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# Comparing Human Observational Studies with Clinical Findings: The Half-life of Perfluorooctanoate (PFOA)

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# Background

- Disparity in 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, with the loss of valuable information.
- The 750-fold difference in the safe dose for PFOA is a good example of this disparity. This difference is 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 (Russell et al., 2015), which until recently were not well understood (DeSilva et al., 2020).
- Exposure information is thus critical in understanding, and possibly resolving, this conundrum in PFOA safe dose, and potentially for similar disparities with other chemistries.

# Methods

- We reviewed human observational studies on PFOA half life, looking carefully at whether sources of exposure in these studies were well characterized.

- We analyzed the clinical study of Elcombe et al. (2013) and subsequent publications on some of its findings by Convertino et al. (2018) and Dourson et al. (2019), looking carefully for relevance to the human observational studies.

- We reviewed data relevant to PFOA exposures in different environmental media, specifically DeSilva et al. (2020) and Emmett et al. (2006).

# PFOA half-life Studies & Corresponding Media, Newest to Oldest

| Reference | Study Population | Half-life (years) | Media |
|---|---|---|---|
| Xu et al., 2020 | Airport employees; drinking water | 1.77 (with background)<br>1.48 (background subtracted) | Work |
| Pizzuro et al., 2019 | Review of numerous literature | 2.3 – 8.5[a] | Not reported |
| Li et al., 2018 | 106 Swedes | 2.7 | Water |
| Gormis et al., 2017 | Population biomonitoring USA & Australia | Men: USA 2.4; Australia 2.1<br>Women: USA 2.1; Australia 1.8 | Not reported |
| Worley et al., 2017 | Residentially community in Alabama | 3.9 | Not reported |
| Fu et al., 2016 | Workers in fluorochemical plant in China | 1.7 (GM by annual decline rate)<br>11.7 (GM by daily clearance rate) | Occupational |
| Gomis et al., 2016 | 4 occupationally exposed ski waxers | 2.0 – 2.8 (mean 2.4) | Work |
| Russell et al., 2015 | Reevaluation of 2 biomonitoring studies | 2.4 | Not reported |
| Yeung et al., 2013a,b | Population cross-sectional in Germany | Halle: 8.2<br>Munster **14.9** | Not reported |
| Zhang et al., 2013 | 86 healthy volunteers | females ≤50 years: 2.3<br>All males and older females: **1.2** | Not reported |
| Seals et al., 2011 | 1,573 former residents in 2 water districts | Higher exposure: 2.9<br>Lower exposure: 8.5 | Water |
| Bartell et al., 2010 | 200 Americans; PFOA in drinking water | Median 2.3<br>95% CI: 2.1-2.4 | Water |
| Brede et al., 2010 | 138 Germans drinking water | 3.26 (GM)<br>(1.03 – 14.67) | Water |
| Olsen et al., 2007 | 26 retired fluorochemical workers | 3.8 (AM); 3.5 (GM) | Occupational |

# Results

## *Kinetic data in human populations?*

- To date, few specific kinetic data in humans have been available and we all have had to rely on assumptions of kinetic findings in other species.

- Elcombe et al. (2013) used PFOA as a Phase 1, cancer chemotherapeutic agent. Kinetics were well described. Subsets of these data were published by Convertino et al. (2018) and Dourson et al. (2019).

- Next table shows average Cmax concentrations after each dose in µM per mg/kg-day for six weeks calculated by Dourson et al. (2019) from data of Elcombe et al. (2013).

**Table 2. Average Cmax concentrations after each dose in µM per mg/kg-day for six weeks (calculated from Elcombe et al. (2013)).**

| Daily Dose mg/kg-day | Average Cmax Concentration after each weekly dose in µM per mg/kg-day | | | | | |
|---|---|---|---|---|---|---|
| week> | 1 | 2 | 3 | 4 | 5 | 6 |
| 0.1 | 250 | 404 | 406 | 504 | 775 | 801 |
| 0.19 | 152 | 259 | 353 | 452 | 501 | 758 |
| 0.38 | 234 | 404 | 530 | 883 | 1012 | 895 |
| 0.57 | 198 | 316 | 454 | 577 | 689 | 833 |
| 0.86 | 217 | 368 | 495 | 670 | 818 | 771 |
| 1.1 | 253 | 362 | 520 | 625 | 700 | 828 |
| 1.4 | 154 | 269 | 397 | 476 | 548 | 599 |
| 1.85 | 163 | 263 | 364 | 474 | 517 | 585 |
| 2.3 | 200 | 310 | 407 | 515 | 559 | 517 |
| Overall Average > | 202 | 328 | 436 | 575 | 680 | 732 |

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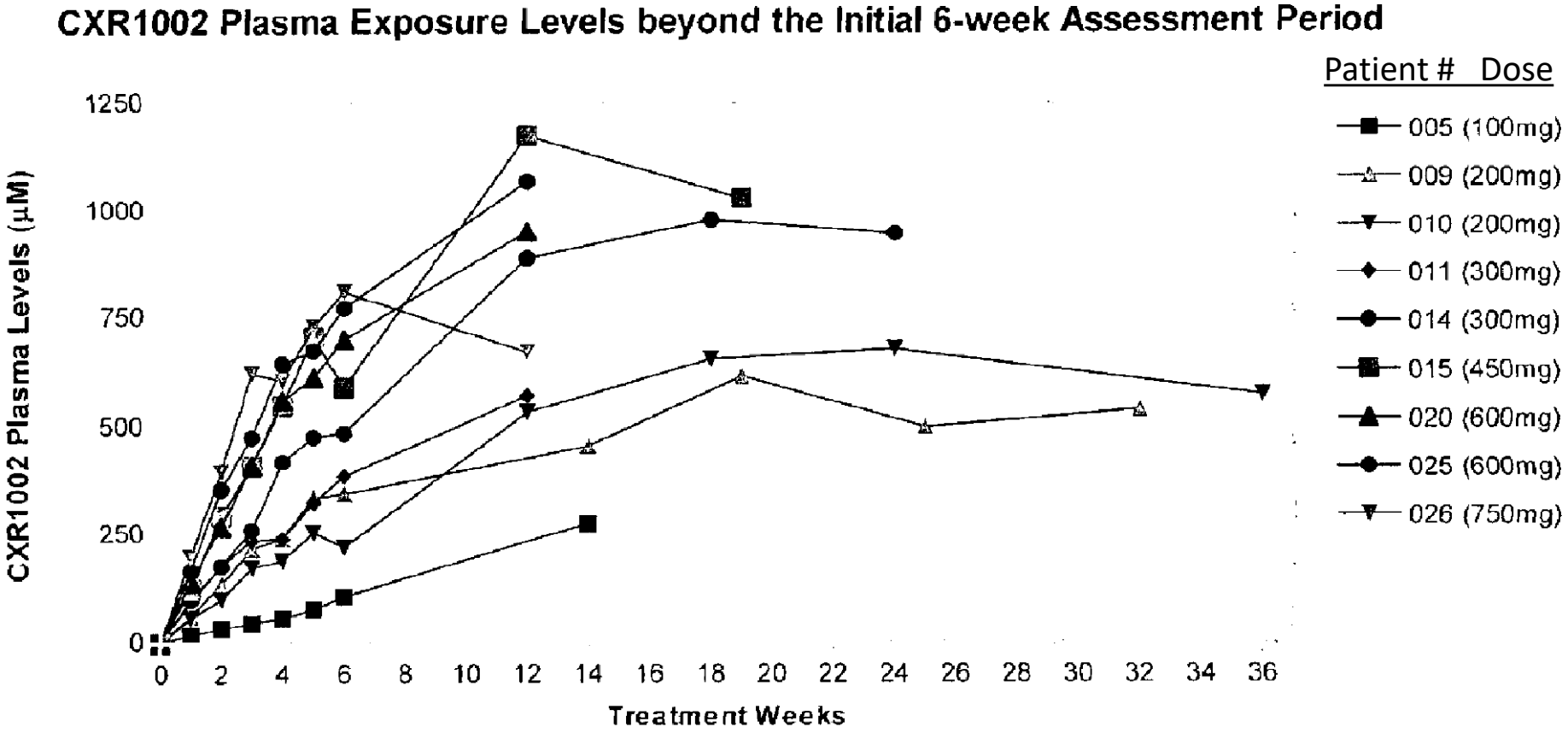
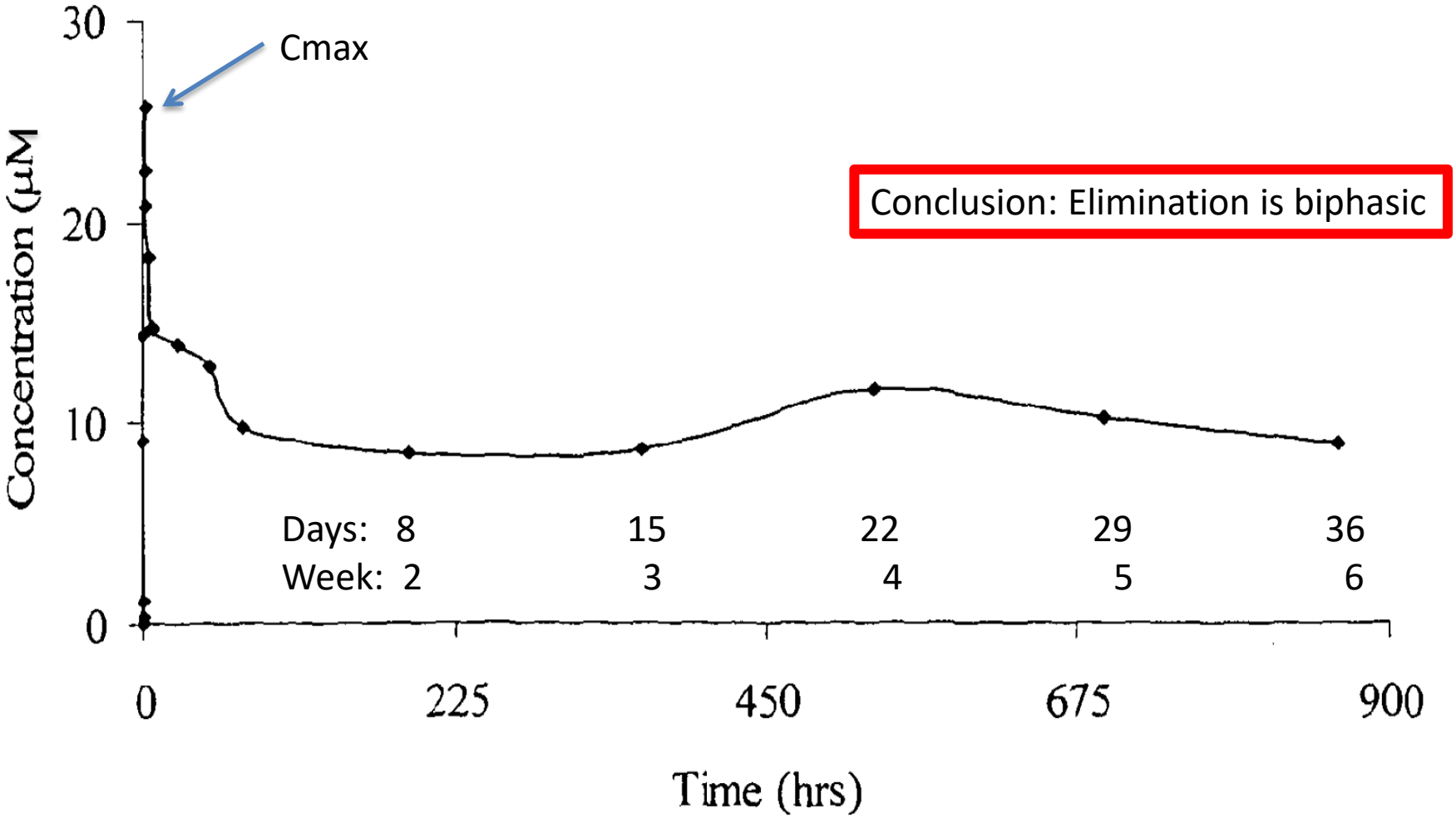
# Elcombe et al. (2013) weekly doses in excess of 6 weeks, shown as Figure 78 of their text.

Conclusion: ½ life is 5-7 weeks

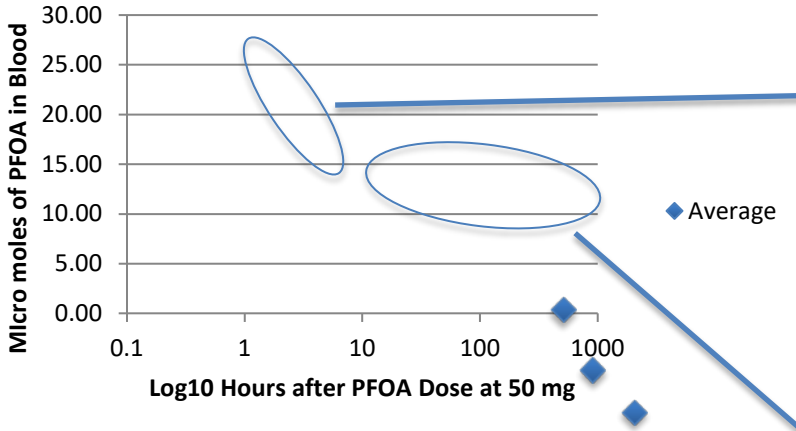
*Figure 78*



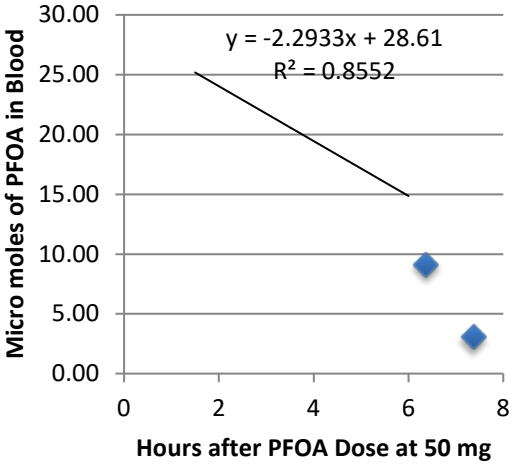
Elcombe et al. (2013), Figure 14. Average concentration of Ammonium Perfluorooctanoate, up to day 37 measured in three patients dosed once with 50 mg/kg-day capsule.



**All Times:** Patients 1, 2, and 3 given 50 mg of PFOA once (Elcombe et al., 2013)

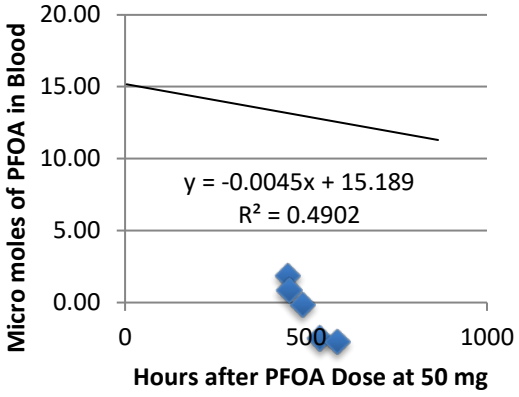



**1st Phase Elimination:** Patients 1, 2, and 3 given 50 mg of PFOA



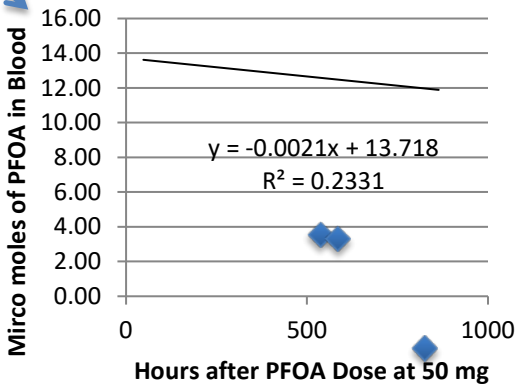

Half life: 6 hours;

**2nd Phase Elimination:** Patients 1, 2, and 3 given 50 mg of PFOA




Half life: 70 days

**2nd Phase Elimination (alternate):** Patients 1, 2, and 3




Half life: 136 days

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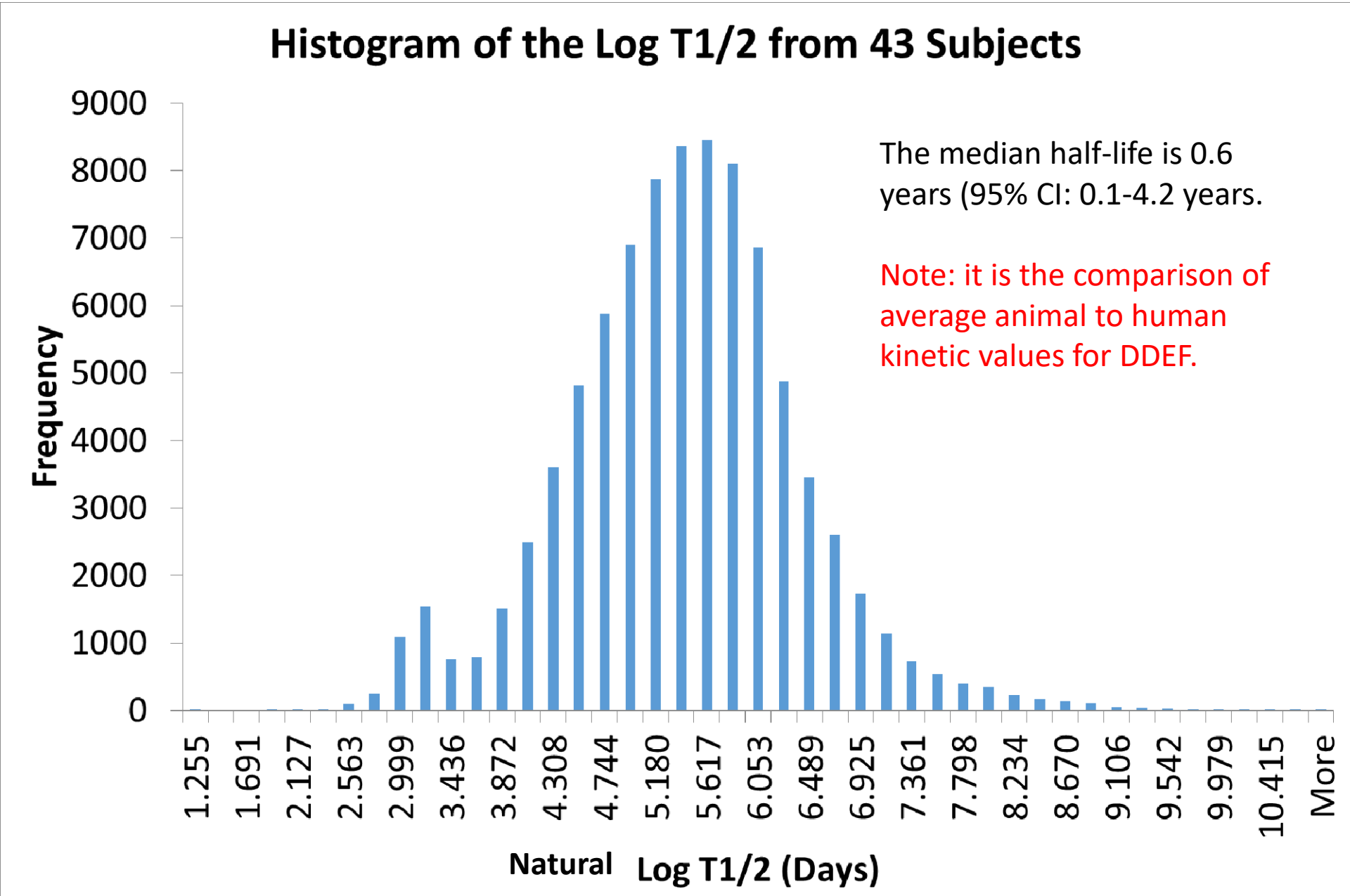
Campbell et al. (2016) based on Elcombe et al. (2013)



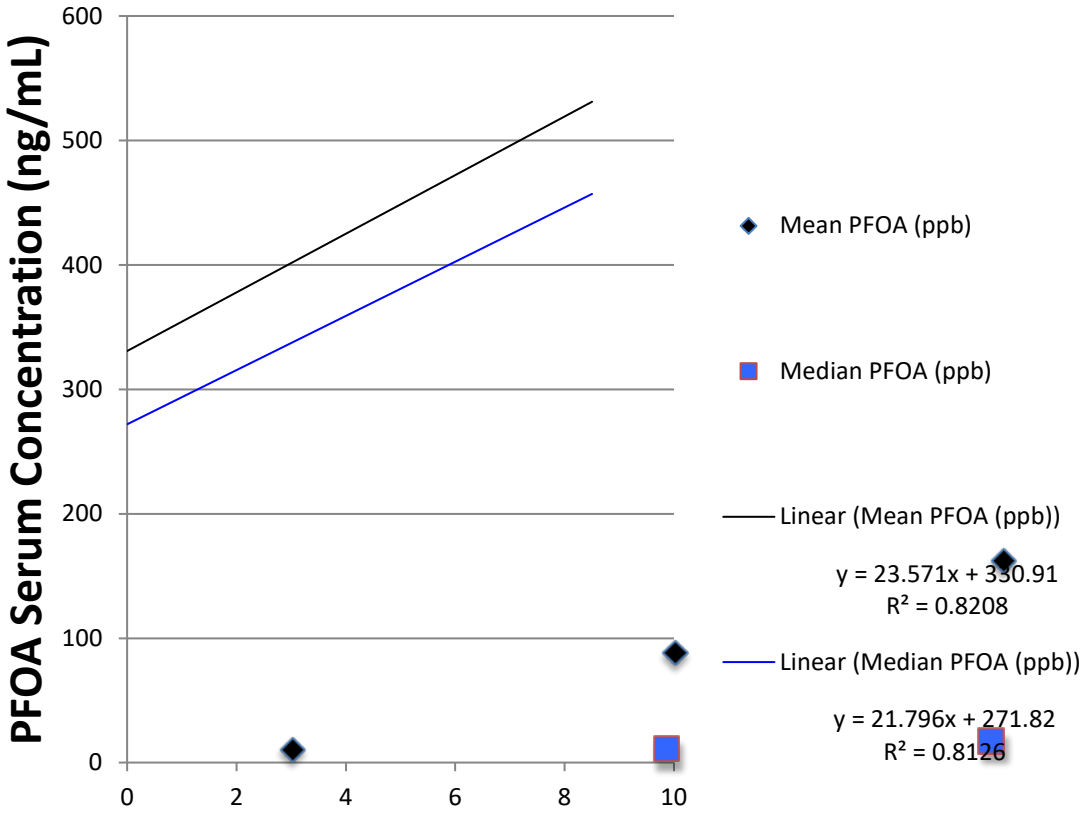
**Data from DeSilva et al. (2020)**

**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 |

## Data from Emmett et al. (2006)

**Figure 4. PFOA concentration versus tap water.**



Data from Emmett et al. (2006)

**Figure 5. PFOA concentration versus local meat.**

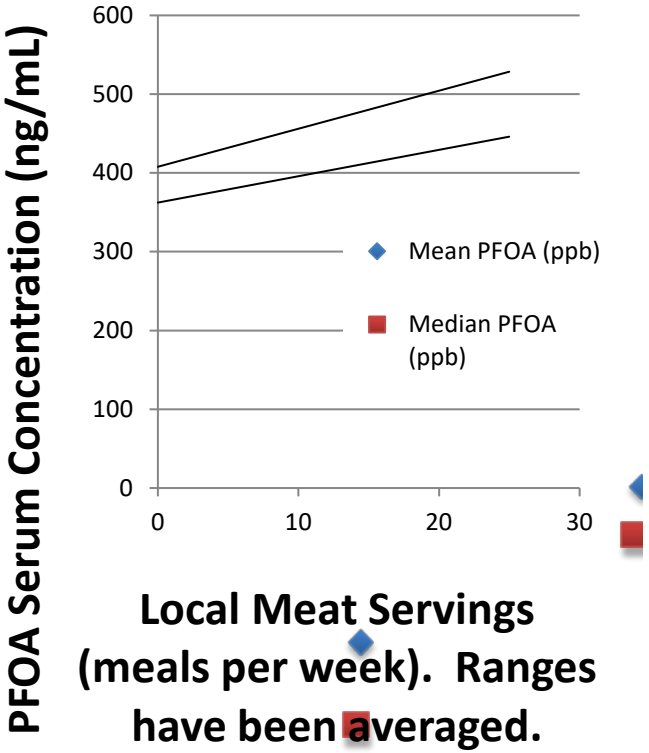
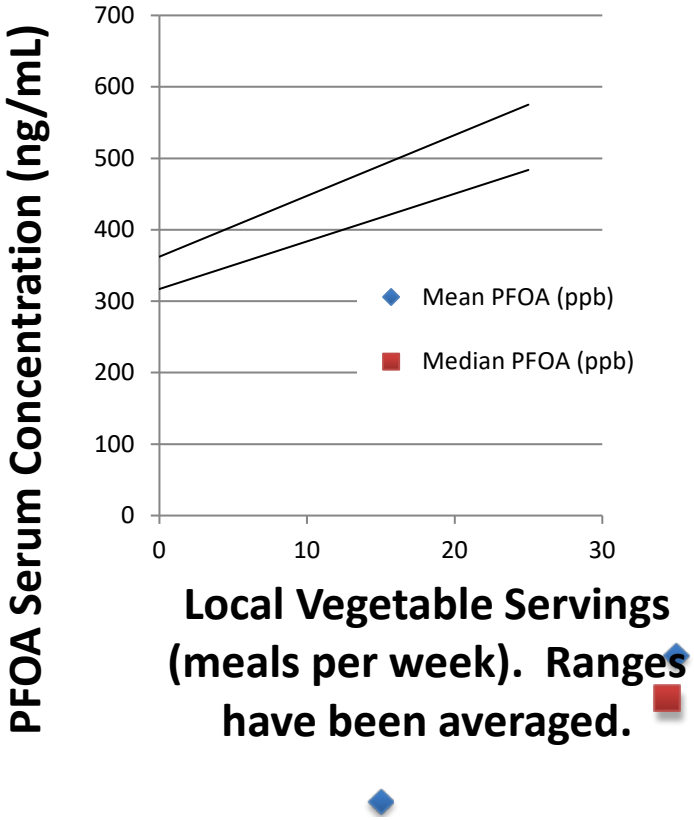



**Figure 6. PFOA concentration versus local vegetables.**



# Three Hypotheses

- First, human observational half-life studies show values that vary from 1.2 years to 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, observational studies may have missed sources of exposure resulting in an overestimation of the half-life.

- 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.

- 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.

# Summary

- Human observational studies show half-life values of PFOA that vary from 1.2 years to 14.9 years. Few of these studies monitored all environmental media.

- Elcombe et al. (2013) study gave half-life estimates of between 50 to 220 days. The Elcombe et al. (2013) study participants were ill, and this may have affected PFOA elimination.

- Recent exposure studies demonstrate that PFOA is found in many environmental media.

- PFOA elimination in humans may be tri-phasic. A human clearance study might be helpful in resolving this.

# Questions for the Panel

- Unrecognized or ongoing exposure in the human observational studies may inflate the half-life of PFOA. Does this statement seem reasonable? Are other routes of exposure possible?
- Table 3 and Figure 2 show PFOA blood levels in 3 patients over 6 weeks administered one dose of 50 mg. Elimination appears biphasic, with half-life estimated in the first phase at 6 hours, and half-life estimated in the second phase at 70 days to 140 days. Does this interpretation seem reasonable?
- Are you aware of other human observational or clinical studies that could shed more light on these estimates?
- We suggest three hypotheses to account for the apparent differences in the half-lives between the human observational and clinical studies. Are these three hypotheses supportable by the available information and/or reasonable based on our understanding of PFOA? If so, which of them, if any, should be further investigated?

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