Case Study Summary
Title: Comparing Human Observational Studies with Clinical Findings: The Half-life of Perfluorooctanoate (PFOA)

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1. **Provide a few sentences summarizing the method illustrated by the case study.**

   An approach is developed to compare human observational studies with clinical findings, using relevant exposure information from a recent international meeting of the Society of Toxicology and Environmental Chemistry (SETAC). Perfluorooctanoate (PFOA) is used as an example.

2. **Describe the problem formulation(s) the case study is designed to address. How is the method described in the case useful for addressing the problem formulation?**

   Overview: Disparity in the results from human observational and clinical studies is not uncommon. Unfortunately, current risk assessment efforts often emphasize judging one set of data as being more relevant than the other, often with the concomitant loss of valuable information. The safe dose assessment for PFOA is a good example of this problem. The estimation of safe doses for PFOA and related chemistries is disparate world wide due in part to differences in understanding of the half-life of these chemicals in humans (Mikkonen et al., 2020). These differences in half-life are likewise disparate, due in part to incomplete information on sources of exposure, which until recently were not well understood. Exposure information is thus critical in understanding, and possibly resolving, this conundrum in PFOA safe dose, and potentially for similar disparities with other chemistries when both human observational and clinical findings are available.

   Human Observational Studies:

   It has been reported that dietary exposure is the dominant source of PFOA exposure when drinking water concentrations of PFOA are low, whereas as drinking water concentrations increase, the ingestion of drinking water becomes the predominant source of exposure (Gleason et al., 2017; Vestergren and Cousins, 2009). In their recent publication, De Silva et al. (2020) reported that only few studies monitored environmental media as important sources of exposure. The authors also noted that diet is likely an important route of exposure for many people but acknowledged that the contribution of diet is difficult to estimate and thus uncertain. In an earlier publication, Russell et al, (2015b) also concluded that ignoring background exposure in PFOA half-life estimation would lead to an overestimation of the half-life. We reviewed PFOA half-life estimation studies published in the literature to determine whether such studies took into account background or ongoing PFOA. The studies in Table 1 are organized by year of publication, with most recent studies listed first. While some of the studies noted that background exposures were negligible and/or did not affect half-life estimates, others did not account for other sources of exposure (e.g., water, food, dust, air and household products).

Table 1. PFOA half-life studies and corresponding media monitoring, newest to oldest. Environmental media categories as per DeSilva et al. (2020).

Reference	Study Population	Model/Half-life (years)	Work	Diet	Dust	Water	PCP[b]	Comments
Xu et al., 2020	Airport employees exposed to PFAS through airport's waterworks followed up for 5 months; blood sampling between commenced within 11 to 14 d after the termination of contaminated drinking-water exposure. A corresponding background PFAS levels observed in a reference population	One compartment, first-order elimination kinetics **1.77** (with background exposure) **1.48** (background exposure subtracted)	**Yes**	**?**	**?**	**?**	**?**	**1.** Half-life estimation can also be influenced by ongoing exposure, which could contribute to explaining the different half-lives reported in different studies. **2.** 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. (2015b) 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. 4. Exposures in water, food, dust, air, and household products not accounted for.
Pizzuro et al., 2019	Review of numerous literature	Mixed **2.3 – 8.5**[a]	**?**	**?**	**?**	**?**	**?**	
Li et al., 2018	106 Swedes in Ronneby, Sweden, exposed to PFAS through contaminated	Linear mixed-effect model	**?**	**?**	**?**	**yes**	**?**	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

Reference	Study Population	Model/Half-life (years)	Work	Diet	Dust	Water	PCP[b]	Comments
	municipal drinking water: 2-year follow-up time	**2.7**						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.
Gormis 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**	**?**	**?**	**?**	**?**	**?**	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 derived from model fitting for men and women. 3. Diet is the major source of PFOA exposure in the general population (Vestergren et al., 2012), provided the exposure to contaminated drinking water is low (Gleason et al., 2017), with dietary intake estimates having been relatively constant between 1999 and 2010, ranging from 0.3 to 0.5

Reference	Study Population	Model/Half-life (years)	Work	Diet	Dust	Water	PCP[b]	Comments
		Australia **2.1** Women: USA **2.1** Australia **1.8**						ng/kg-bw/day for PFOA (Vestergren et al., 2012). 4. Background human exposure was likely dominated historically by consumer product-related contaminated media.
Worley et al., 2017	Residentially exposed community in the vicinity of Decatur, Alabama	One-compartment model **3.9**	**?**	**?**	**?**	**?**	**?**	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. 2. An inclusion criterion was participants having no current or past occupational exposure to PFAS.
Fu et al., 2016	Workers in a fluorochemical plant in China	First-order elimination	**Yes**	**?**	**?**	**?**	**?**	1. Study noted that the intrinsic half-life might be even shorter due to the high levels of ongoing exposure to PFAAs.

Reference	Study Population	Model/Half-life (years)	Work	Diet	Dust	Water	PCP[b]	Comments
		1.7 (GM by annual decline rate) **11.7** (GM by daily clearance rate)						2. Study noted that the huge difference between two estimated approaches indicated that there were other important elimination pathways of PFAAs 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 PFAA body burden. 6. Study assumed no new inputs of PFAA in these workers.
Gomis et al., 2016	4 men occupationally exposed ski wax technicians; followed after marked reduction of occupational exposure	One-compartment pharmacokinetic model First and last sample **2.0 – 2.8** (mean **2.4**)	**Yes**	**?**	**?**	**?**	**?**	1. Average reported as intrinsic (i.e., corrected for the ongoing exposure) elimination half-life. 3. 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., 2015b	Re-evaluation of two biomonitoring studies of the general population	**2.4**	**?**	**?**	**?**	**?**	**?**	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).

Reference	Study Population	Model/Half-life (years)	Work	Diet	Dust	Water	PCP[b]	Comments
	from Brede et al. (2010) and 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	Population-based cross-sectional biomonitoring in two German cities 2000-2009	Halle: **8.2** Munster **14.9**	**?**	**?**	**?**	**?**	**?**	1. Values are population halving times. 2. Study notes that half-life suggest an ongoing or additional exposure to PFOA or one of its precursor compounds, DiPAPs (polyfluoroalkyl phosphate diesters), known to metabolize rapidly to PFCA (perfluorocarboxylates).
Zhnag et al., 2013	86 healthy volunteers in Shijiazhuang (capital city) and Handan (industrial city), Hebei province, China	One-compartment model **2.3** (AM) **1.7** (GM)	**?**	**?**	**?**	**?**	**?**	1. Study used volume of distribution (V) values of 170 and 230 mL/kg to estimate the half-lives for all PFCAs and PFSAs, respectively. 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 ears in males and

Reference	Study Population	Model/Half-life (years)	Work	Diet	Dust	Water	PCP[b]	Comments
		(young females, ≤50 years) 2.8 (AM) **1.2** (GM) (all males and older females)						older females. 3. Exposures from other sources not discussed.
Seals et al., 2011	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**	**?**	**?**	?	**Yes**	**?**	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; drinking water	First order	**?**	**?**	?	**Yes**	**?**	1. Study notes higher estimated half-life for homegrown vegetable consumers, indicative of an

Reference	Study Population	Model/Half-life (years)	Work	Diet	Dust	Water	PCP[b]	Comments
	exposure to PFOA, follow-up after installation of charcoal filter. Repeated sampling, follow-up after 1 year	elimination Mixed models, 5 samples per Person Median **2.3** 95% CI 2.1-2.4						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. Exposure from other sources not accounted for.
Brede et al., 2010	138 Germans residentially exposed community via drinking water contamination in Arnsberg (Germany); follow – up 2 years after installation of charcoal filters	First order elimination First and last Sample (Linear multivariate regression analysis) **3.26** (GM)	**?**	**?**	?	**Yes**	**?**	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.

Reference	Study Population	Model/Half-life (years)	Work	Diet	Dust	Water	PCP[b]	Comments
		(1.03 – 14.67)						4. Authors also suggested that the influence of the background exposure may be greater in the study group from Arnsberg resulting in overestimated half-lives. 5. Authors 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	26 retired fluorochemical production workers; followed for 5 years. Repeated samplings with batch-wise analysis	First order elimination. First and last sample **3.8** (AM **3.5** (GM)	**Yes**	**?**	**?**	**?**	**?**	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.

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
b: Personal care products

***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 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 43 patients. Patients were in various stages of cancer, but had good liver and kidney function. Blood levels of PFOA were carefully monitored. A subset of these data was published by Convertino et al. (2018) and another subset of these data was published by Dourson et al. (2019).

Table 2 shows individual Cmax concentrations after the first dose in the study cohort. 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 dependent on the dose administered, with an R^2 value of only 0.18, as shown in Figure 1. Overall, the average Vd appears to reflect the blood compartment plus a small volume of other readily available tissues.

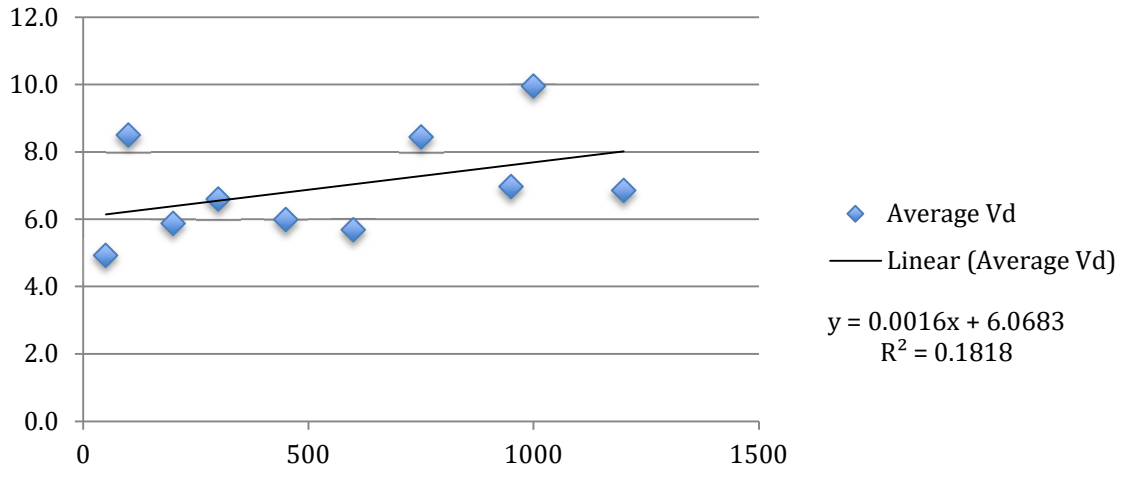
Table 2. Cmax in patients after a single dose (Elcombe et al. (2013) and resulting Volume of Distribution (Vd).

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
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

a) Information on patients 19 and 38 were not listed in Elcombe et al. (2013).
b) An average body weight of 75 kg was used as per Convertino et al. (2018).
c) Vd = Dose (mg) ÷ [Cmax (umoles) x 414 ug/umole/L ÷ 1000 ug/mg]

Figure 1. Average Volume of Distribution in Liters with Weekly Dose in mg (data from Elcombe et al. (2013).



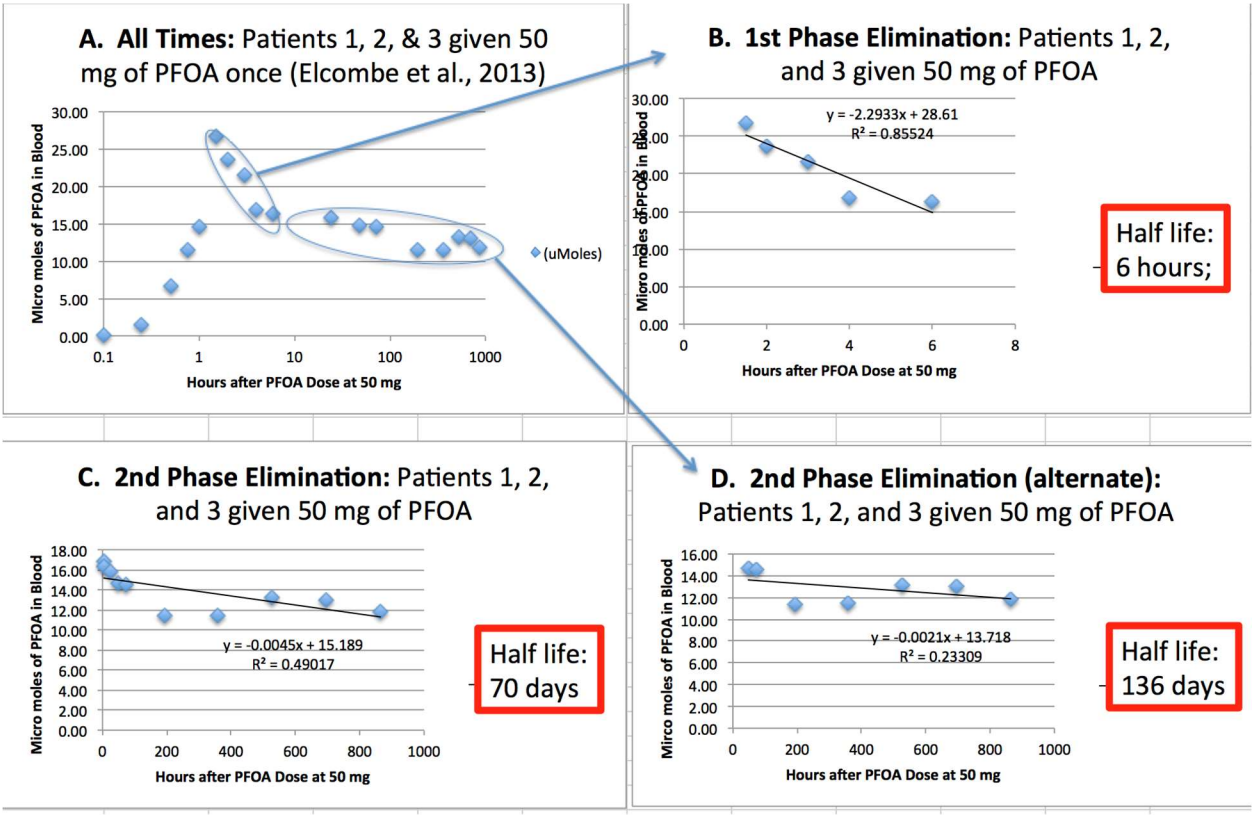
Three patients received only one dose of PFOA during this 6-week study. Table 3 shows the results of the blood levels in these patients and figure 2 shows their timeline. It is obvious from Table 3 and figure 2 that the elimination of PFOA is biphasic in these 3 patients. After an initial rise to the Cmax, PFOA is eliminated in the first phase with a half-life estimated at about 6 hours (panel B). Afterwards, PFOA is eliminated much more slowly approximating a half-life of 70 days (panel C) or ~140 days (panel D) depending on the choice of staring point of the presumed second phase.

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

Figure 2. Average Timeline of blood PFOA values in 3 patients administered only one dose of 50 mg



Although the results of Table 3 and Figure 2 are only in 3 patients, the first phase of 6 hour elimination is confirmed when viewing the results from the other patients who likewise got one dose in week one and whose blood PFOA levels were also monitored (although not as closely as in the first 3 patients). Table 4 shows the results in patients with a Cmax of 2 hours. Figure 3 shows their timeline. It is obvious from Table 4 and figure 3 that the elimination of PFOA is also biphasic in these 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 5 hours (panel C). Afterwards, PFOA is eliminated much more slowly. A *very* rough approximation of a half-life is 105 days focusing on only two data points at 4 and 24 hours (panel D). An estimation of this first phase is also possible from a different set of patients whose Cmax is at 3 hours. This estimation also approximates 6 hours (data not shown, but available upon request).

Moreover, while the results of Table 3 and Figure 2 are only in 3 patients, the estimate of half-life of between 70 to 140 days appears to be roughly consistent with additional data from Elcombe et al. (2013, 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.

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 markedly 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.

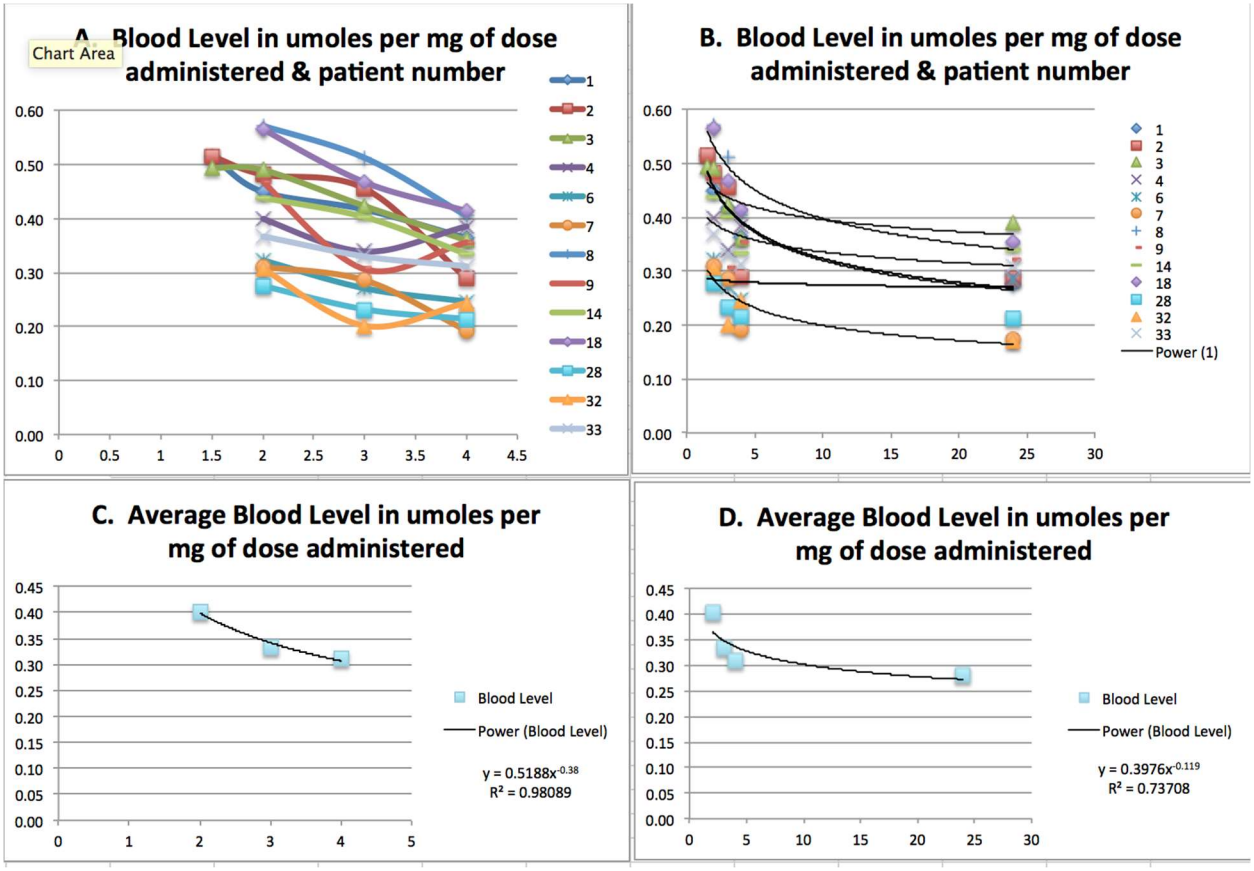
An additional finding from this initial analysis of the Elcombe et al. (2013) clinical trial is that the kinetics appear to be independent of the administered dose. Thus, our initial thought that the second phase of PFOA elimination might be due to renal resorption up to a certain concentration (as what might be expected from figure 2, panels C or D, is not confirmed in Table 4 or Figure 3, panels B and D, or perhaps renal resorption is not a primary reason for this slower second phase. Otherwise, 24-hour concentrations at higher administered doses would be much lower than that observed. It may be that binding to plasma proteins, or inculcation of PFOA into blood tissue membranes is occurring rather rapidly and it is this depot and its slow release that is causing the lengthy second phase to PFOA's half-life,

Table 4. Blood Level in umoles per patient with a Cmax at 2 hours*

Dose	Time of Blood Sample (hours)					
mg/person	0	1.5	2	3	4	24
50	0	25.72	22.48	20.82	18.19	13.81
50	0	25.79	24.07	22.76	14.45	14.27
50	0.14	24.64	24.49	21.15	17.98	19.53
50	0.1	-	19.95	16.94	19.26	14.39
100	0.21	-	32.32	27.07	24.62	28.18
100	0	-	30.91	28.55	19.26	17.29
200	0	-	114.25	102.46	81.02	70.37
200	0	-	93.43	61.21	71.13	64.58
300	0	-	131.24	120.77	100.33	101.72
600	0	-	338.52	280.28	248.26	213.23
750	0	-	206.86	173.85	160.39	159.66
950	0	-	291.69	191.19	231.38	160.6
1200	0	-	441.43	395.64	373.92	371.41

* Shaded areas were used to estimate the phase 1 half-life

Figure 3. Time line of averaged blood PFOA values in patients with various administered doses and a two-hour Cmax.



***Relevant Exposure Information*:**

As summarized nicely by DeSilva et al. (2020), dietary exposure to PFAS when detected 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. While diet is likely an important route of exposure for many people, it is difficult to estimate and thus uncertain.

However, DeSilva et al. (2020) also found that diet was more important than indoor exposure on average but that inhalation and dust ingestion dominated for some study participants, particularly 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.

PFOA concentrations in ambient air and water in the communities surrounding contaminated sites has been studied over time as describe 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).

As shown in Table 5 DeSilva et al. (2020) gives percentage estimates of the source contributions for PFOA in these different environmental media. It is clear from this information that sources of PFOA are diverse and no one environmental medium consistently dominates human exposure. A similar pattern is seen with other longer chain PFAS chemistries.

Table 5. Literature estimates of source contributions (%) to adult exposures to PFOA[a]

Exposure Medium (~% of total)				Location	Reference[b]
Diet	Dust	Water	Consumer Goods		
16	11	-	58	North America, EU	f
85	6	1	3	Germany Japan	g
77	8	11	-	Norway	h
66	9	24	-	US	i
41	-	37	-	Korea	j
99	-	<1	-	China	k
47	8	12	-	North America	c
95	<2.5	-	-	Finland	e
89	3	-	-	Norway	d
91	-	3	-	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)

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, first row). This group, without tap water consumption, actually had more serum PFOA than other groups who stated consumption of 1 to 2 tap water drinks per day.

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 4, 5 and 6. For example, Figure 4 shows PFOA serum levels with tap water consumption, including no tap water consumption. Figure 5 shows an increase in PFOA serum levels with an increase in local meat consumption. Figure 6 shows an increase in PFOA serum levels with an increase in local vegetable consumption.

Figure 4. PFOA concentration versus tap water.

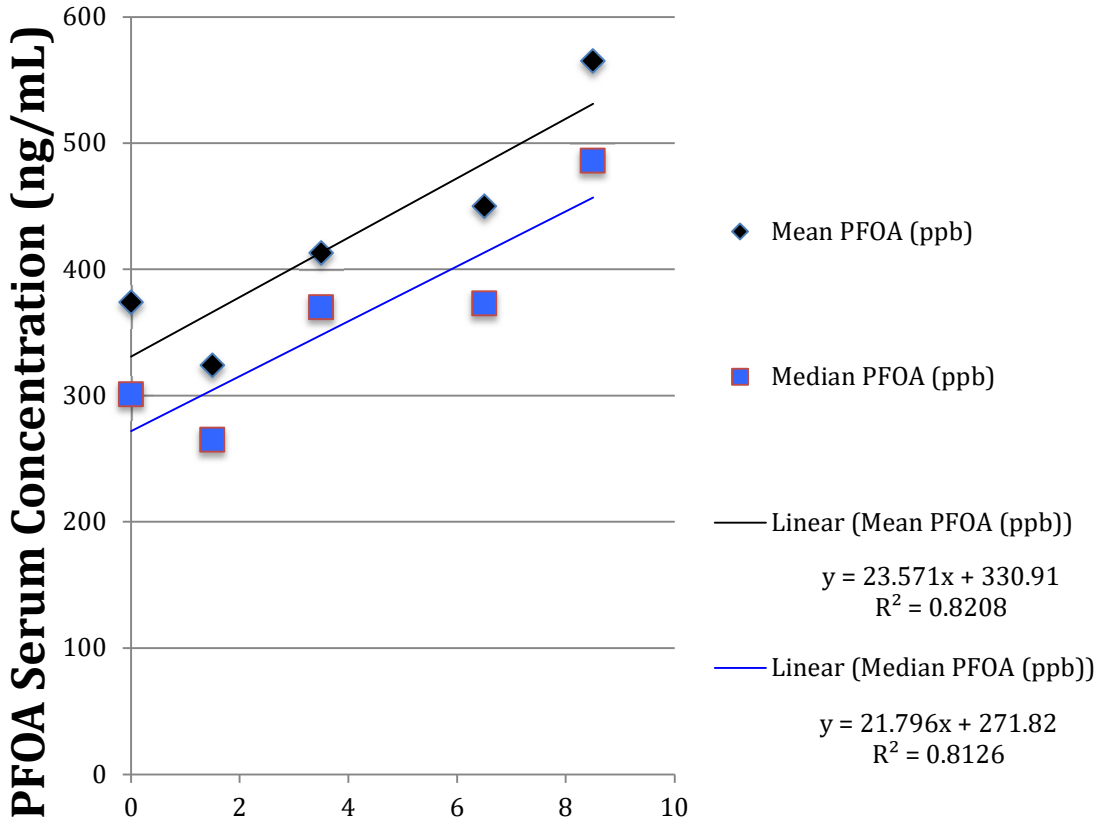


Figure 5. PFOA concentration versus local meat.

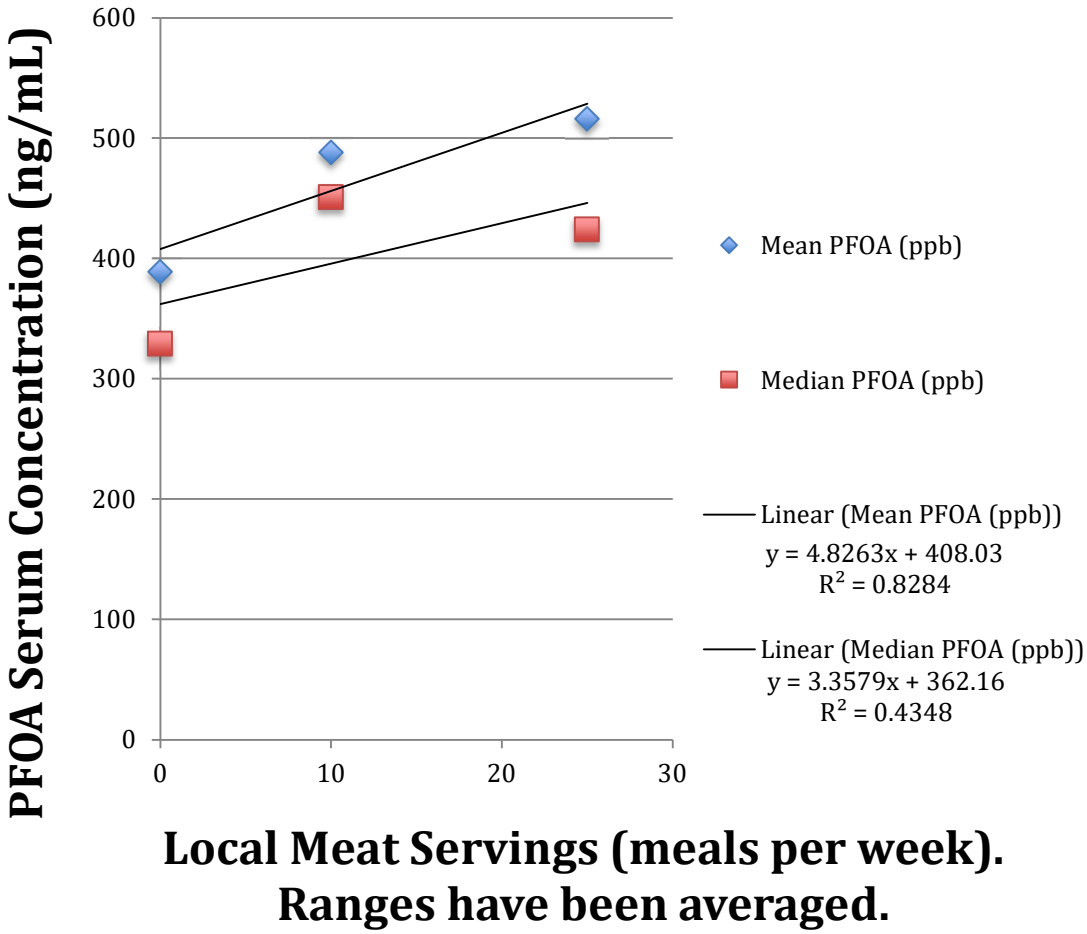
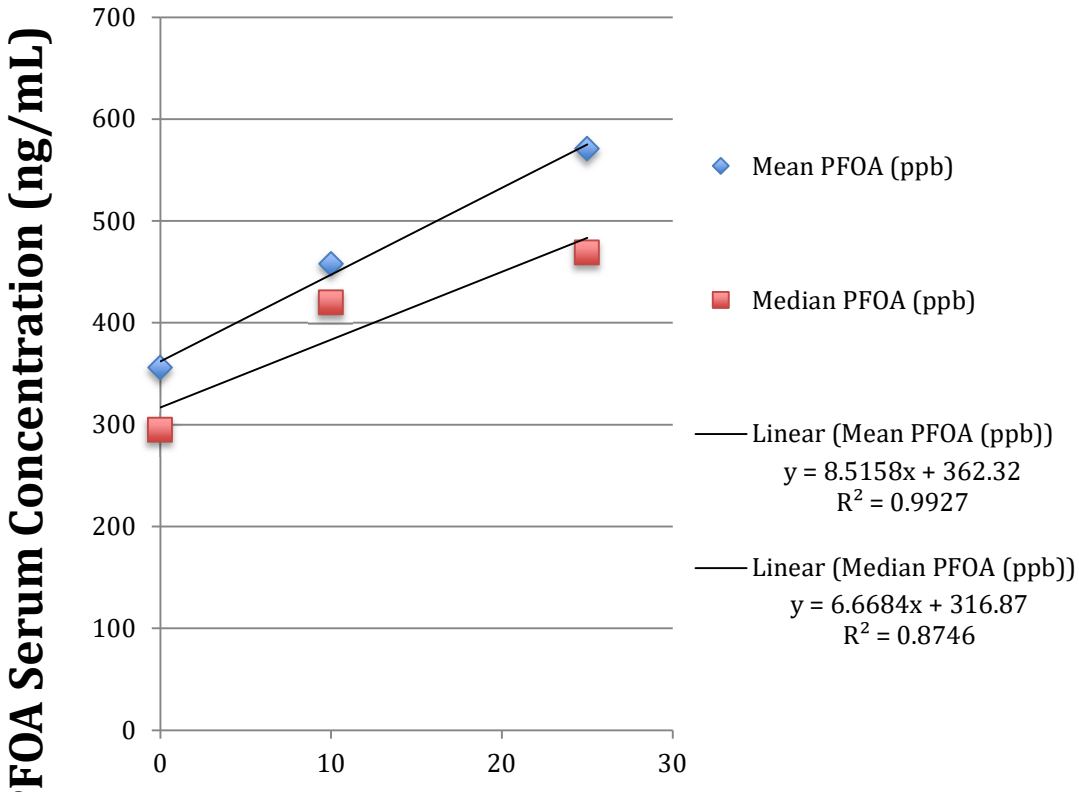


Figure 6. PFOA concentration versus local vegetables.



***Integration*:**

This is a preliminary research case study where 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 offer and comment on three hypotheses for the disparity in half-life estimates for PFOA between the human observational studies and the clinical findings of Elcombe et al. (2013):

- First, the human observational half-life studies show values that vary from a low of 1.2 years to a high of 14.9 years as shown in Table 1. Few studies monitored environmental media as described by DeSilva et al. (2020) as important sources of exposure. Thus, these observational studies may have missed sources of exposure possibly resulting in an overestimation of the half-life. See Russell et al. (2015) for a theoretical basis of this hypothesis, and Tables 1 and 5, and Figures 4, 5, and 6 for supporting information.

- 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; 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 significantly less than the general population. See Figure 4 of Campbell et al. (2016) that shows an average half-life at 0.6 years, and Figure 2 of this text that shows a bi-phasic elimination and an estimated second-phase half-life of ~140 days (0.4 years) from 3 patients given only one dose.
- Third, the kinetics in humans may be tri-phasic, with a slower tertiary terminal half-life that is not observable in the Elcombe et al 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 1 shows that many human observational studies 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 these human observational studies are likely overestimated, consistent with the suggestion by Russell et al. (2015). This is not to say that the original research was misguided. Rather it is that our current understanding of PFOA and PFAS chemistries has improved tremendously. We now have information that 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 be the principal source of PFOA in human serum from these studies.

As to the second hypothesis, the clinical human findings are suggestive, but by no means conclusive of the expected half-life of PFOA in humans. After all, these were sick individuals and although entry into the clinical trial necessitated good liver and kidney function, this is not a guarantee of similar kinetics in the general population. Then again, the overall kinetics appeared to be similar among these individuals, with some exceptions, and individuals had different types of cancers. Moreover, the expectation might be that sick individuals would eliminate foreign chemicals like PFOA less efficiently and could potentially represent a sensitive subpopulation. However, if the half-life estimates from this clinical study are to be believed, then the opposite actually happened.

As to the third hypothesis, at least two possibilities exist. First, it might be that low doses of PFOA over time result in an up-regulation of proteins that make plasma binding, or renal or biliary resorption more efficient. Either one of these possibilities would lead to a longer tertiary half-life. Alternatively, PFOA may inculcate to 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. Importantly, PFOA would not be able to participate in hydrogen-hydrogen binding and 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.

Conducting such an analysis is especially important in light of the large disparity in safe doses worldwide, for example, between the EPA and ATSDR positions and that of the Committee on Toxicology (2009), the United Kingdom's top advisory body. For example, a comparable PFOA drinking water level by the COT (2009) would be about 10,000 ppt using the same assumptions as EPA (2016) [UK PFOA TDI of 1.5 µg/kg bw-day x 70 kg bw x 0.2 RSC ÷ 2 L/day ~ 10 µg/L or 10,000 ppt]. The reason for this disparity in government positions appears to be the assumption that the differences in AUCs between experimental animals and humans can be worked into the assessment by ATSDR (2018) and EPA (2016), where the COT (2009) does not consider this difference to be scientifically justified, based in part, on the determination of the PFOA half-life in the US on the basis of water-only consumption.

3. **Comment on whether the method is general enough to be used directly, or if it can be extrapolated, for application to other chemicals and/or problem formulations. Please explain why or why not.**

   The integration of clinical findings in humans with human observational studies is an important area of effort regardless of the chemical or drug of concern.

4. **Discuss the overall strengths and weaknesses of the method.**

   This method integrates three lines of evidence and allows the development of different hypotheses to explain disparate result in published human studies. It also suggests research that may allow a better integration of available information. This method is preliminary and would benefit from additional research, study and deliberation.

5. **Outline the minimum data requirements and describe the types of data sets that are needed.**

   This preliminary case study would benefit from additional data on measured human exposures from different environmental media. These data could be developed from a more careful review of published human observational studies, or *de novo* human studies with an emphasis on total PFOA exposures, similar to that described by Emmett et al. (2006). A PFOA clearance study in normal human subjects PFOA without any intake, or any appreciable but measured intake, would also be beneficial. If the estimated half-life of PFOA described in either Figure 2 of this case study or by Campbell et al. (2016) is approximately correct, then such a clearance study should be able to estimate results after about 14 weeks.

Does your case study:

A. Describe the dose-response relationship in the dose range relevant to human exposure?

Many of the human observational studies are in the range of expected human exposures. However, several of these observational studies are conducted in worker populations that have higher than background exposures. The human clinical study has exposures at the high end of these occupational exposures and into the range of doses found in experimental animal studies.

B. Address human variability and sensitive populations?

Variability in the appropriate kinetic parameter in the human population, such as PFOA clearance, may be possible from some of the human observational and clinical data, but this research case study does not currently address this 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 kinetic extrapolation from experimental animals to humans.

C. Address background exposures or responses?

This research case study directly addresses background exposures. Additional information in this area would be welcome.

D. Address incorporation of existing biological understanding of the likely mode of action?

The mode of action for PFOA and related compounds is still debated. However, as a fatty acid mimic (Elcombe et al., 2013), and essentially inert, PFOA may act through a simple bimolecular interaction in cell membranes, such as receptor binding and inhibition of enzymes. If so, then the appropriate default position for dosimetric adjustment might be more related to Cmax (IPCS 2005, page 39).

E. Address other extrapolations, if relevant – insufficient data, including duration extrapolations, interspecies extrapolation?

The conundrum described here lies in different estimates of PFOA half-life between human observational studies that purport to demonstrate a longer value and the sole human clinical study that appears to show a shorter value. The half-life from the observational studies varies from about 1 to 14 years. The clinical study gives estimates of 140 to 220 days. Both sets of information have advantages and difficulties. The observational studies include large populations from around the globe, but generally do not address all potential PFOA exposures; the clinical study is well conducted with numerous monitoring times, but is conducted in a limited population of sick individuals.

F. Address uncertainty?

Numerous uncertainties are described. Additional work is needed in determining additional exposures from the published human observational studies, or conducting new work with careful consideration of the multiple sources of exposure. Additional review and analysis of the sole human clinical study would be valuable; such a study is currently being conducted (Clewell, personal communication). A clearance study could also be conducted in a normal human population.

G. Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?

This preliminary case study does not estimate the probability of response.

H. Work practically? If the method still requires development, how close is it to practical implementation?

The integration of several lines of evidence to further study what appears to be disparate findings in human observational and clinical studies is practical and applicable to other chemistries.

References

Agency for Toxic Substances and Disease Registry (ATSDR). Exposure Investigation Report - Perfluorochemical Serum Sampling in the Vicinity of Decatur, AL, Morgan, Lawrence, and Limestone Counties. Division of Community Health Investigation; 2013. https://www.atsdr.cdc.gov/hac/pha/Decatur/Perfluorochemical_Serum%20Sampling.pdf

Antti T. Mikkonen, Jennifer Martin, Michael L. Dourson, Andrea Hinwood, Mark S. Johnson. 2020. Suggestions for Improving the Characterisation of Risk from Exposures to Per and Polyfluorinated Alkyl Substances (PFAS). Environmental Toxicology and Chemistry 2021;01:1-16. https://doi.org/10.1002/etc.4931.

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

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

Campbell, J., B. Allen, G. Olsen, C. Elcombe, E. Doyle, J. Evans, H. Clewell. 2016. Evaluation of the Short-term Clearance of Perflourooctanoic Acid (PFOA) in a Clinical Trial Using a PBPK Model and Markov Chain Monte Carlo Analysis. Poster at the Society of Toxicology Annual Meeting.

Convertino, M., Church, T.R., Olsen, G.W., Liu, Y., Doyle, E., Elcombe, C.R., Barnett, A.L., Samuel, L.M., MacPherson, I.R., Evans, T.R., 2018. Stochastic pharmacokinetic-pharmacodynamic modeling for assessing the systemic health risk of perfluorooctanoate (PFOA). Toxicol. Sci. 163 (1), 293–306

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

Dourson, Michael L., Bernard Gadagbui, Chijioke Onyema, Patricia M. McGinnis, Raymond G. York. 2019. Data derived Extrapolation Factors for developmental toxicity: A preliminary research case study with perfluorooctanoate (PFOA). Regulatory Toxicology and Pharmacology. 108: 104446.

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

Gleason, J.A., Cooper, K.R., Klotz, J.B., Post, G.B., Van Orden, G., 2017. Health-based Maximum Contaminant Level Support Document: Perfluorooctanoic Acid (PFOA) - Appendix A. New Jersey Drinking Water Quality Institute, Health Effects Subcommittee. Cited in Gormis et al. (2017).

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

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

IPCS (International Programme on Chemical Safety), 2005. Chemical-specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/concentration-Response Assessment. Geneva Switzerland. https://apps.who.int/iris/bitstream/handle/10665/43294/9241546786_eng.pdf;jsessionid=B768CD63C4F93BC4F2388483532665D6?sequence=1.

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

Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, et al. 2007. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and

perfluorooctanoate in retired fluorochemical production workers. Environ Health Perspect 115(9):1298–1305, PMID: 17805419, https://doi.org/10.1289/ehp.10009.

Olsen GW, Chang SC, Noker PE, Gorman GS, Ehresman DJ, Lieder PH, et al. 2009. A comparison of the pharmacokinetics of perfluorobutanesulfonate (PFBS) in rats, monkeys, and humans. Toxicology 256(1–2):65–74, PMID: 19059455, ttps://doi.org/10.1016/j.tox.2008.11.008.

Pizzurro DM., Seeley M, Kerper LE., Beck BD. 2019. Interspecies differences in perfluoroalkyl substances (PFAS) toxicokinetics and application to health-based criteria. Regul. Toxicol. Pharmacol. 106: 239-250.

Russell MH, Himmelstein MW, Buck RC. 2015a. Inhalation and oral toxicokinetics of 6:2 FTOH and its metabolites in ammals. Chemosphere 120:328–335, PMID: 25180935, https://doi.org/10.1016/j.chemosphere.2014.07.092.

Russell MH, Waterland RL, Wong F. 2015b. Calculation of chemical elimination halflife from blood with an ongoing exposure source: the example of perfluorooctanoic acid (PFOA). Chemosphere 129:210–216, PMID: 25149361, https://doi.org/10.1016/j.chemosphere.2014.07.061.

Seals R, Bartell SM, Steenland K. 2011. Accumulation and clearance of perfluorooctanoic acid (PFOA) in current and former residents of an exposed community. Environ Health Perspect. 119(1):119-24.

Schultes L, Vestergren R, Volkova K, Westberg E, Jacobson T, Benskin JP. 2018. Per- and polyfluoroalkyl substances and fluorine mass balance in cosmetic products from the Swedish market: implications for environmental emissions and human exposure. *Environ Sci-Process Impacts* 20:1680-1690. DOI: 10.1039/c8em00368h.

Shin H, Vieira V, Ryan P, Detwiler R, Sanders B, Steenland K, Bartell S. 2011a. Environmental fate and transport modeling for perfluorooctanoic acid emitted from the Washington Works Facility in West Virginia. *Environmental Science & Technology* 45:1435-1442.

Shin HM, Vieira VM, Ryan PB, Detwiler R, Sanders B, Steenland K, Bartell SM. 2011b. Environmental Fate and Transport Modeling for Perfluorooctanoic Acid Emitted from the Washington Works Facility in West Virginia. *Environmental Science & Technology* 45:1435-1442. DOI: 10.1021/es102769t.

Vestergren R and Cousins IT, 2009. Tracking the pathways of human exposure to perfluorocarboxylates. Environ Sci Technol 43:5565-5575.

Vestergren, R., Berger, U., Glynn, A., Cousins, I.T., 2012. Dietary exposure to perfluoroalkyl acids for the Swedish population in 1999, 2005 and 2010. Environ. Int. 49, 120–127. Cited in Gormis et al. (2017).

Worley RR, Moore SM, Tierney BC, Ye X, Calafat AM, Campbell S, et al. 2017. Perand polyfluoroalkyl substances in human serum and urine samples from a residentially exposed community. Environ Int 106:135–143, PMID: 28645013, https://doi.org/10.1016/j.envint.2017.06.007.

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

Yeung LWY., Robinson SJ, Koschorreck J, Mabury SA, 2013a. Part I. A Temporal Study of PFCAs and Their Precursors in Human Plasma from Two German Cities 1982–2009. Environ. Sci. Technol. 47, 3865–3874.

Yeung LWY, Robinson SJ, Koschorreck J, Mabury SA, 2013b. Part II. A Temporal Study of PFOS and Its Precursors in Human Plasma from Two German Cities in 1982–2009. Environmental science & technology 47, 3875–3882.

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