Highlights of "The Dilemma of Perfluorooctanoate (PFOA) Human Half-life"

- PFOA half-life estimates vary widely among human observational studies. They cannot all be correct.
- Differences most likely due to varying degrees of unmeasured PFOA exposures among studies.
- PFOA half-life of ~1.5 years by Xu et al. (2020) appears to be most reliable estimate since background exposures were subtracted.
- Clinical study of Elcombe et al. (2013) was used to estimate PFOA half-life of ~200 day (~0.5 years).
- Thus, a range in the PFOA half-life appears to lie between 0.5 and 1.5 years.

The Dilemma of Perfluorooctanoate (PFOA) Human Half-life

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Abstract

Disparity in the results from human observational and clinical studies is not uncommon, but risk assessment efforts often judge one set of data more relevant with the loss of valuable information. The assessment for perfluorooctanoate **(**PFOA) is a good example of this problem. The estimation of its safe dose is disparate among government groups due in part to differences in understanding of its half-life in humans. These differences are due in part to incomplete information on sources of exposure in the human observational half-life studies, which have been routinely acknowledged, but until recently not well understood. Exposure information is thus critical in understanding, and possibly resolving, this disparity in PFOA safe dose, and potentially for disparities with similar chemistries when both human observational and clinical findings are available. We explore several hypotheses to explain this disparity in PFOA half-life from human observational studies in light of findings of a clinical study in humans and relevant exposure information from a recent international meeting of the Society of Toxicology and

Environmental Chemistry (SETAC). Based on information from both human observational studies and clinical data, we proposed a range for the half-life for PFOA of 0.5 to 1.5 years, which would likely raise many existing regulatory safe levels if all other parameters stayed the same.

Introduction

Perfluorooctanoate's (PFOA) toxicity is in the general range of 1 mg/kg-day [e.g., European Food Safety Authority (EFSA, 2020)]. Safe doses for PFOA can vary by up to 750-fold among government organizations by one estimate (Dourson et al., 2019; Mikkonen et al., 2020), or perhaps by over 200-fold by another estimate (COT, 2021).[1] These differences may be due in part to the different choices of critical effect and methods for extrapolation from experimental animal data to humans. Such extrapolation involves not only the relevance of the critical effect seen in experimental animals to humans, but also to the differences in the estimations of the half-life of PFOA.

Half-life estimates of PFOA in humans have been made in numerous observational studies. These estimates vary widely. Russell et al. (2015) and Bartell (2012) observed that many of these estimates may not have accounted for background or ongoing PFOA exposures, and that failing to do so could result in a larger than actual (or intrinsic) PFOA half-lives. In particular, Bartell (2012) predict that unaccounted background exposures that contribute 20% of the total exposure, result in a 50% error in the projected PFOA half-life after two half-lives have elapsed between

[1] In 2020, EFSA derived an intake of 0.63 ng/kg-d (TWI of 4.4 ng/kg) for the sum of PFOA, PFNA, PFHxS and PFOS. If this is applied to individual PFAS chemicals as well, then the range in estimated safe doses would be ~250. Or, if we take the contribution of PFOA/PFNA to the intake by the mother of 0.187 ng/kg-d, then the range in safe doses would be ~860.

the sampling time points. However, this 50% error in the PFOA half-life would be also found at unaccounted background exposures of between 5 and 10 % after five half-lives have elapsed between the sampling time points. Thus, small levels of unaccounted background exposures may have large impacts on half-life estimates and are important to consider.

So are some sources of PFOA exposure being missed? Dietary exposure is reported to be the dominant source of PFOA exposure when drinking water concentrations of PFOA are low, whereas when drinking water concentrations increase, this route becomes the predominant source of exposure (Gleason et al., 2017; Vestergren and Cousins, 2009). DeSilva et al. (2020) also noted that diet is likely an important route of exposure for many people in the general population, but acknowledged that few studies monitored other environmental media as important sources of exposure. Emmett et al. (2006) also showed multiple sources of PFOA in environmental media in a community residing near a production plant. Thus, estimates of half-life in human observational studies are likely to be uncertain, if multiple sources of exposure are not monitored. Other sources of uncertainty in these exposures include study design, temporal relationships among serum samples, lack of data on direct exposure to PFOA used in consumer products, concentrations of PFOA precursor compounds in environmental media, levels of PFOA in food, the choice of model to estimate the half-lives, and assumptions of steady state and volume of distribution (Lorber and Egeghy, 2011; Sunderland et al., 2019).

Adding to this mix of human observational studies is a lone clinical study by Elcombe et al. (2013) who administered PFOA to 42 adult humans, both male and female, in a phase 1, range-finding, clinical trial for cancer chemotherapy. Doses were given once weekly as an oral tablet

from 50 to 1200 mg for up to 6 weeks. Blood concentrations of PFOA over time were closely monitored, including a pre-dose measurement where PFOA was found in four individuals. Based on a limit of quantification of 5 ng/ml (0.012 uM) from Convertino et al. (2018), who also published on this clinical study, and using ½ of this limit for individuals without detectable baseline measurements, the average PFOA concentration before dosing in this group of patients was approximately 0.022 uM (~9 ug/L). Adequate kidney and liver function and physical integrity of the gastrointestinal tract were important criteria for acceptance of patients into the trial. Specific parameters measured can be found in the supplementary files of Convertino et al. (2018). The daily mg/kg-day doses were estimated by Dourson et al. (2019) as 0.1 to 2.3 mg/kg-day and approximated exposures in the experimental animal studies that caused toxicity. Nine individuals continued on this therapy after completion of this 6 week study.

The Elcombe et al. (2013) study is a patent application, and its data set is unique. To date it has not been used in the development of PFOA safe doses by any of the various government agencies, mainly because it did not show up in routine literature reviews, as demonstrated by the general lack of its citation. However, both Convertino et al. (2018) and Dourson et al. (2019) have published parts of these data. The former study was more related to the choice of critical effect. The latter study was more related to the development of a data-derived-extrapolation-factor between mice and humans. A third study is in progress (H. Clewell presentation at *ARA*, 2021).

The purpose of this research was to explore several hypotheses to explain the disparity in half-life estimates from human observational studies in light of findings of a clinical study in

humans by Elcombe et al. (2013) and relevant exposure information from a recent international meeting of the Society of Toxicology and Environmental Chemistry summarized by DeSilva et al. (2020).

Methods

A number of human observational studies estimating PFOA half-life were reviewed to ascertain whether background exposures were determinable. This list is not exhaustive but fairly reflects the field of studies used by regulatory authorities. The recent publications by DeSilva et al. (2020) and Emmett et al. (2006) were then analyzed in more detail, since both groups of investigators estimated sources of PFOA in different environmental media and in different populations. DeSilva et al. (2020) studied more the general population; Emmett et al. (2006) studied a contaminated community. We then analyzed sole clinical study on PFOA by Elcombe et al. (2013) for additional insights on its half-life. Findings from these human observational studies, exposure information, and the human clinical study were then compared.

Based on this comparison, we offer several hypotheses for the disparity in half-life estimates for PFOA among the human observational studies:

- First, the human observational half-life studies show PFOA half-life values that vary from a low of 1.2 years to a high of 14.9 years, but few studies were shown to monitor environmental media. Thus, these studies may have missed sources of exposure possibly resulting in an overestimation of the half-life, as suggested by Russell et al. (2015) and Bartell (2012).
- Second, although participants had good liver and kidney function, the Elcombe et al.

(2013) study participants were ill and may have had different kinetics when compared with healthy individuals resulting in more PFOA excretion or less PFOA resorption. Thus, any resulting half-life may be underestimated when compared with the human observational studies.

A third hypothesis is also possible, specifically that the kinetics in humans changes over time with the upregulation of transporter proteins in the kidney or carrier sites in the plasma, with the resulting development of a slower tertiary terminal half-life that is not observable in the shorter Elcombe et al study, but which approximates the generally larger half-life found in the longer-term human observational studies. We did not pursue this hypothesis, but may do so in future work.

Results

***Relevant Exposure Information*:**

As previously mentioned, dietary exposure has been identified as the major source of PFOA exposure in the general population (Vestergren et al., 2012; Gleason et al., 2017). Available data indicate that dietary intake estimates have been relatively constant between 1999 and 2010, ranging from 0.3 to 0.5 ng/kg-bw/day for PFOA (Vestergren et al., 2012). PFOA concentrations in ambient air and water in the communities surrounding contaminated sites have also been studied over time as described by Shin et al. (2011a, 2011b). These authors show that transport of PFAS in air was found to be faster than in soil and groundwater, and so for people living in areas with contaminated air, estimated inhalation exposure exceeded that via water ingestion in the early time period but was less than water ingestion afterwards. Perhaps surprisingly, PFAS has also been detected in cosmetic products; the estimated absorbed dose through dermal exposure is on the order of <0.006 --3.1 ng/kg/day, with the high end exceeding

dietary exposure in Sweden (Schultes et al., 2018).

Efforts have been made toward estimating total intakes of PFOA in humans. Applying a scenario-based approach that represented realistic situations where age- and gender-specific exposure occurs in the everyday life of consumers, Trudel et al. (2008) reported that consumers in North America and Europe are likely to experience ubiquitous and long-term uptake doses of PFOA in the range of 1 to 130 ng/kg-day. Vestergren and Cousins (2009) compiled estimated daily intakes of PFOA of male adults for populations of typical background exposure (with drinking water concentration of PFOA of 1.3 ng/L), elevated water concentrations (drinking water concentration of 40 ng/L), point sources of drinking water contamination (519 ng/L), and occupational exposure (indoor concentrations of 1 ug/m3). The estimated intakes for the male adults under these scenarios were 3.4, 4.1, 12.6 and 158 ng/kg-day. By combining exposure media concentrations with contact rates, an approach referred to as "forward-based", Fromme et al. (2009) estimated an average general adult population exposure to PFOA including all potential routes of 2.9 ng/kg-day, with an upper end estimate of 12.6 ng/kg-day, dominated by dietary exposure in western countries (in both Europe and North America). Using a similar model based on exposure media concentrations of PFOA and contact rates, Lorber and Egeghy (2011) reported the central tendency intake estimate for adults and children to be 70 and 26 ng/day, respectively. A market basket survey of a wide range of Canadian foods conducted by Tittlemeier et al. (2007) estimated the adult exposure to be 70 ng/day (or 1.1 ng/kg-day, assuming a 62 kg adult (Lorber and Egeghy, 2011). Exposure estimates reported in the literature include an average adult intake of PFOA of 10 ng/kg-day, with a high estimate of 20 ng/kg-day in a limited diet survey in the United Kingdom (Lorber and Egeghy, 2011); an intake of 31

ng/kg-day, described as the highest intake, based on dietary intakes of 21 food samples in Norway (Haug et al., 2011); average adult population intakes of 1.6 and 1.3 ng/kg-day for two different survey sample years in Australia (Thompson et al., 2010); a range of 0.044 to 3 ng/kg-day in North America (Gebbink et al., 2015); a range from 0.16 to 0.55 ng/kg-day for Finnish children at 10.5 years of age (Balk et al., 2019); a median intake of 0.28 ng/kg-day (range 0.072-1.81 ng/kg-day) in Norwegian adults (Poothong et al., 2020); and an estimate of 0.03 ng/kg-day for of Exposure (pg/kg Body Weight/Day) of Irish adults PFOA via non-dietary sources (i.e., air, dust, and drinking water combined) (Harrad et al., 2019).

In a recent publication, De Silva et al. (2020) compared environmental media as important sources of exposure to the general population. The authors showed that dietary exposure to PFAS have been reported in milk, meat, vegetables, fruits, and bread in the low ng/g range. In homogenized whole meals, a similar concentration range was reported, although the maximum concentration observed was 118 ng PFOA per gram of fresh food. They also found that diet was more important than indoor exposure on average, but that inhalation and dust ingestion dominated for some study participants, particularly in the people with the highest blood concentrations. In fact, some epidemiologic evidence suggests indoor exposure is important enough to be empirically associated with serum/blood levels and may be the dominant exposure route for some people.

As shown in Table 1, DeSilva et al. (2020) gives percentage estimates of the source contributions for PFOA in these different environmental media for the general population. It is clear from this information that sources of PFOA in the general population are diverse and no one environmental medium consistently dominates general human exposure. A similar pattern is

seen with other longer chain PFAS chemistries.

Other studies have looked at exposures in contaminated communities. For example, Emmett et al. (2006) also did a specific analysis of PFOA serum levels in residents near a fluoropolymer production facility by looking at the contributions from air, water and occupational exposures, personal and dietary habits, and relationships to age and gender. These authors stated:

> "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."

Emmett et al. (2006) further suggest that other sources of PFOA are possible. For example, on page 12 Emmett et al. (2006) state:

> "The reason for the higher serum PFOA levels in those aged 60 and above is not entirely clear, multivariate analysis shows the increased consumption of drinking water in this group does not fully explain the observed increase."

Finally, Emmett et al. (2006) show on page 23 a blood serum level of 374 ng/mL of PFOA in 20 humans without any tap water consumption (Table 5 of these investigators, first row). This group, without tap water consumption, actually had similar or slightly more serum PFOA than other groups who stated consumption of 1 to 2 tap water drinks per day. However, the serum PFOA estimates in people aged 60 and above in the Emmett et al. (2006) study account for only direct consumption of tap water as drinking water but do not account for potential exposure to PFAS in the tap water through cooking or consumption of other beverages (e.g., tea or coffee). Examples of other literature demonstrating similar findings include pharmacokinetic modeling to characterize PFOA (Lorber and Egeghy, 2011) and a review of the pathways of human exposure to PFAS (Sunderland, et al. 2019).

We have analyzed the findings of Emmett et al. (2006), specifically their Table 5, and show that a significant level of PFOA is coming from sources other than water, demonstrated in Figures 1, 2 and 3 below. For example, Figure 1 shows PFOA serum levels with tap water consumption, including no tap water consumption. Figure 2 shows an increase in PFOA serum levels with an increase in local meat consumption. Figure 3 shows an increase in PFOA serum levels with an increase in local vegetable consumption. While it certainly is possible that current tap water consumption does not reflect historical data, there is no question that drinking this contaminated water currently adds to the PFOA serum concentration as shown in Figure 1. In like fashion, there is no question that eating local vegetables, and perhaps local meats also add to the serum PFOA concentration as shown in Figures 2 and 3. Although the results in local vegetables might be due to cooking with contaminated water (the zero data point in Figure 3), local vegetables, likely cooked in the same water, are shown to add even more to the serum level of PFOA.

Human Observational Studies of PFOA Half Life

Based in part on these findings we then reviewed a selection of readily available human observational studies on the estimation of PFOA half-life as shown in Table 2 to determine whether such studies accounted for background or ongoing PFOA exposures as shown in Table 1. Studies in Table 2 are organized by year of publication, with most recent studies listed first. Estimates of PFOA half-life vary widely, with a low value of 1.2 years by Zhang et al. (2013) to a higher value of 14.9 years by Yeung et al. (2013a). Few studies accounted for sources of exposure in water, food, dust, air and household products. However and importantly, nearly all authors acknowledge the limitation of addressing other PFOA exposures in their

discussion sections suggesting that their estimated PFOA half-life might be smaller.

Both Bartell (2012) and Russell et al. (2015) caution against the estimation of PFOA half-life without a good sense of background exposures. In particular, Bartell (2012, Figure 1) show graphically that the actual PFOA half-life is 50% of the nominal value when unaccounted background exposures lie between 8% and 20% depending on the number of half-lives monitored. Thus, PFOA half-lives estimated from exposed populations would be more than twice as high as the actual PFOA half-lives, if unaccounted background exposures were even just 8% of the total exposure and the time between serum measurements was 5 half-lives.

Among studies in Table 2, only the recent study by Xu et al. (2020) directly accounted for the contribution of background PFOA exposure to the PFOA half-life by subtracting it out. Without background subtracted, the authors estimated half-life of PFOA of 1.77 years. With background subtracted out of the total exposure, the PFOA half-life was determined to be 1.48 years. Based on our review of these observational studies, the half-life of 1.48 years reported by Xu et al. (2020) appears to be the most appropriate value to consider in the development of safe PFOA doses, since it alone directly subtracted background exposures.[2] Of course, being a newly published study, few government authorities have had the chance to consider it in their evaluations of PFOA safe dose.

[2] All other studies incorporate unknown sources of PFOA exposure, including the Bartell et al. (2010) with a PFOA half-life value of 2.3 years that U.S. EPA (2016) used for deriving its RfD. However, Bartell et al. (2010) lowered their half-life estimate to 2.1 years when homegrown vegetable consumption was considered.

Human Clinical Findings:

To date, few specific kinetic data in humans have been available, necessitating the reliance of assumptions from the kinetic findings in experimental animals, for example in the estimation of the volume of distribution that is often used in part in determining a chemical's clearance, which is associated with its half-life. Fortunately, Elcombe et al. (2013) administered PFOA in single weekly doses for 6 weeks as a cancer chemotherapeutic agent in a phase 1 clinical trial to 42 patients.

Appendix Table 1 shows individual Cmax concentrations after the first dose in this clinical study. Initial volumes of distribution (Vd) from this administration varied between 3.5 to 12.7 liters, with an average value of 6.8 liters, or ~91 ml/kg, using an average body weight of 75 kg given by Convertino et al. (2018). Vd does not appear to be very dependent on the dose administered, with an R2 value of only 0.18, as shown in Appendix Figure 1. Overall, the average initial Vd appears to reflect the blood compartment plus a small volume of other readily available tissues.

Three patients received only one dose of PFOA during this 6-week study. Table 3 shows the results of the blood levels in these patients and figure 4 shows their timeline. It is obvious from these displays that the elimination of PFOA is biphasic in these three patients. After an initial rise to the Cmax, PFOA is eliminated in the first phase with a half-life estimated at about 6 hours (Figure 3, panel B). Afterwards, PFOA is eliminated much more slowly approximating a half-life of ~150 days (Figure 3, panel C) or ~200 days (Figure 3, panel D) depending on the choice of staring point of the presumed second phase. Importantly, PFOA concentrations on

which these latter estimates are made are in the range of the potential renal resorption limit of 12 to 24 uMoles based on an estimated renal transporter Km of 5 ug/ml from this clinical study (ARA, 2021).

Although these results are only in three patients, the first phase of 6 hour elimination is approximated when viewing the results from additional patients all of whom likewise got one dose in week one and whose blood PFOA levels were also monitored (although not as closely as in the first three patients). Table 4 shows the results in ten patients with a Cmax of 2 hours. Figure 5 shows their timeline. It is obvious from Table 4 and figure 5 that the elimination of PFOA is also biphasic in these ten patients. After an initial rise to the Cmax at 2 hours, PFOA is eliminated in the first phase with a half-life estimated at about 4.4 hours (panel B). Afterwards, PFOA is eliminated much more slowly. A *very* rough approximation of a half-life is 29 days focusing on only two time points, specifically 24 and 168 hours (panel C). However, this half-life is very likely underestimated, since eight of these ten patients had PFOA blood concentrations well in excess of the potential renal resorption limit of 12 to 24 uM. An estimation of this first phase is also possible from a different set of patients whose Cmax is at 3 hours. This estimation approximates 6 hours (data not shown, but available upon request).[3]

[3] An additional finding from this initial analysis of the Elcombe et al. (2013) clinical trial is that the kinetics appear to be dependent on the administered dose as shown in Table 4. Otherwise, 168-hour concentrations at higher administered doses would be much lower than that observed, because of the phase 1 half-life of approximately 6 hours. Thus, our initial thought that the second phase of PFOA elimination might be due to renal resorption up to a certain concentration, such as between 12 and 24 uM, as possibly shown in Figure 3, panels C or D, may need to be expanded. It may be that binding to plasma proteins, or the incorporation of PFOA into blood tissue membranes is occurring rather rapidly and it is this depot and its slow release that is also causing the lengthy second phase to PFOA's half-life.

The estimate of half-life of between ~140 to ~200 days is also not inconsistent with additional data from Elcombe et al. (2013, their Figure 78, e-page 72) in 9 patients given PFOA beyond 6 weeks. Here steady state appears to occur, arguably, somewhere between 12 and 36 weeks; the general rule of thumb for estimation of a half-life from a steady state value would place a half-life at about one fifth of this range, or ~2 to 7 weeks, or ~14 to 50 days. However, this latter estimate includes at least two phases of PFOA half-life in patients given higher doses, which results in blood concentrations much greater than the presumed renal resorption limit of 12-24 uMoles. Thus, a PFOA half-life derived from data in patients with the lowest dose, even though it is based on only a few in number, is likely to be a truer value from this clinical study, since their terminal PFOA concentrations are at or below the renal resorption limit of 12-24 uM.

While these variable half-life estimates are based on a human clinical trial, and therefore do not suffer from the use of assumptions based on experimental animals, they are nevertheless derived from very few cancer patients whose kinetic handling of PFOA may differ with the normal human population. Campbell et al. (2016) have also studied this population. Their estimate of the second phase half-life of PFOA is ~220 days. However, a more recent analysis of these data by these same investigators places the half-life at 1 to 2 years (*ARA*, 2021).

***Integration of Findings*:**

We review human observational literature on PFOA half-life; analyze the Elcombe et al. (2013) clinical study on PFOA for additional insights on its half-life; and then compare both sets of data through the lens of exposure information from a recent international meeting of SETAC.

Based on this analysis, we comment on two hypotheses for the disparity in half-life estimates for PFOA among the human observational studies and the clinical findings of Elcombe et al. (2013):

First, the human observational half-life studies from either general populations or populations living in contaminated areas show values that vary from a low of 1.2 years to a high of 14.9 years as shown in Table 2. Few studies monitored all environmental media as described by DeSilva et al. (2020) or suggested by Emmett et al. (2006) as important sources of exposure. Thus, these observational studies may have missed sources of exposure that would result in an overestimation of the half-life. See Bartell (2012) and Russell et al. (2015) for a theoretical basis of this hypothesis, and Tables 1 and 2, and Figures 1, 2, and 3 for supporting information.

Second, although participants had reportedly good liver and kidney function, the Elcombe et al. (2013) study participants were ill and may have had different kinetics when compared with healthy individuals; specifically, these individuals may have excreted PFOA more efficiently than healthy individuals, or bound it or resorbed it less efficiently, leading to a half-life that was less than the general population. Campbell et al. (2016) shows an average half-life at ~220 days, and Figure 3 of this text that shows a bi-phasic elimination and an estimated second-phase half-life of ~200 days from 3 patients given only one dose.

A third hypothesis, or speculation is possible. Specifically, the kinetics in humans may be tri-phasic, with a slower tertiary terminal half-life that is not observable in the Elcombe et al. (2013) study, but which approximates the longer half-life found in the human observational studies. One way to study this latter hypothesis would be to do a long-term clearance study in humans, where

PFAS exposures were rigorously avoided, and daily elimination of PFAS that is already part of the body burden was monitored. To our knowledge, such a clearance study has not been done.

As to the first hypothesis, Table 2 shows that many human observational studies, both to the general population and those contaminated with PFOA, did not monitor potential PFOA exposures in relevant environmental media. Coupled with the exposure findings of DeSilva et al. (2020) from the recent SETAC meeting and Emmett et al. (2006), the data collectively suggest that half-life estimates from many of these human observational studies are likely overestimated, consistent with the suggestion by Bartell (2012) and Russell et al. (2015). In particular, an unaccounted for 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. This is not to say that the original research in these studies was misguided. Rather it is that now our current measurement of PFOA and PFAS exposures has improved tremendously. This improvement allows a more thoughtful approach in the estimation of half-life estimate for PFOA based on human observational studies, since we now know that drinking water is not the sole source, and may not even have been the principal source of PFOA in human serum from some of these studies.

In this regards, the most recent study by Xu et al. (2020) appears to have developed a more thoughtful estimate of PFOA half-life by subtracting out background exposure, even though other sources of exposure to this worker population were not monitored. Their value of half-life with the background subtracted out was 1.48 years. Of all the studies we reviewed, this value of PFOA half-life appears to be the best one available to use for subsequent safe dose assessment,

361 even though its estimate maybe somewhat high since not all environmental media were
362 measured. In fact, EPA (2021) has recently used this study in its evaluation of another PFAS
363 chemistry, lending support to our choice of this study for the half-life of PFOA.[4]
364
365 As to the second hypothesis, the clinical human findings suggest a half-life of between 140 days
366 200 days in our analysis. Importantly, these estimates are based on PFOA concentrations that
367 appear to be at or below the limit of renal resorption of 12 to 24 uMoles or 5 to 10 ug/mL (*ARA*,
368 2021). Other estimates of 220 days (Campbell et al., 2016) or 1 to 2 years (H. Clewell
369 presentation at *ARA*, 2021) are found for this same study. The advantage of any of these
370 estimates is that the PFOA dose and subsequent blood concentrations were carefully monitored,
371 and the estimated daily doses were in the range showing toxicity in experimental animals. In
372 addition, the low dose patients clearly show a biphasic elimination, and the second phase appears
373 to be occurring at a concentration that is near or below the resorption limit of the kidney for
374 PFOA in humans.
375
376 However, these estimates are by no means conclusive of the expected half-life of PFOA. After
377 all, these individuals were not healthy and although patient entry into the clinical trial
378 necessitated good liver and kidney function, this is not a guarantee that the kinetics of PFOA
379 elimination would match those in the general population. Then again, the overall kinetics
380 appeared to be similar among individuals in this study, with some exceptions, and individuals
381 had different types of cancer. Moreover, an expectation might be that sick individuals would

[4] Quote from EPA (2021) "As such, the two data sets [for PFBS] will not be combined and the half-life estimated by Xu et al. (2020) is presumed to better predict human dosimetry at environmental levels. The average half-life reported by Xu et al. (2020) (mean: 43.8 days or 1,050 hours) was assigned for t½,H."

eliminate foreign chemicals like PFOA less efficiently and could potentially represent a sensitive subpopulation. If however the half-life estimates from this clinical study are to be believed when compared with the human observational studies, the opposite actually happened.

Health Canada (2018) also addressed the potential renal absorption limit. According this agency, PFOA kinetics are non-linear at high dose, similar to what we found in the clinical study by Elcombe et al. (2013). The non-linearity is hypothesized to be due to the saturation of organic ion transporters (OATs) responsible for renal reabsorption at high doses, resulting in a higher excretion rate at high doses than at low doses. With increasing dose, serum levels did not increase proportionally. However, at lower doses in some studies, serum levels increased proportionally, and steady state was reached more rapidly than expected at high doses with classical kinetics (4–5 half-lives). Citing Loveless et al. (2006) and Lou et al. (2009), Health Canada (2018) indicated that kinetics is consistent with linear first order processes at lower gavage doses closer to those relevant to human environmental exposures, and serum levels are proportional to administered dose. These findings are consistent with the second phase of PFOA elimination as shown in our Figure 3.

As to a potential third hypothesis, or speculation, at least two possibilities exist. First, it might be that low doses of PFOA over time result in an up-regulation of proteins that bind PFOA in plasma, or that make PFOA renal or biliary resorption more efficient. Either one of these would lead to a longer tertiary half-life. Alternatively, PFOA may be taken up into plasma membranes to such an extent that desorption time is lengthened. This possibility may be reasonable since PFOA is a linear fatty acid mimic that lies within the chain length of naturally occurring fatty

acids in plasma membranes, and since PFOA would not be able to participate in hydrogen-hydrogen binding, it would therefore be expected to desorb over time. In either of these two possibilities, the half-life would be increased from that seen in the clinical study and be more akin to that found in the human observational studies. We are not aware of other research into this hypothesis but it remains an interesting speculation and we encourage follow up by other investigators.

Conducting such an analysis as shown in this research is especially important in light of the large disparity in safe doses worldwide; differences from 200-fold and upwards exist. The reason for these disparities in government positions may be related to the expected difference in the underlying databases, or based on the assumption that the differences in PFOA half-life between experimental animals and humans can be worked into the assessment by some groups but not others.

Discussion

A conundrum exists in the PFOA half-life estimates for PFOA from readily available human observational studies, which show a range of 1.2 years to 14.9 years (Table 2). We explored 2 hypotheses for this conundrum using findings from a both a clinical study that gives estimates of PFOA half-life of 140 to 200 days (Figure 4), 220 days (Campbell et al., 2016) or 1 to 2 years (H. Clewell presentation at *ARA*, 2021), and from a review of recent findings from an international SETAC meeting published by DeSilva et al. (2020) and specific exposure information by Emmett et al. (2006). Both the human observational studies and the sole clinical study have advantages and difficulties. The observational studies include large populations from around the globe, including both general and contaminated populations, but generally do not

address all potential PFOA exposures, as the authors of these studies generally acknowledge. The clinical study is well conducted with numerous monitoring times, but is focused on a limited population of patients in various stages of cancer given generally a higher dose than what might be expected in a normal human population.

A preliminary version of this research was reviewed at the Alliance for Risk Assessment (*ARA*), Beyond Science and Decisions workshop XII held virtually on February 24 and 25, 2021.[5] Discussion on this topic was extensive and numerous suggestions were made for improvement (*ARA*, 2021), many of which have been incorporated into this manuscript. Uncertainties still remaining in this research include the fact that while many of the human observational studies are in the range of expected human exposures, several of these observational studies are conducted in worker populations that have higher than background exposures. Thus, differing estimates of half-life in these human observational studies shown in Table 2 may be the result of this disparity in the underlying exposures.

Uncertainties in the human clinical study by Elcombe et al. (2013) also exist. Doses given were at the high end of the human observational studies on occupational exposures and into the range of doses found to be toxic in experimental animal studies. Thus, differences in exposure between the human observational studies and this sole clinical study may add to the disconnect in half-life estimates between these two groups of data. Then again, PFOA safe dose assessment most often depends on extrapolation of results from experimental animal to humans, and comparisons of kinetic data between animals and humans is best done when doses are similar. In this regard, the clinical study may be more helpful than observational studies since the doses given in the clinical

[5] See: https://tera.org/Alliance%20for%20Risk/ARA_Dose-Response.htm.

study are in the range of the experimental animal toxicity.

Figure 3 clearly shows a biphasic elimination with a much slower elimination in the range of 12 uM to 24 uM (5 to 10 ug/mL) in three patients. This concentration coincides with, or is lower than, the level at which saturation of transporter may be occurring in humans (*ARA*, 2021). Specifically, the level of saturation of transporter in human blood/serum, as determined in the Elcombe et al. clinical study, is likely in the upper end of blood PFOA concentrations from occupational exposures, with a Km value of ~5 ug/mL (H. Clewell presentation at *ARA*, 2021).

Variability in the appropriate kinetic parameter in the human population, such as PFOA clearance, may be determinable from some of the human observational and clinical data, but this research does not currently address such variability. Importantly, it is the average kinetic parameter in humans, such as clearance, that is compared to the average kinetic parameter in experimental animals that forms the basis of the extrapolation from experimental animals to humans in any safe dose determination (IPCS, 2005; U.S. EPA, 2014). Thus, understanding this potential *human* variability, while important, cannot be a part of the *animal to human* extrapolation by definition, guidelines and practice.

Additional thought is needed in determining which of the various human observational studies are most appropriate for estimating PFOA half-life. Obviously, not all of the estimates in Table 2 can be correct, and nearly all investigators invoke ongoing and unmeasured PFOA exposures as one reason for these differences. At this point, the most reliable study appears to be Xu et al. (2020), although even here the authors state that not all PFOA exposures were likely

475 monitored. The corresponding PFOA half-life is 1.48 years. Conducting new human
476 observational studies would necessitate careful consideration of the potential multiple sources of
477 exposure, which we now know are available from recent work by DeSilva et al. (2020) and the
478 prior work of Emmett et al. (2006).
479
480 The sole human clinical study also gives a range of PFOA half-life estimates, either 140,
481 200, or 220 days, and possibly 1 to 2 years. The lower limits of this range are based on three
482 patients who only received one dose. The upper value is based on a PBPK analysis on all patients
483 that is currently being developed (H. Clewell presentation at *ARA*, 2021). The integration of
484 several lines of evidence to further study what appears to be disparate findings in human
485 observational and clinical studies is practical and applicable to other chemistries. Moreover, the
486 integration of clinical findings in humans with human observational studies is an important area
487 of effort regardless of the chemical or drug of concern. This research integrates three lines of
488 evidence and allows the exploration of two hypotheses to explain disparate result of PFOA half-
489 life in published human studies. It also suggests that additional research into the sources of
490 PFOA exposure, for example through a more careful review of published human observational
491 studies or *de novo* human studies with an emphasis on total PFOA exposures, may allow a better
492 integration of available information similar to that described by Emmett et al. (2006).
493
494 **Conclusion**
495 PFOA half-life estimates vary widely among human observational studies. They cannot
496 all be correct. Differences are most likely due to varying degrees of unmeasured PFOA
497 exposures among these studies as explained by Bartell (2012). The PFOA half-life of ~1.5 years
498 by Xu et al. (2020) appears to be the most reliable estimate since background exposures were

499 subtracted out, although these authors did not measure other potential sources of exposure either,
500 so this estimate is likely to be somewhat high. The clinical study of Elcombe et al. (2013) was
501 also used to estimate PFOA half-life. We determined values of ~150 to ~200 days (~0.5 years)
502 based on measurement in 3, admittedly sick, patients at levels at or below which saturation of
503 renal resorption might have been occurring. If not, then these estimates are likely to be somewhat
504 low. Thus, a range in the PFOA half-life appears to lie between 0.5 and 1.5 years, which would
505 likely raise existing regulatory safe levels. We encourage the continuation of this research by
506 other investigators.

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Figure Captions

Figure 1. PFOA concentration versus tap water; data from Emmett et al. (2006).

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

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

Figure 4. Average timeline of blood PFOA values in 3 patients administered only one dose of 50 mg/kg-day and followed for 6 weeks. Panel A is all data. Panel B is data for the first 6 hours and reflects the first phase of elimination. Panels C and D reflect time points after 6 hours and different estimates of the second phase of elimination. Shaded area reflects the presumed area of renal resorption saturation with a Km of 5ug/ml or 12 uM (see text). Note scale changes in x-

axis.

Figure 5. Timeline of averaged blood PFOA values in patients with various administered doses and a two-hour Cmax. Panel A is all data. Panel B is data for the first 4 hours and reflects the first phase of elimination. Panel C reflects time points after 4 hours and a different estimate of the second phase of elimination. See text. Note scale changes in x-axis.

Appendix Table 1. Cmax in patients after a single dose (Elcombe et al. (2013) and resulting initial Volume of Distribution (Vd).

Patient[a]	Dose (mg)	Single Dose (mg/kg)[b]	Single Dose Cmax (μM)	Volume of Distribution Vd (Liters)[c]
1	50	0.67	25.72	4.7
2	50	0.67	29.79	4.1
3	50	0.67	24.64	4.9
4	50	0.67	19.95	6.1
5	100	1.33	23.66	10.2
6	100	1.33	32.32	7.5
7	100	1.33	30.91	7.8
8	200	2.67	114.25	4.2
9	200	2.67	93.43	5.2
10	200	2.67	58.6	8.2
11	300	4.00	111.65	6.5
12	300	4.00	122.9	5.9
13	300	4.00	85.32	8.5
14	300	4.00	131.24	5.5
15	450	6.00	231.36	4.7
16	450	6.00	164.05	6.6
17	450	6.00	163.18	6.7
18	600	8.00	338.52	4.3
20	600	8.00	413.39	3.5
21	600	8.00	203.29	7.1
22	600	8.00	198.74	7.3
23	600	8.00	236.13	6.1
24	600	8.00	282.55	5.1

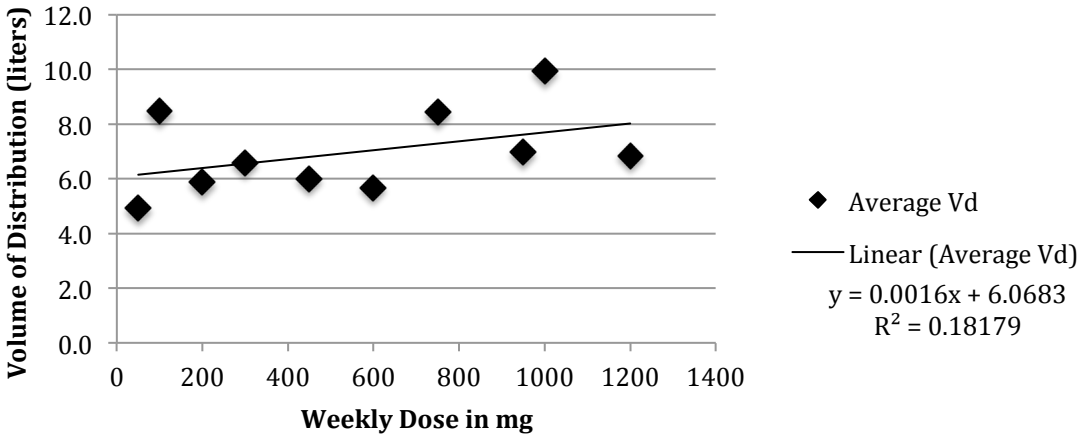
Patient[a]	Dose (mg)	Single Dose (mg/kg)[b]	Single Dose Cmax (μM)	Volume of Distribution Vd (Liters)[c]
25	600	8.00	230.00	6.3
26	750	10.00	200.07	9.1
27	750	10.00	240.51	7.5
28	750	10.00	206.86	8.8
29	950	12.67	352.58	6.5
30	950	12.67	332.61	6.9
31	950	12.67	347.52	6.6
32	950	12.67	291.69	7.9
33	1200	16.00	441.43	6.6
34	1200	16.00	559.64	5.2
35	1200	16.00	316.74	9.2
36	1200	16.00	708.42	4.1
37	1200	16.00	418.44	6.9
38	1200	16.00	314.43	9.2
40	1000	13.33	189.71	12.7
41	1000	13.33	232.54	10.4
42	1000	13.33	358.73	6.7
			Average	6.8

Information on patients 19 and 38 was not listed in Elcombe et al. (2013).

An average body weight of 75 kg was used as per Convertino et al. (2018).

Vd = Dose (mg) ÷ [Cmax (umoles) x 414 ug/umole/L ÷ 1000 ug/mg]

Appendix Figure 1. Average volume of distribution (Vd) in liters with weekly dose in mg (developed from Elcombe et al. (2013).



Figures

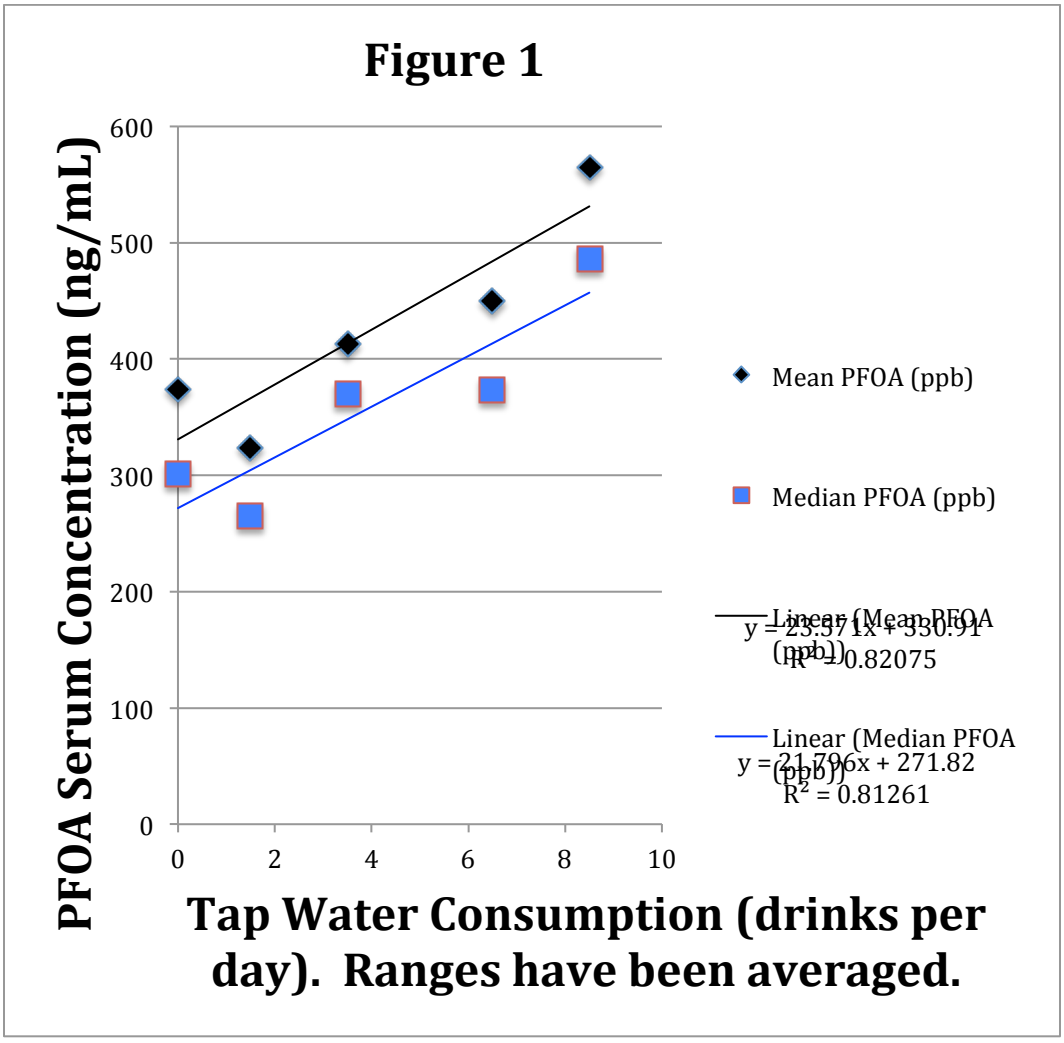


Figure 1
PFOA Serum Concentration (ng/mL)
600
500
400
300
200
100
0
0
2
4
6
8
10
Tap Water Consumption (drinks per day). Ranges have been averaged.
Mean PFOA (ppb)
Median PFOA (ppb)
Linear (Mean PFOA (ppb))
y = 23.371x + 330.91
R² = 0.82075
Linear (Median PFOA (ppb))
y = 21.796x + 271.82
R² = 0.81261

Figure 2

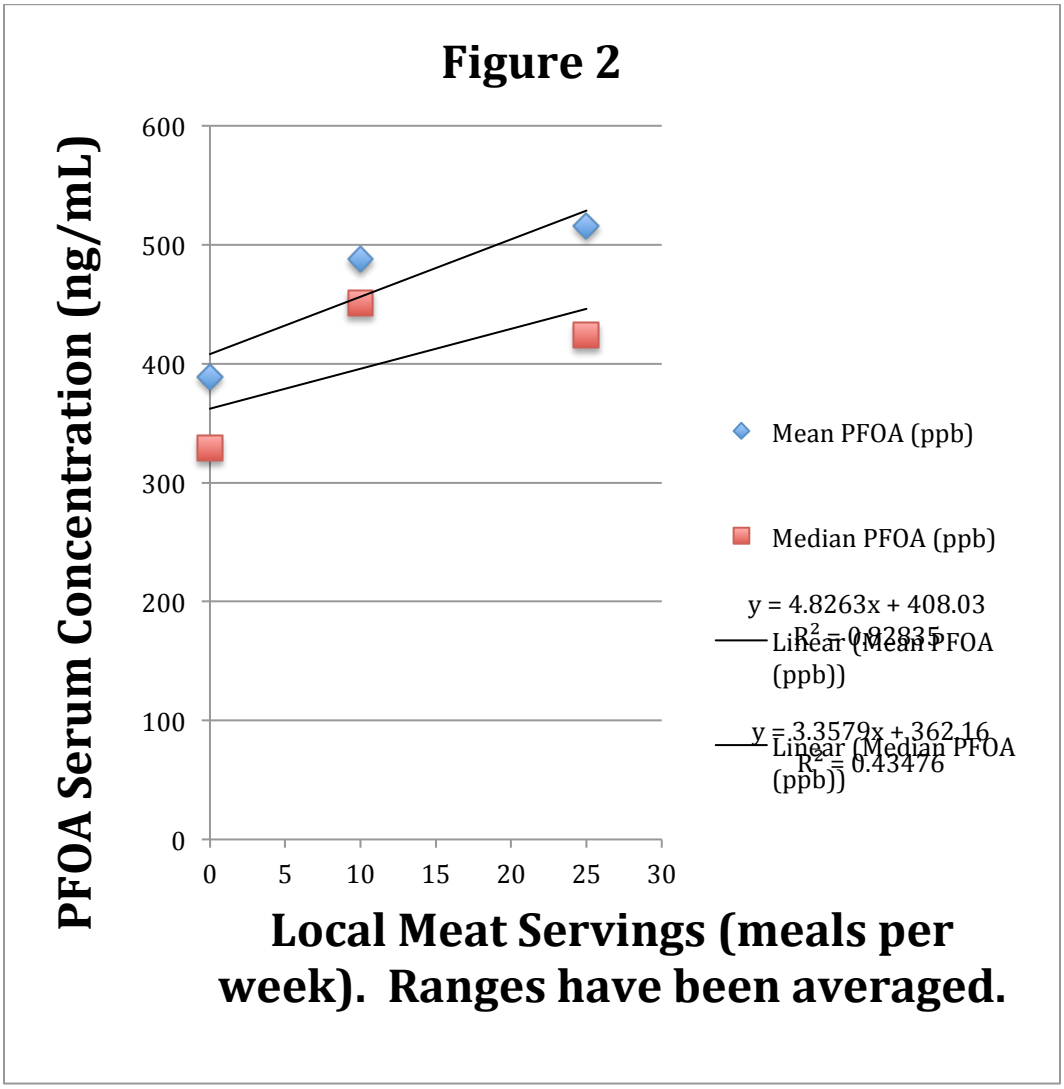

PFOA Serum Concentration (ng/mL)
600
500
400
300
200
100
0
0
5
10
15
20
25
30
Mean PFOA (ppb)
Median PFOA (ppb)
y = 4.8263x + 408.03
R² = 0.82835
Linear (Mean PFOA (ppb))
y = 3.3579x + 362.16
R² = 0.43476
Linear (Median PFOA (ppb))
Local Meat Servings (meals per week). Ranges have been averaged.

Figure 3

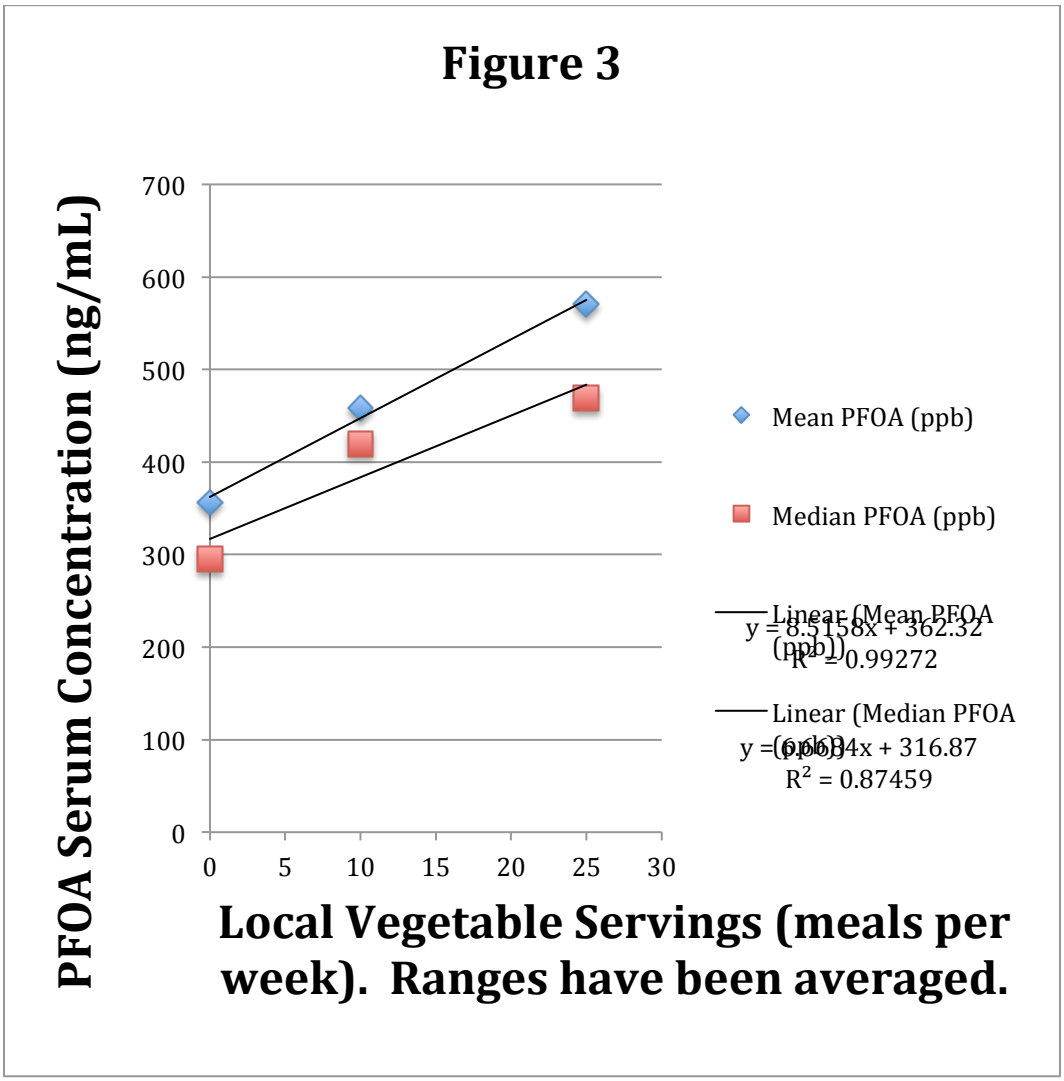

PFOA Serum Concentration (ng/mL)
700
600
500
400
300
200
100
0
0
5
10
15
20
25
30
Mean PFOA (ppb)
Median PFOA (ppb)
Linear (Mean PFOA (ppb))
y = 8.5158x + 362.32
R² = 0.99272
Linear (Median PFOA (ppb))
y = 6.6634x + 316.87
R² = 0.87459
Local Vegetable Servings (meals per week). Ranges have been averaged.

Figure 4

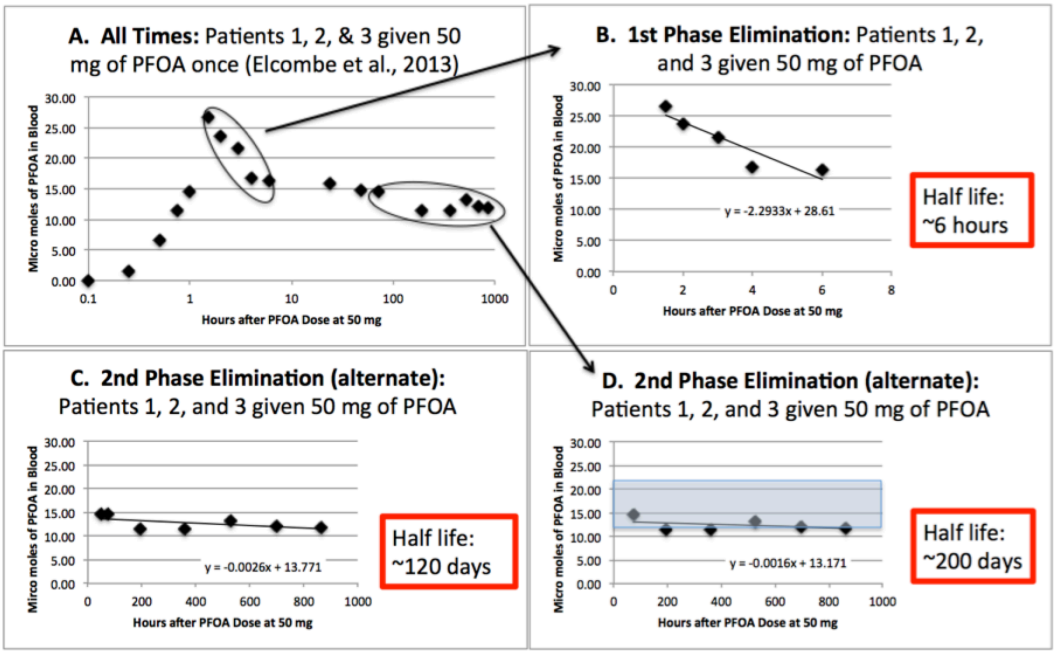
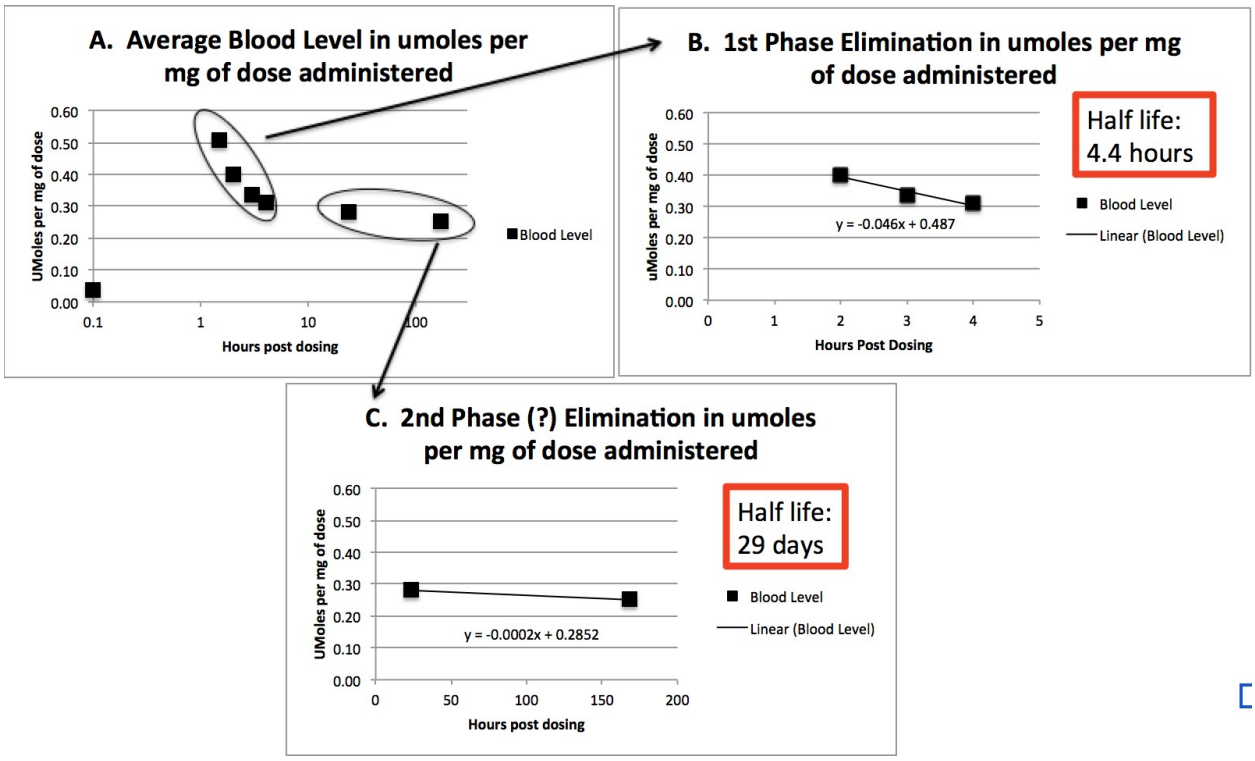

A. All Times: Patients 1, 2, & 3 given 50 mg of PFOA once (Elcombe et al., 2013)
Micro moles of PFOA in Blood
Hours after PFOA Dose at 50 mg
B. 1st Phase Elimination: Patients 1, 2, and 3 given 50 mg of PFOA
y = -2.2933x + 28.61
Half life: ~6 hours
C. 2nd Phase Elimination (alternate): Patients 1, 2, and 3 given 50 mg of PFOA
Mirco moles of PFOA in Blood
y = -0.0026x + 13.771
Half life: ~120 days
D. 2nd Phase Elimination (alternate): Patients 1, 2, and 3 given 50 mg of PFOA
y = -0.0016x + 13.171
Half life: ~200 days

Figure 5.


A. Average Blood Level in umoles per mg of dose administered
UMoles per mg of dose
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.1
1
10
100
Hours post dosing
Blood Level
B. 1st Phase Elimination in umoles per mg of dose administered
uMoles per mg of dose
y = -0.046x + 0.487
Half life: 4.4 hours
Blood Level
Linear (Blood Level)
0
1
2
3
4
5
Hours Post Dosing
C. 2nd Phase (?) Elimination in umoles per mg of dose administered
UMoles per mg of dose
y = -0.0002x + 0.2852
Half life: 29 days
Blood Level
Linear (Blood Level)
0
50
100
150
200
Hours post dosing

Tables

Table 1. Literature estimates of source contributions (%) to adult exposures to PFOA[a]

Exposure Medium (~% of total)				Human Exposure Estimates (ng/kg-day)	Location	Reference[b]
Diet	**Dust**	**Water**	**Consumer Goods**			
16	11	-	58	1-130	North America, EU	f
85	6	1	3	3.4	Germany, Japan	g
77	8	11	-	31	Norway	h
66	9	24	-	1	US	i
41	-	37	-	20.5-231	Korea	j
99	-	<1	-	12.06	China	k
47	8	12	-	0.044-3	North America	c
95	<2.5	-	-	0.16-55	Finland	e

89	3	-	-	Median: 0.28 (range 0.072-1.81)	Norway	d
91	-	3	-	0.03	Ireland	l

a) Adapted from DeSilva et al. (2020), as part of the Society for Toxicology and Environmental Chemistry (SETAC) Focused Topic Meeting on Environmental Risk Assessment of PFAS held in Durham, NC, USA August 12-15, 2019.

b) References as per DeSilva et al. (2020)

Table 2. Studies with PFOA half-life estimates (years), newest to oldest, and corresponding media monitoring. Environmental media categories are per DeSilva et al. (2020)

Study population	Half-life (years)	Media	Comments
Xu et al., 2020 Workers: airport employees in Sweden exposed to PFAS through airport's waterworks followed up monthly for 5 months; blood sampling between commenced within 11 to 14 d after the termination of contaminated drinking-water exposure. A corresponding background PFAS level observed in a reference population. Individuals exposed to PFOA-contaminated drinking water only at work and had a PFAS-free water supply at home.	One compartment, first-order elimination kinetics **AM 1.77 (95% CI 1.43, 2.31)** (with background exposure) **AM 1.48 (95% CI 1.19, 1.96)** (background exposure subtracted)	**Occupational**	1. A reference population without PFAS contamination in the municipal drinking water was used to represent Swedish general background. 2. Study acknowledges that PFAS with long half-lives, only 5 months is relatively short to estimate the half-life. 3. Half-life estimation can also be influenced by ongoing exposure, which could contribute to explaining the different half-lives reported in different studies. 4. In this study, the estimated half-life of PFOA was shortened after subtracting background level. This result is in line with the finding of Russell et al. (2015) that if the background exposure compared to the contaminated level is not small, then ignoring the background exposure will lead to an overestimation of half-life. 5. Study suggests shorter half-life than published estimates likely due to a possible time-dependent elimination process, with more rapid elimination in the first few months after the end of exposure. 6. Exposures from food, dust, air, and household products not accounted for, but study indicated that municipal water drinking water did not show

			elevated PFOA levels and thus, there was no longer ongoing drinking-water exposure at home as long as people had no other source of drinking water.
Pizzuro et al., 2019 Review of numerous literature	Mixed **2.3 – 8.5**[a]	N.R.	

Li et al., 2018 Community: 106 Swedes in Ronneby, Sweden, exposed to PFAS through contaminated municipal drinking water: 2-year follow-up time	Linear mixed-effect model **AM 2.7 (95% CI 2.5, 2.9)**	**Water**	1. Study assumed there was no additional PFAS exposure other than the background level of the control population. 2. Study excluded outliers that suggest ongoing exposure greater than the background of the control population. 3. Study notes that the variability between individuals, and between men and women, have not yet been adequately explained. 4. In this study, serum samples were analyzed during a 2-year period and each individual's samples were not analyzed in the same batch. All samples were however analyzed at the same laboratory with the same methods and work-up procedure. 5. Half-life was estimated in participants between 6 and 33 months after end of exposure to PFAS-contaminated drinking water. 6. Exposures in water, food, dust, air, and household products not accounted for but study assumed exposure levels in the general population from all sources were negligible.
Gomis et al. 2017 Population-based cross-sectional biomonitoring data from USA (NHANES, 1999-2013) and Australia (2003-2011)	Population-based pharmacokinetic modelling Men: USA **2.4;** Australia **2.1**	N.R.	1. The historical intake from cross-sectional biomonitoring data of PFOA estimated using a population-based (one-compartment) pharmacokinetic model. 2. Intrinsic elimination half-life was derived from model fitting for men and women. 3. Study noted that background human exposure was likely dominated historically by consumer product-related contaminated media.

	Women: USA **2.1;** Australia **1.8**		
Worley et al., 2017 Community: drinking water exposure to PFAS, following application of contaminated sewage sludge from a facility to agricultural fields (N=153); follow-up for six years	One-compartment pharmacokinetic model First and last sample **3.9**	N.R.	1. Study claimed the pharmacokinetic modeling approach accounted for ongoing exposure, and this allowed for greater confidence in the estimated half-life. 2. Population still had ongoing exposure to PFOA, and PK modeling approach based only on water intake was used to account for ongoing exposure. 3. Study suggested drinking water exposures likely the primary driver of PFOA serum concentrations in this community, based on ATSDR (2013) finding no relationship between a participant's proximity to agricultural fields that received contaminated sewage sludge and serum PFAS concentration. 4. An inclusion criterion was participants having no current or past occupational exposure to PFAS.
Fu et al., 2016 Occupational workers in a fluorochemical plant in China	First-order elimination **1.7** (GM by annual decline rate) **4.1**	**Occupational**	1. Study noted that the intrinsic half-life might be even shorter due to the high levels of ongoing exposure to PFOA. 2. Study noted that the huge difference between two estimated approaches indicated that there were other important elimination pathways of PFOA other than renal clearance in human. 3. Difference in the Cl_{renal} values of PFOA obtained from different sources suggest Cl_{renal} was not correlated with the PFOA body burden.

	(GM by daily clearance rate)		4. Study assumed no new inputs of PFAA in these workers although exposures in food, dust, air, and household products were not accounted for.
Gomis et al., 2016 Ski waxers: 4 men technicians occupationally exposed to ski wax; followed after marked reduction of occupational exposure	One-compartment pharmacokinetic model First and last sample **2.0 – 2.8** (mean **2.4**)	**Occupational**	1. Average reported as intrinsic (i.e., corrected for the ongoing exposure) elimination half-life. 2. Background exposure considered exposure from diet and drinks only. 3. Dermal exposure assumed negligible as dermal absorption has been shown to be minor.

Russell et al., 2015 Re-evaluation of two biomonitoring studies of the general population from Brede et al. (2010) and Bartell et al. 2010	**2.4**	**N.R.**	1. Value reported as intrinsic ("true") half-life, representing the average of independent estimates of 2.5 years (Brede et al., 2010) and 2.3 years ((Bartell et al., 2010). 2. Study notes that published literature does not explicitly account for ongoing exposure and that the rate of intrinsic elimination can be determined if the influence of ongoing exposure and changes in physiology (such as body weight) are accounted for. *3.* Study further notes that in many studies, rate of elimination is evaluated without considering the potential impact of any ongoing source of exposure, resulting in estimation of an apparent, instead of intrinsic, elimination half-life. If there is an ongoing exposure that is only reduced but not eliminated, this results in an apparent rate of elimination that is slower than the intrinsic rate of elimination. In this case, the apparent elimination half-life will always be longer than the intrinsic half-life.
Yeung et al., 2013a, 2013b General population: Population-based cross-sectional biomonitoring in two German cities 2000-2009	Halle: **8.2** Munster **14.9**	**N.R.**	1. Values are population halving times. 2. Study notes that half-life suggests an ongoing or additional exposure to PFOA or one of its precursor compounds, DiPAPs (polyfluoroalkyl phosphate diesters), known to metabolize rapidly to PFCA (perfluorocarboxylates).

Zhang et al., 2013 General population: healthy volunteers in Shijiazhuang (capital city) and Handan (industrial city), Hebei province, China N=86; Ages – females < 50 years (N=20) and all male and females > 50 years (N=66). One-time sample of serum and spot sample of urine	One-compartment model AM **2.3** GM **1.7** (young females, ≤50 years) AM 2.8 GM **1.2** (all males and older females)	**N.R.**	1. Study used volume of distribution (V) value of 170 mL/kg to estimate the half-life for PFOA. 2. Study notes that values should be considered as upper limit estimates of the biological half-life because the estimates ranged from 0.5 to 10 years in young females, and from 1.2 to years in males and older females. 3. Background or ongoing exposures or exposures from food, air, dust, and consumer products not discussed.
Bartell et al., 2012 Evaluated the potential bias from background exposures in recently published half-life estimates for PFOA: Bartell et al. (2010) (US residential cohort); Brede et al. (2010) (German	N.A.	**Water; Occupational**	1. Study investigated the magnitude of bias introduced by unaccounted background exposures, providing a simple closed-form equation that can be used in the study design and evaluation of published half-life estimates that do not account for background exposures. 2. Study noted that if the true half-life is 2.3 years, an approximate bias fraction of 1.6% was estimated for the occupational cohort, 2.7% for the US residential cohort, and 26% for men in the German residential cohort, because of lack of adjustment for background exposures. 3. Study noted that an unbiased estimate of the elimination rate and half-

residential cohort), and Olsen et al. (2007) (occupational cohort). These studies did not adjust for background exposures.			life can be obtained provided the background biomarker concentration is treated as a constant and is subtracted from all observed concentrations before log transformation and linear regression. 4. Inaccurately assuming background to be 0 can lead to substantial bias.
Seals et al., 2011 Community: 1,573 former residents in two water districts with higher and lower PFOA exposure levels	Multivariate linear regression Higher exposure level: **2.9** Lower exposure level: **8.5**	**Water**	1. Study notes that the cross-sectional nature of the analysis (that relies on model-based estimation of the initial concentrations instead of directly observed values) used in the estimation of half-life limits ability to draw inferences from the analysis. 2. Study assumes exposure was uniform within a water district, both between individuals and over time. 3. Study notes that excluding individuals with PFOA serum concentrations < 15 ng/mL are likely to have shorter half-lives on average than retained participants. 4. Study concludes that 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.

Bartell et al., 2010 200 Americans (172 public water drinkers and 28 bottled water drinkers); drinking water exposure to PFOA, follow-up after installation of charcoal filter. Repeated sampling, follow-up after 1 year	First order elimination Mixed models, 5 samples per person Median **2.3** (95% CI 2.1, 2.4)	**Water**	1. Study notes higher estimated half-life for homegrown vegetable consumers, indicative of an ongoing PFOA exposure that is artificially inflating the half-life estimates for those individuals. 2. Study indicated water systems remained contaminated with PFOA to some extent for days to weeks after filtration began, due to contaminated water already being present in storage tanks and in the distribution systems and that it may have taken weeks or months for the systems to become free of PFOA, during which time our participants may have continued to be exposed via drinking water, albeit at ever decreasing rates. 3. Study indicates that their half-life estimate depends on the additional assumption that ongoing PFOA exposures only contribute negligible amounts to current serum PFOA concentrations. 4. Study indicates nonnegligible post filtration exposures may have occurred among some of the participants because of homegrown/local produce consumption, PFOA contaminated water consumption at work or other locations, or other exposure pathways. 5. Study notes that ongoing exposures in one of the communities are minimal at present, except for local/homegrown produce consumption from contaminated soils. 6. Study indicates their mean half-life is heavily influenced by the 12-month serum PFOA measurements and should therefore be viewed as a preliminary estimate that will be improved by collection of later blood

			samples.

Brede et al., 2010 Community: 138 Germans residentially exposed community via drinking water contamination in Arnsberg (Germany); follow-up for 2 years after installation of charcoal filters	First order elimination First and last Sample (Linear multivariate regression analysis) GM **3.26** (range: 1.03 – 14.67)	**Water**	1. PFOA levels decreased in all study participants from Arnsberg; five residents in the reference areas had increasing PFOA concentrations. 2. PFOA intake refers only to the consumption of drinking water between October 2006 and October 2008; other sources are not considered; exact amount and duration of the PFOA contamination of the drinking water not known; PFOA exposure (via drinking water and other sources) after filter installation not estimated, so these factors were not considered in half-life calculations; PFOA background exposure of the study population not estimated. 3. Although five residents had increasing PFOA concentrations, authors suggest decline of PFOA concentrations in the reference groups may be due to a decrease of the PFOA background exposure. 4. Study also suggested that the influence of the background exposure may be greater in the study group from Arnsberg resulting in overestimated half-lives. 5. Study noted PFOA levels of the exposed population were uniform enough to result in stable half-life estimations. 6. Background exposure not adjusted (Russell et al., 2015).
Olsen et al., 2007 Occupational workers: 26 retired fluorochemical production workers (N=26, 44	First order elimination First and last sample AM **3.8** (95% CI 3.1,	**Occupational**	1. Study noted that it is unlikely that the potential for non-occupational exposures substantially distorted the elimination rates. 2. Study discussed other sources of exposure, but none was measured in households of participants.

males, 2 females); 5-year follow-up time. Repeated samplings with batch-wise analysis.	4.4) GM **3.5** (95% CI 3.0, 4.1)		

a: Most community studies report half-lives of 2-3 years. The 8.5-year value was derived from a study of retired workers who had been occupationally exposed to PFOA and may not accurately reflect half-life values in exposed communities.

AM – arithmetic mean; GM – geometric mean; 95% CI – 95% confidence interval; N.R. – not reported.

Table 3. Patients 1, 2, and 3 given one dose of PFOA at 50 mg and follow for 6 weeks (Elcombe et al., 2013)*

Time (hours)	Average Concentration (uMoles)	Patients		
		1	2	3
0.1	0.05	0.00	0.00	0.14
0.25	1.50	0.35	3.06	1.08
0.5	6.68	1.11	7.62	11.3
0.75	11.54	9.17	8.39	17.05
1	14.55	14.41	8.55	20.69
1.5	**26.72**	**25.72**	**29.79**	**24.64**
2	23.68	22.48	24.07	24.49
3	21.58	20.82	22.76	21.15
4	16.87	18.19	14.45	17.98
6	16.36	14.67	17.52	16.9
24	15.87	13.81	14.27	19.53
48	14.70	12.76	13.28	18.07
72	14.58	9.70	15.60	18.43
192	11.43	8.54	17.15	8.60
360	11.48	8.63	18.61	7.20
528	13.18	11.58	21.47	6.50
696	12.98	10.23	20.96	5.00

864	11.82	8.89	20.08	6.50

* Highlighted text is the Cmax

Table 4. Blood Level in uMoles per mg of dose in patients with a Cmax at 2 hours.

	Dose	Time of Blood Sample (hours)						
Patient	mg/person	0.1	1.5	2	3	4	24	168
1	50	0.006	0.51	0.45	0.42	0.36	0.28	0.17
2	50	0.006	0.52	0.48	0.46	0.29	0.29	0.34
3	50	0.14	0.49	0.49	0.42	0.36	0.39	0.17
4	50	0.10	-	0.40	0.34	0.39	0.29	0.26
6	100	0.21	-	0.32	0.27	0.25	0.28	0.26
7	100	0.006	-	0.31	0.29	0.19	0.17	0.12
8	200	0.006	-	0.57	0.51	0.41	0.35	0.32
9	200	0.006	-	0.47	0.31	0.36	0.32	0.30
14	300	0.006	-	0.44	0.40	0.33	0.34	0.27
18	600	0.006	-	0.56	0.47	0.41	0.36	0.30
28	750	0.006	-	0.28	0.23	0.21	0.21	0.21
32	950	0.006	-	0.31	0.20	0.24	0.17	0.20
33	1200	0.006	-	0.37	0.33	0.31	0.31	0.26
	Avg	0.04	0.51	0.40	0.33	0.31	0.28	0.25