urinary clearance. The MCMC analysis was focused on estimating the terminal half-life that would be observed at much lower plasma concentrations.

The PFOA volume of distribution (Vd) estimated by the MCMC analysis of the Elcombe et al. (2013) study is 0.175 L/kg, which is consistent with the Vd of 0.14 L/kg for the monkey estimated using a two-compartment pharmacokinetic model with saturable resorption (Andersen et al. 2006). Vestergren et al. 2009 incorrectly attributed the order-of-magnitude differences in apparent Vd between single and repeated exposures of monkeys (Butenhoff et al. 2004) to duration of exposure (single vs. repeated dosing). However, both the single and repeated monkey exposures are consistent with a Vd of 0.14 L/kg using a two-compartment model with saturable resorption (Andersen et al 2006).

<u>The Role of Inter-Individual Variation in Affecting Study Results and in Applying Such Results to a Wider Human Population</u>

Interindividual variation in clearance rates is often seen in studies that have examined it (e.g., Gomis et al. 2017; Harada et al. 2005; Li et al, 2018; Zhang et al. 2013). There is some evidence of a sex

difference, especially due to clearance in menstrual blood; some evidence of age difference; possible roles of diet and level of normal fatty-acid uptake and processing. This could affect the generalizability of findings from particular study populations to represent a general human population. There seems no clear way to measure or adjust for such effects in a consistent way, given the population heterogeneity among studies.

Site-Related Non-Point Source and General Population Background PFOA Exposures

It is difficult to estimate site-related non-point source and general population background when exposures contributing to serum PFOA are not fully characterized (e.g., water, diet, dust, dermal, air, other). Several studies rely on NHANES or neighboring reference population in the same region/country. For example, Seals et al. (2011) subtracted a standard background serum concentration from the cohort and found that half-life was sensitive to magnitude of background PFAS serum concentration. The authors also found a shorter half-life (2.9 years) for water districts with higher exposure concentrations and a longer one (8.5 years) for water districts with higher exposure concentrations. Xu et al. (2020) found that subtracting background exposures resulted in a reduced half-life (from 1.77 years to 1.48 years). This is lower than those identified in some other studies such as by Bartell et al. (2010) and Li et al. (2018) when background was subtracted (5-month span of serum monitoring). Bartell (2010) also found that those consuming homegrown vegetables had a longer half-life likely due to underestimated background from site-related non-point sources of exposure.

Inadequate accounting for these types of background exposures could result in considerable bias of the half-life estimate, yielding an overestimation of PFOA's intrinsic elimination half-life (Russel et al. 2015). This is especially true for longer follow-up periods and low water exposure concentrations and in populations where multiple site-related exposure pathways are complete (e.g., Bartell et al. 2010 and Seals et al. 2011). In cases where PFOA exposure is much higher than background, there might be little bias from disregarding background unless the follow-up time is long (several half-lives) (e.g., Xu et al. 2020). A small background with a short time for evaluation of the half-life introduces less bias according to Bartell (2012). Bartell (2012) attributes a potential bias to general population background of approximately 1%-26%.

The Issue of Mixture of Several PFOA Isomers and Precursors is Poorly Dealt with in Almost All Studies, Lending Unreducible Uncertainty to the Estimation Process

It is recognized that PFOA is found in technical formulations, the environment, and human biomatrices as linear and multiple structural isomers (US EPA 2016, Loveless et al. 2006, Zhang et al. 2013, Xu et al. 2020). It is also recognized that branched isomers of PFOA display distinct pharmacokinetics compared to the linear isomer of PFOA, with dissociation constants for branched isomers indicating that they are much less tightly bound to human serum albumin and biomonitoring data showing that they display higher renal clearance (US EPA 2016, Beesoon et al. 2015, Zhang et al. 2013). However, it is common for epidemiological studies reporting on PFOA elimination half-lives to use analytical methods that do not resolve isomers or that include the area under the branched isomers during quantification of PFOA chromatograms (Olsen et al. 2007, Brede et al. 2010, Bartell et al. 2010, Seals et al. 2011, Li et al. 2018, Xu et al. 2020), even in instances where it was recognized that exposure involves linear and branched PFOA isomers (Xu et al. 2020). A similar situation exists for potential PFOA precursors that may be metabolized into PFOA *in vivo* (Vestergren et al. 2012). While the majority of epidemiology-based elimination half-life estimates did not account for the effect of branched PFOA isomers or PFOA precursors, it is unclear what effect this on the directionality or magnitude of the bias in the half-life estimates.

If a mixture of PFOA isomers is measured, with branched ones having faster clearance (shorter half-life), then an overall estimate for total PFOA is an amalgam that weighs the different isomers by their relative concentrations. Those relative concentrations change over time as the faster-eliminated ones diminish in body burden faster than the slower (linear) isomer. Most studies do not follow individual isomers and are

not clear about the mix of isomers entailed. Only Zhang et al. (2013) examined isomers separately and found the faster clearance of branched isomers by a factor of about 2. The lack of resolution (or even clear description) of how the isomer-mix potential is handled is a shortcoming that applies across virtually all the studies reviewed. Simple sensitivity analyses we conducted suggest that the bias introduced by failing to distinguish PFOA isomers may not be substantial, if indeed (as seems the case) the mixtures are dominated by the linear isomer and if [as Zhang et al. (2013) found] the intrinsic half-lives of the branched isomers are on the order of one-half the half-life of the linear isomer. This is not expected to be the case if the exposure mixture were enriched in branched PFOA isomers. Nonetheless, any application of the estimated half-life to a further analysis of PFOA risks needs to be aware that some bias is introduced by using a single number to address a mixture of isomers, with the nature and size of the bias depending on the mixture proportions and on the time elapsed to result in a relative enrichment of the body burden in longer-half-life isomers (as the shorter-half-life ones are more quickly cleared). This interacts with any considerations of different toxicity potential among PFOA isomers.

We Recommend Using a Range of Half-life Estimates Rather than Choosing a Single Study

Some studies estimate half-life by following declining body burden over time after the source of high exposure that produced a high burden has ceased. Other studies estimate urinary clearance by relating amounts in daily urine to that day's body burden as estimated from serum concentration. Each method has its needed assumptions and potential pitfalls. All are subject to bias. Since the needed assumptions and potential pitfalls are somewhat different across methods, the similarity of half-life estimates using different approaches adds robustness to the overall estimated range by showing that the roles of pitfalls and biases may be minor.

At this time, we recommend using a *range* of half-life estimates for PFOA in humans, since no single study is clearly superior. Again, the similarity across studies adds confidence that the overall understanding of half-life of PFOA in humans has not been skewed by a particular study-specific shortcoming or assumption. A range of 1-3 years seems appropriate, since studies with longer estimates are the ones that appear to suffer from a bias toward longer estimates arising from ongoing exposures during observed declines in serum levels (when such ongoing exposure is substantial compared to the body burden).

While one could pick a central point in the range to represent a "central" estimate, this should not be regarded as a statistical summary – that is, the range should not be regarded as a statistical confidence limit and the selected central estimate should not simply be a mean across studies. The reason for this stance is that studies differ not simply by sampling variability, but also because they have different sets of potential pitfalls and biases from a study design perspective. In addition, they often focus on specific subpopulations of subjects that might not be representative of the general human population (for different reasons and potentially different extents across studies) without a clear means to resolve which factors are important or how one might adjust for them.

Attention Should be Paid to How the Estimated Half-Life in Humans is to be Used

Humans evidently have a markedly longer half-life than animals, especially rodents. More thought is needed on how the factors that *cause* the especially long half-life among humans might affect how the resulting body burden relates to the available compound to cause toxic effects. That is, it may be that the very avidity of binding and renal reabsorption that makes for a long human half-life may sequester the compound away from sites of potential toxic effect. Naively equating body burden with internal dose may markedly overestimate potential toxicity in humans.

- Relating body burden to toxic effect (and the potential role of sequestering away from sites of toxicity noted above) depends on the understanding of the mode of action of the toxic effects of concern.

- Different uses of the half-life may raise different questions about how the human/rodent differences play out. Cross-species body burden adjustment may have different considerations than those needed for time-averaging variable human exposure, for instance.

The similarity of volumes of distribution across animal species suggests that PFOA concentrations at sites of toxic action may be related to body burden (and body burden differences across species can be allowed for by half-life adjustment), but our point is that this aspect needs to be thought through explicitly rather than simply assumed, and reasons for why the high sequestering in humans may not affect the utility of body burden as an internal dose measure need to be articulated.

Recommendations for Future Researchers

We recommend that researchers setting out to use human data to estimate PFOA half-life in humans or who are embarking on a new study to measure this parameter consider the following in their study designs:

- The need to analyze for and examine the various isomers (branched and linear) separately – including the need to be explicit about which isomers are measured and how they are distinguished. The same consideration is applicable to PFOA precursors.
- The need to ensure that ongoing exposures (i.e., site-related non-point source exposures and general population background exposures) in populations followed for body burden decline is estimated and accounted for in any analysis, with a preference for using populations with small such ongoing exposure vis-à-vis the body burdens being followed. Consumption of locally grown vegetables and food in areas with site-related environmental contamination has been an important factor to consider.
- Related to the above, the need to estimate intrinsic clearance or half-life (the rate in relation to body burden) rather than simple empirical rates of body burden decline (which can be biased by ongoing minor exposures).
- The need to consider how subpopulations might systematically differ in half-life, especially because of sex (and the influence of menstruation and childbirth) and age. Other factors, such as dietary fatty acid intake patterns (and the consequent need for avid uptake that also captures PFOA) should be considered if possible. How such factors bear on generalizing findings to a wider human population should be addressed.
- The need to consider whether there are further variations in half-life among individuals for reasons of diversity in physiology and diet, and how analyses can account for such a possibility (rather than assuming all variation is simply statistical sampling error).