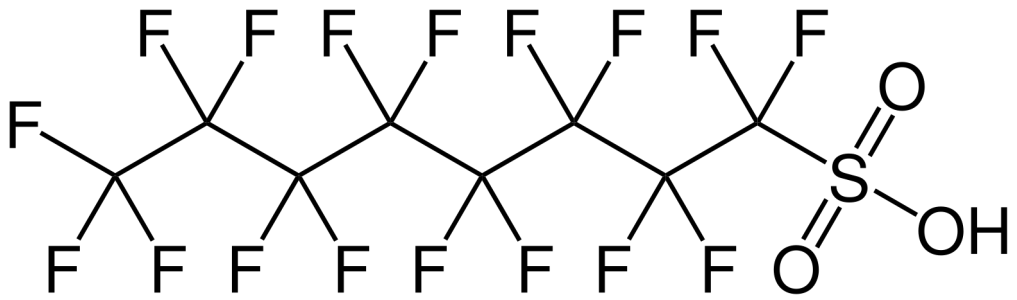
PERFLUORO-OCTANE SULFONATE (PFOS): WHAT DOSE-RATE IS "SAFE"?

Dourson, Green, Crouch, and 26 other scientists …

Estimating safe doses of perfluoro-octane sulfonate (PFOS):
an international collaboration.

Arch Toxicol (2025). https://doi.org/10.1007/s00204-025-04134-9

Perfluoro-octane sulfonic acid

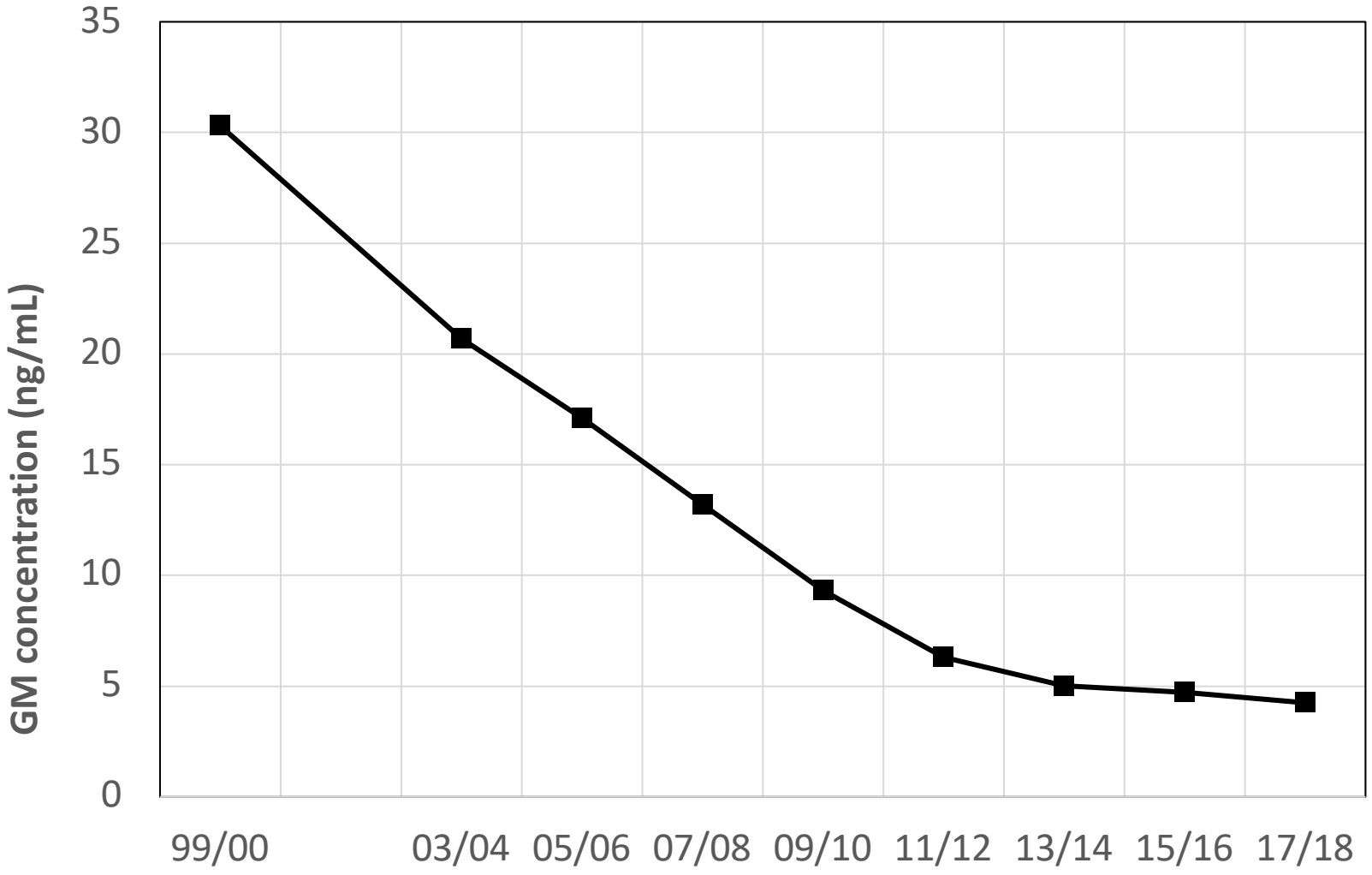


Perfluoro-octane sulfonate (PFOS)

- **Persistent**
- **Bioaccumulative**
  - C-F covalent bond-length exceptionally short
  - Years-long half-lives of elimination in humans
    - Much more rapid elimination-rates in rats & mice

- **Ubiquitous**
- **Exposures change over time, due to regulatory / industry actions**

Median PFOS in blood-serum, general population, U.S.A. (1999 – 2018; NHANES)



Three general types of PFOS exposures …

- **General U.S. & European populations**
- **Occupational exposures**
- **Exposures *via* ingestion of highly contaminated fish**

3M Company workers, U.S. & Belgium

Year	ng/mL PFOS in serum	Statistic	Job title (number of workers sampled)	Factory location
2000	**260**	Geometric mean (GM)	Process Engineer (11)	Antwerp
1998	**391**	GM	Engineer/Lab (23)	Decatur
2000	**490**	GM	Cell operator (25)	Antwerp
2000	**570**	Median	QC Lab (9)	Cottage Grove
2000	**1,190**	GM	Maintenance (10)	Antwerp
1998	**1,299**	GM	Maintenance (11)	Decatur
1998	**1,481**	GM	Chemical Operator (47)	Decatur
2000	**1,660**	GM	Chemical Operator (45)	Antwerp
2000	**1,670**	Median	PFOS production area (29)	Cottage Grove
1998	**1,970**	GM	Cell operator (5)	Decatur

Workers, and fishermen/families, in China

Year(s)	ng/mL PFOS in serum	Measure	Population (number of subjects sampled)	Location
2008-2012	**1,725**	Median	All workers (302)	Hubei Hongxin Chemical Plant
2012	**3,540**	Median	Fishery family (7)	Tangxun Lake
2008-2012	**5,544**	Median	Sulfonation department (101)	Hubei Hongxin Chemical Plant
2012	**10,400**	Median	Commercial fishery employee (39)	Tangxun Lake
2012	**31,400**	Highest	Commercial fishery employee (1)	Tangxun Lake
2008-2012	**118,000**	Highest ever measured	Hongxin Chemical Plant (1)	Hubei

Epidemiologic evidence of PFOS-induced health effects?

In highly-exposed workers?

- No reliable evidence of PFOS-induced health effects

In highly-exposed consumers of contaminated fish/water-fowl?

- No reliable evidence of PFOS-induced health effects

In general populations in U.S. / Europe?

- Many equivocal & inconsistent associations; no reliable evidence
- This is not surprising …

PFOS in drinking water:
differing views as to what concentration is safe

World Health Organization (2022)

PFOS not known to harm human health …

U.S. EPA's Office of Drinking Water (2024)

Only safe concentration = zero (MCLG)

Safe-enough concentration = 4 nanograms/liter

Our group of 29 scientists (2025)

$\gtrapprox$ 140 –700 ng/L

High-dose laboratory animal bioassays

- Studies in **Sprague Dawley rats** and of **cynomolgus monkeys**
- Rat data are extensive … but of uncertain mechanistic relevance to humans
- Monkey data are limited … but of presumed relevance to humans
- NOELs and LOELs for the “most sensitive (adverse?) endpoints” …

Lab Animal Species	Year	ng/mL PFOS in blood-serum	Statistic	Study-result (number of animals)
Monkey	1999	**39,000**	Geometric mean (GM)	NOEL @ 0.15 mg/kg/d (12)
Monkey	1999	**127,000**	GM	LOEL @ 0.75 mg/kg/d (12)
Rat	~2002	**~19,700**	Mean	NOEL @ 1 mg/kg/day (9 – 14)
Rat	~2002	**~45,000**	Mean	LOEL @ 2 mg/kg/day (9 – 14)

Our use of bioassay results was standard & straightforward. We:

- Chose “key studies” in rats and in monkeys
- Determined and used “points of departure” in relationships between blood-serum PFOS concentrations and observed effects
- Applied “appropriately conservative” uncertainty/safety factors

Monkey Study (Seacat et al., 2002)

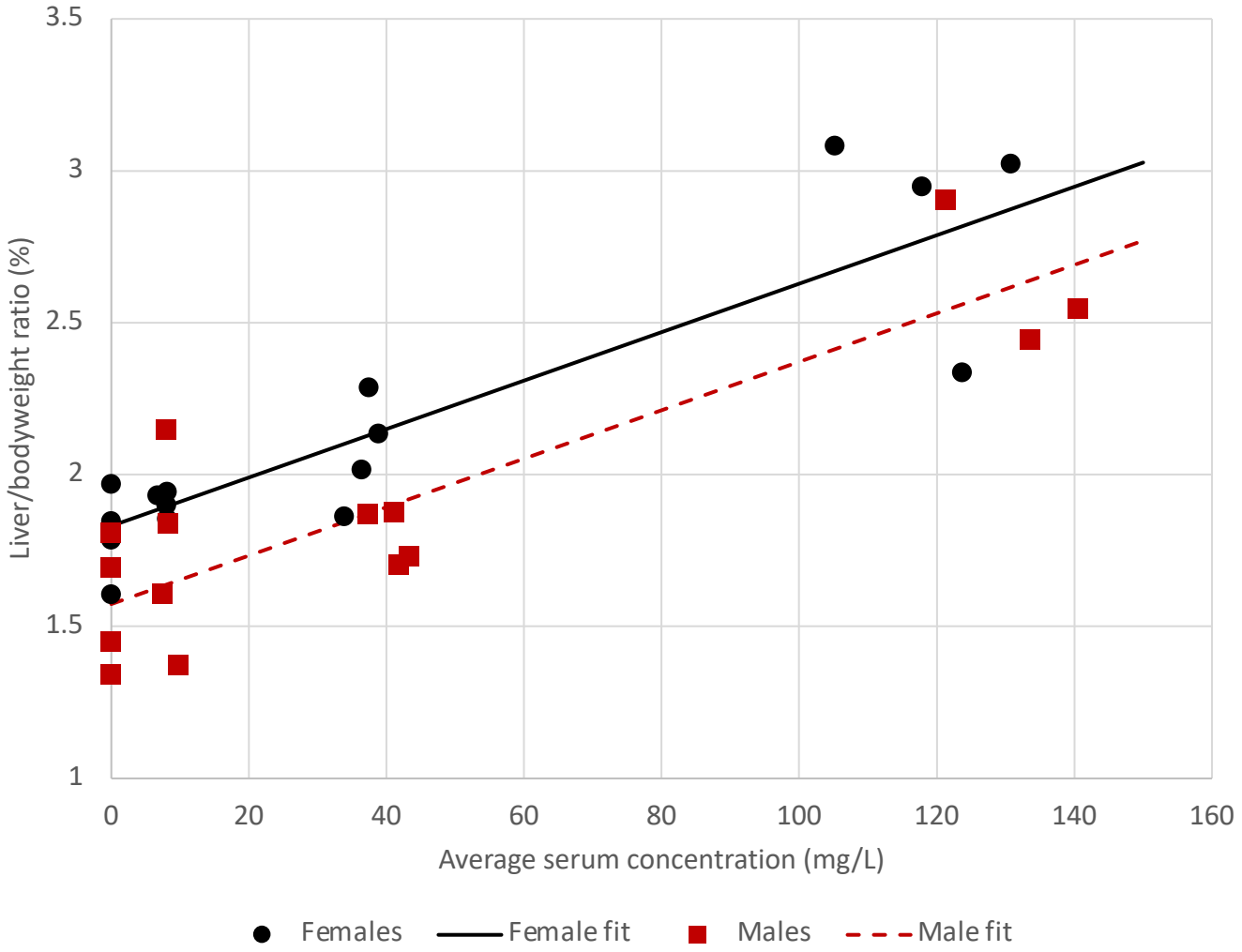
Assumptions:

- 20% increased ratio of liver wt./body wt., or 1 SD increment from mean control group ratio
- Exposure-metric is average serum concentration of PFOS over 26-week study
- 1-compartment model adequate approximation for serum concentration

Methods:

- Average concentration over 26 weeks of fitted model (omit 3 measurements)
- Control group assigned zero serum-concentration of PFOS (negligible)

Results:


3.5
3
2.5
2
1.5
1
Liver/bodyweight ratio (%)
0
20
40
60
80
100
120
140
160
Average serum concentration (mg/L)
Females
Female fit
Males
Male fit

Rat 2-yr bioassay (Butenhoff et al. 2012; and lab reports)

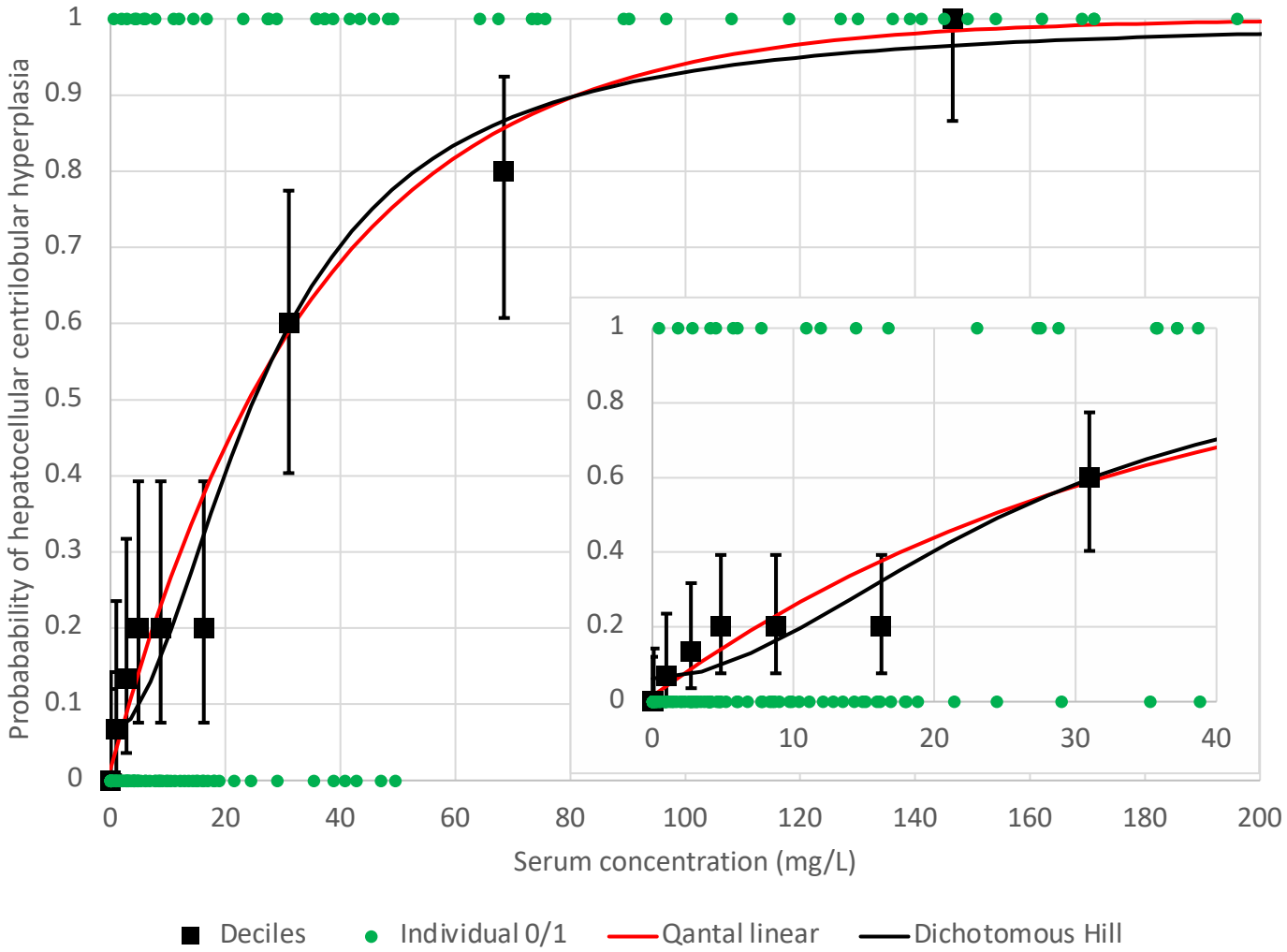
Assumptions:

- Non-neoplastic liver effects at sacrifice determined by serum concentration at sacrifice
- Serum-concentrations in equilibrium at sacrifice (short half-lives)
- Include all rats no matter when sacrificed, including the recovery group

Methods:

- Most sensitive endpoint hepatocellular centrilobular hypertrophy in males
- Effects present or absent
- BMDL using 10% extra risk (effectively no background)

Results:


Probability of hepatocellular centrilobular hyperplasia
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
120
140
160
180
200
Serum concentration (mg/L)
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
Deciles
Individual 0/1
Qantal linear
Dichotomous Hill

Effects in neonatal rats (Thibodeaux et al. (2003), Lau et al. (2003))

Assumption:

- Exposure metric is maternal serum level in last few days of gestation (Grasty et al. 2003)
- Approximated by maternal serum level at 21 days gestation

Methodology:

- Individual rat data not available: group averages only
- Use serum average concentrations in Figure 3 of Thibodeaux et al. (2003)

Result:

- 19.7 µg/mL maternal serum level

Rat Parental Toxicity/Neonatal effects (Luebker et al. (2005); and lab reports)

Assumption:

- Relevant period of dosing for demonstrated effects unclear; assume end of gestation serum concentration

Methods:

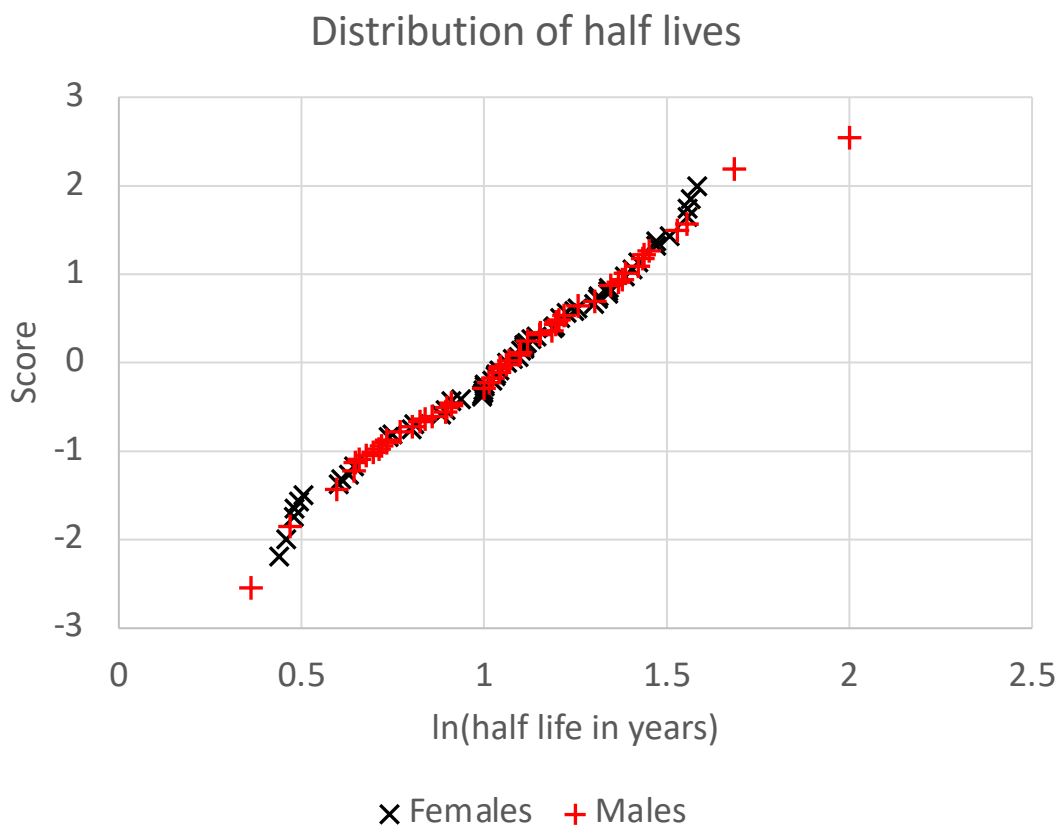
- Studies unsuitable for analysis of individual animals
- Use reported serum concentration at NOAEL

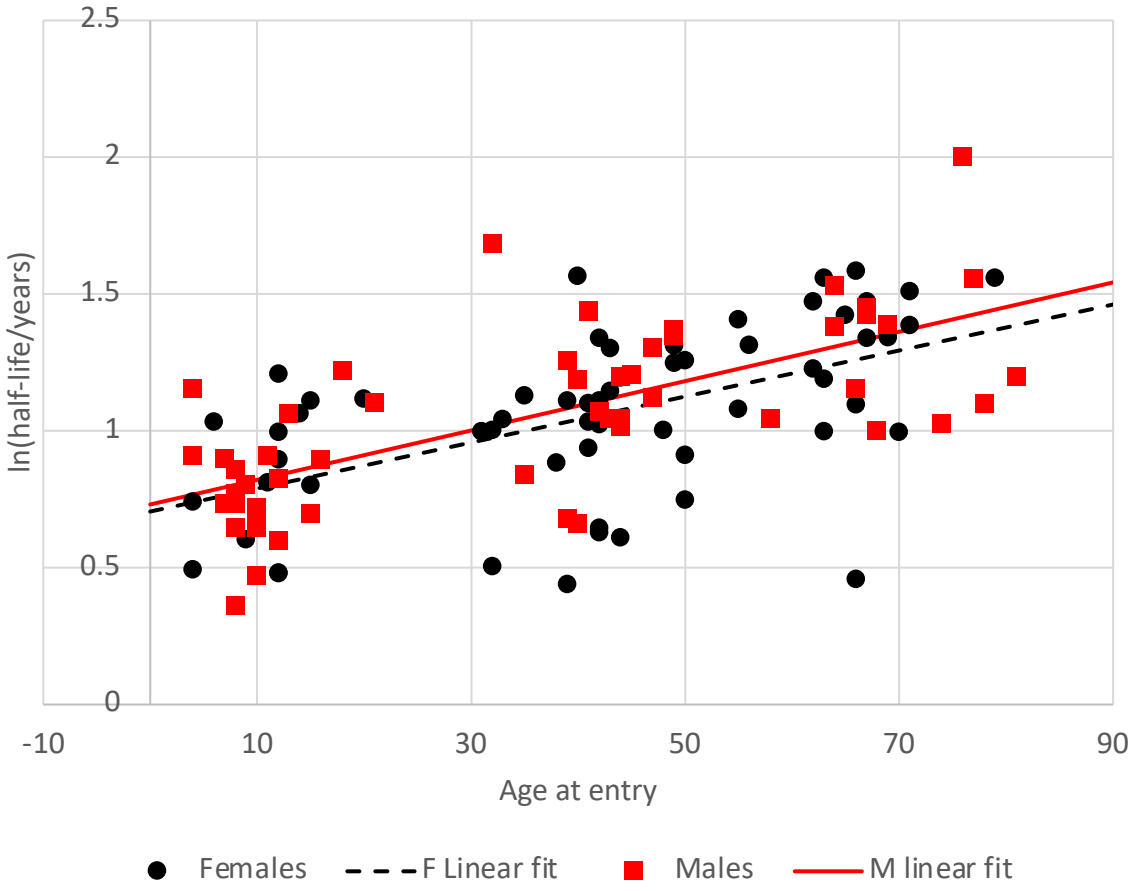
Result:

- 4.52 µg/mL maternal serum level

Half-life of PFOS in humans (Li et al. 2022)

- 114 people in Ronneby, Sweden exposed to PFOS from AFFF-contaminated drinking water
- Initial L-PFOS concentrations 12 – 680 ng/mL, GM 150 ng/mL
- 60 female, 53 male values available (age & half-life)
- L-PFOS -- lognormal distribution overall, median 2.88 years, SD (ln) 0.32
- Clear age effect, consistent with linear on log scale
- Uncertainty in PFOS isomer mix accounted for using Li et al. 2022 reported half-lives
- U.S. EPA (2024) missed this updated paper, and used Li et al. (2018) mean value of 3.4 years





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Safe Dose Estimates

- Safe dose-rates for appear to be on the order of
  20 – 100 ng PFOS / person / day

- U.S. EPA's (2024) estimate is 0.1 ng PFOS / person / day

- Primary reasons for this discrepancy?

Reasons for discrepancies

- Lack of clear epidemiologic evidence
- Different remits
- Public / political pressures
- Litigation
- None of this is U.S. EPA's fault