Per- and Polyfluoroalkyl Substances (PFAS)

(Yes, the acronym is plural and singular—think “deer.”)

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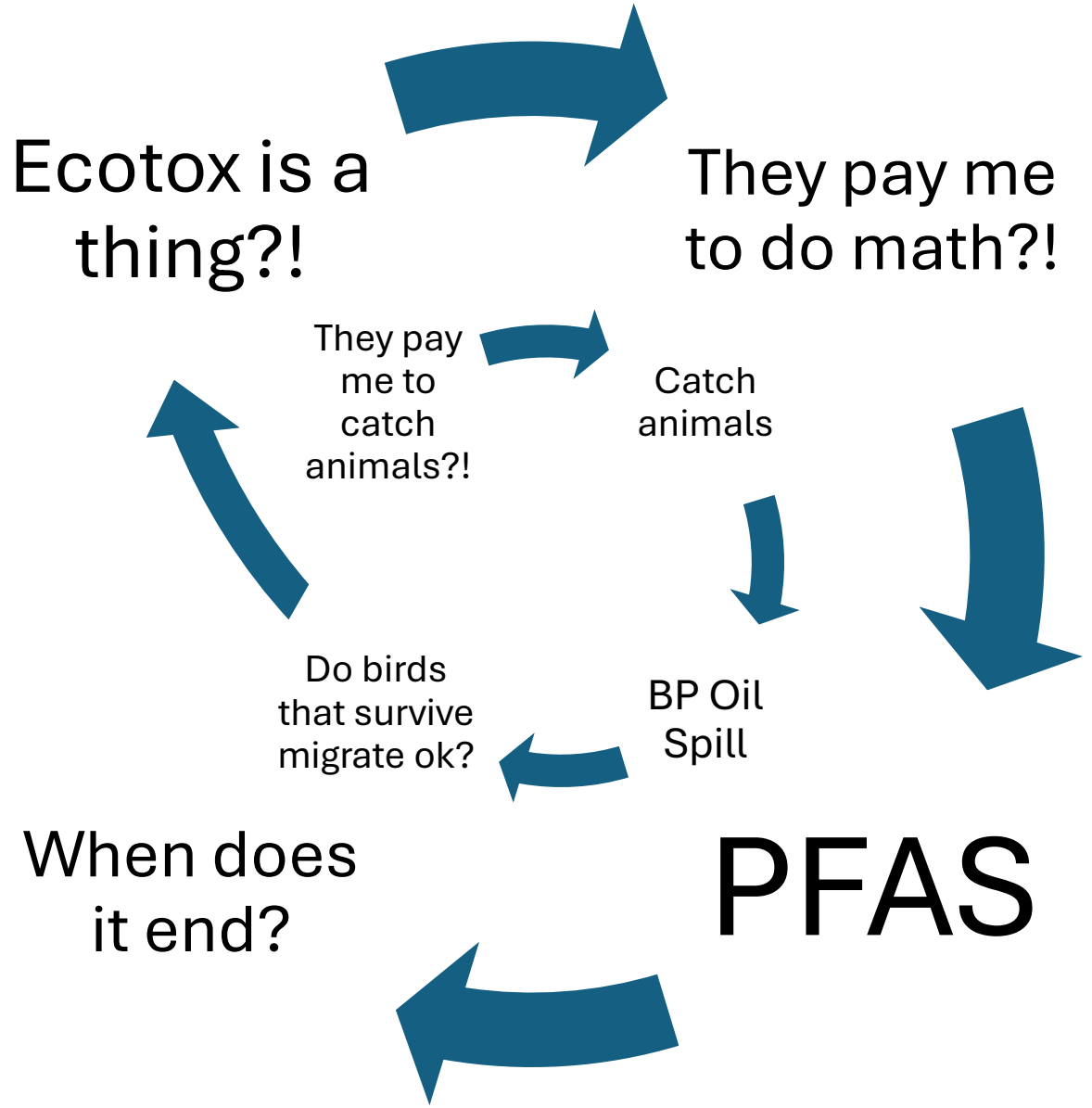
Defense Centers for Public Health-Aberdeen

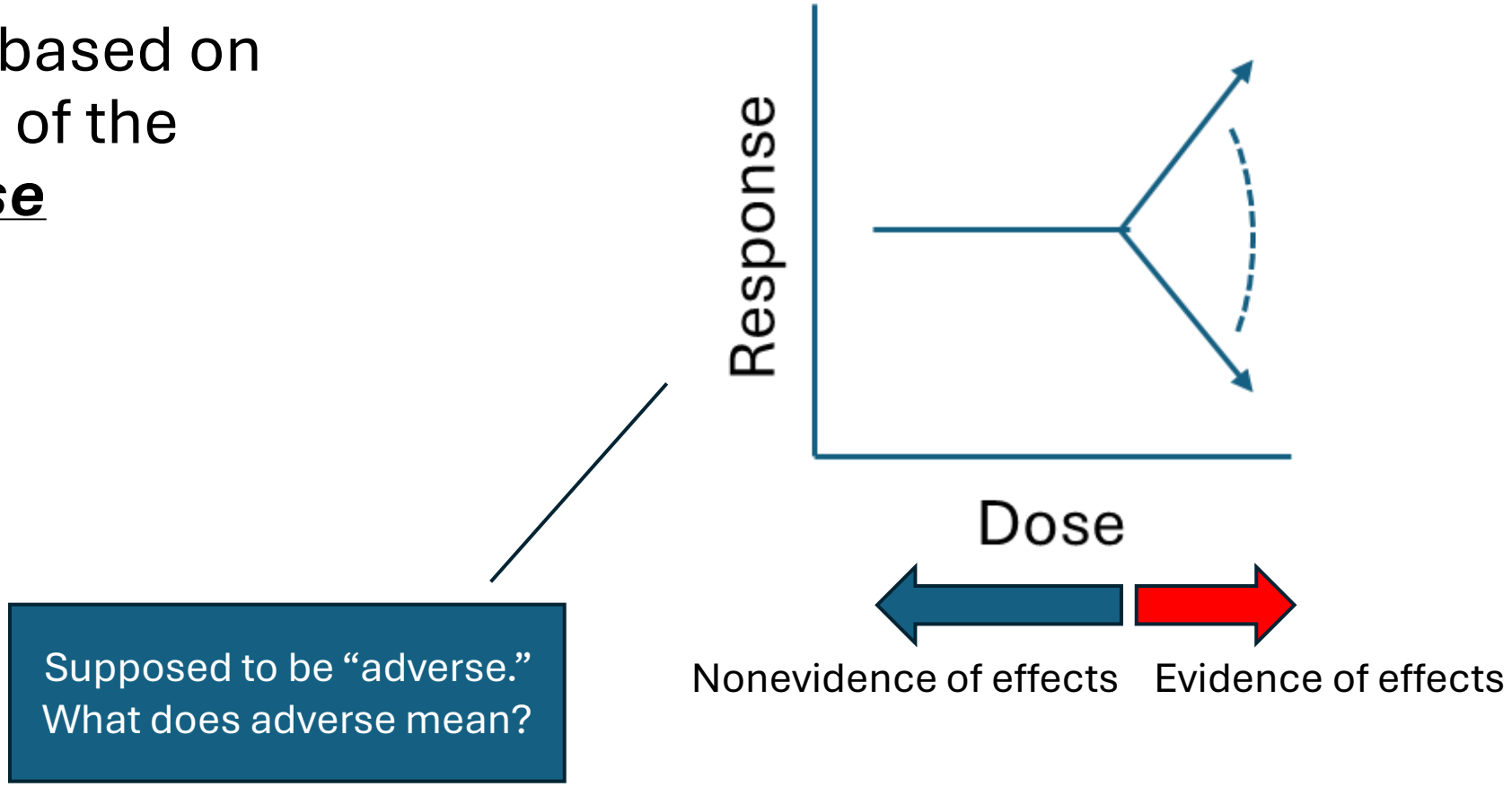
Who am I?

- Quantitative EcoToxicologist
- Work with Dr. Yonkos
  - Terrestrial organism exposure to PFAS
- DoD Biologist in Public Health Toxicology Directorate.
  - Support risk+hazard assessments



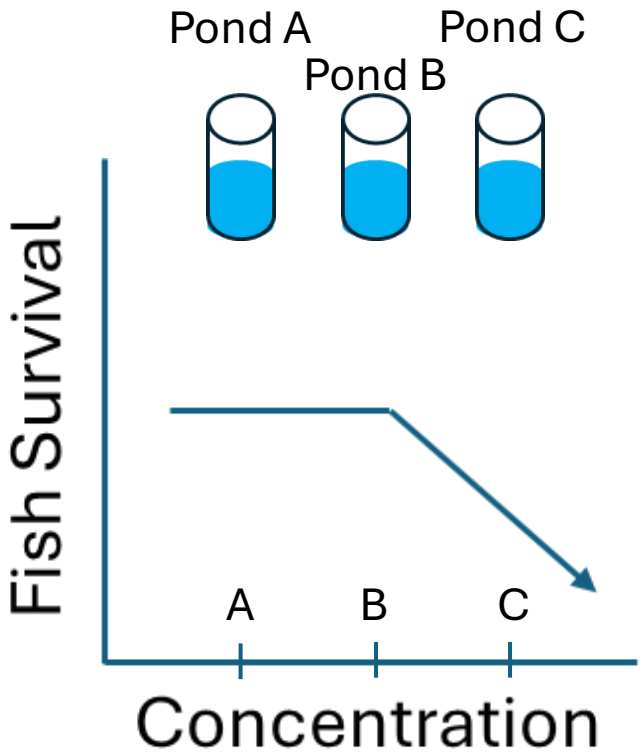
Some toxicology paradigms to consider.

- “Dose makes the poison”
- Regs are usually based on the identification of the ***highest safe dose***



Some (eco)toxicology paradigms to consider

- (Eco)Risk: the probability that exposure overlaps effect thresholds



- Pond C more likely to see effects that Pond A.
- Pond B is maybe a concern.

Why TOX101?

- Which of these headlines are about exposure and which are about effects? (hint: mostly exposure…)

Are you putting PFAS on your armpits?

19 hours ago

THE BALTIMORE BANNER

Commentary: Protect the Chesapeake watershed from 'forever chemicals'

Jan 2 · Chase Brockstedt

THE BALTIMORE SUN

Forever chemicals a continued threat to human health

THE BALTIMORE SUN

Gore-Tex maker polluted some Marylanders' drinking water with 'forever chemicals,' officials say. The question is how ...

The New York Times

North Carolina 'Forever Chemical' Plant Violates Human Rights, U.N. Panel Says

REUTERS

US military says it is immune to dozens of PFAS lawsuits

Outside

Best PFAS-Free Running Jackets

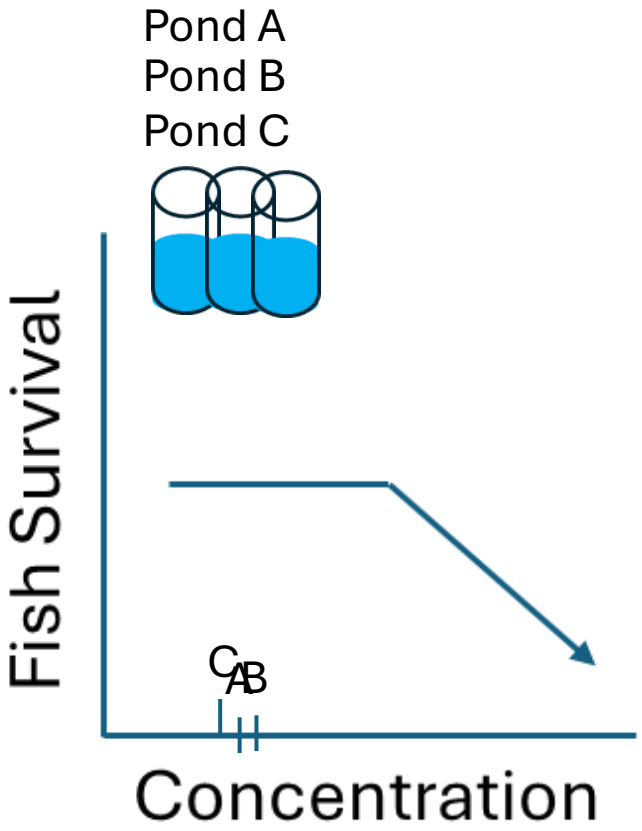
The Washington Post

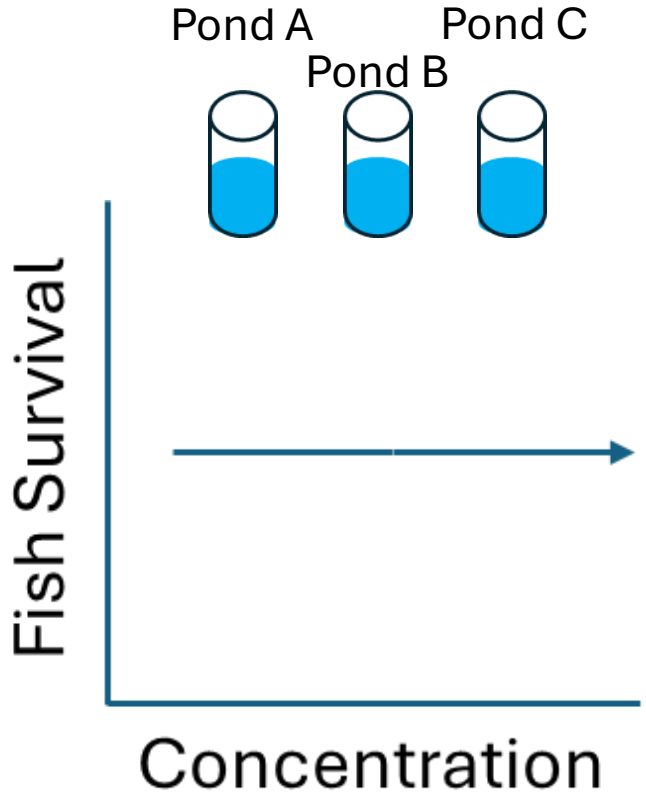
Md.'s largest water utility sues DuPont, 3M over 'forever chemicals'

BANGOR DAILY NEWS

Penobscot County town finds high PFAS levels in drinking water near Superfund site

What is the best way to reduce risk?





Make exposure closer to zero?

Make less impactful chemical?

Ok, back to why you're here.

- History of PFAS:
  - Roy Plunkett, Discovery of "Teflon" PTFE, DuPont and WWII
  - Needed water- and oil-repellent material with low reactivity with all sorts of chemicals.
  - W.L. Gore leaves DuPont to make his own ePTFE and "Gore-Tex."
  - All of the original manufacturing processes of PTFE needed per- and polyfluoroalkyl substances (PFAS) as intermediates.
  - New breakthroughs as these intermediates became the almost equally useful product.

Figure 1.1 Depiction of the discovery of polytetrafluoroethylene by Roy Plunkett and his assistant, Jack Rebok [3].
Courtesy: The DuPont Co.

Ebnesajjad, Sina. (2017). *Expanded PTFE Applications Handbook - Technology, Manufacturing and Applications*. Elsevier. Retrieved from https://app.knovel.com/hotlink/pdf/id:kt0114HXU2/expanded-ptfe-applications/roy-plunkett-prime-s

Where are PFAS used?

- All over.

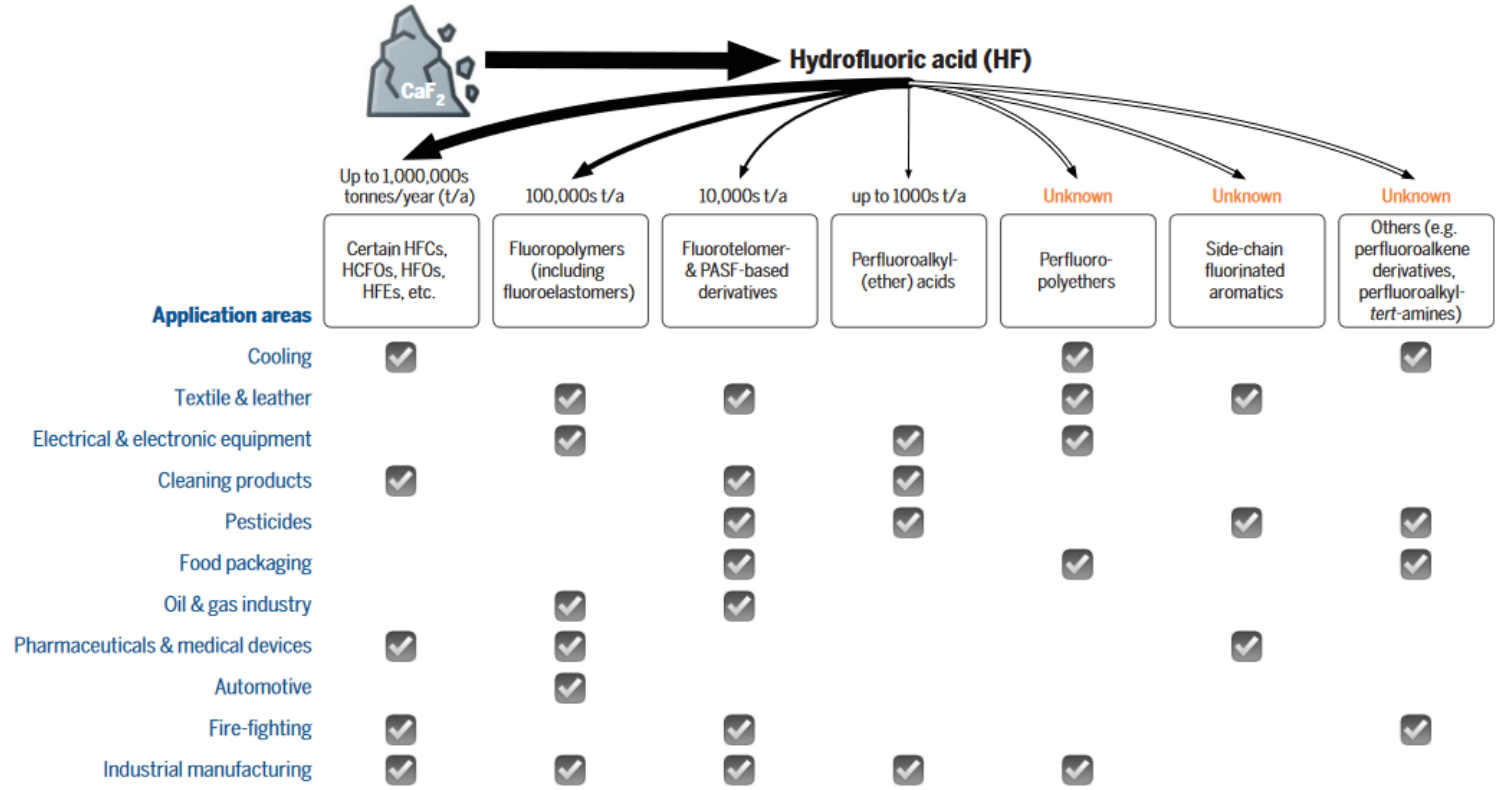


Fig. 1. Non-exhaustive summary of PFAS manufacturing, from production to consumer use. Numerous product fluxes are reasonably documented, but considerable lacunae remain. See text for details and citations. HFC, hydrofluorocarbon; HCFO, hydrochlorofluoroolefin; HFO, hydrofluoroolefin; HFE, hydrofluoroether; PASF, perfluoroalkanesulfonyl fluoride.

Evich MG, Davis MJB, McCord JP, Acrey B, Awkerman JA, Knappe DRU, Lindstrom AB, Speth TF, Tebes-Stevens C, Strynar MJ, et al. 2022. Per- and polyfluoroalkyl substances in the environment. Science. 375(6580):eabg9065. doi:10.1126/science.abg9065.

These issues are not new.

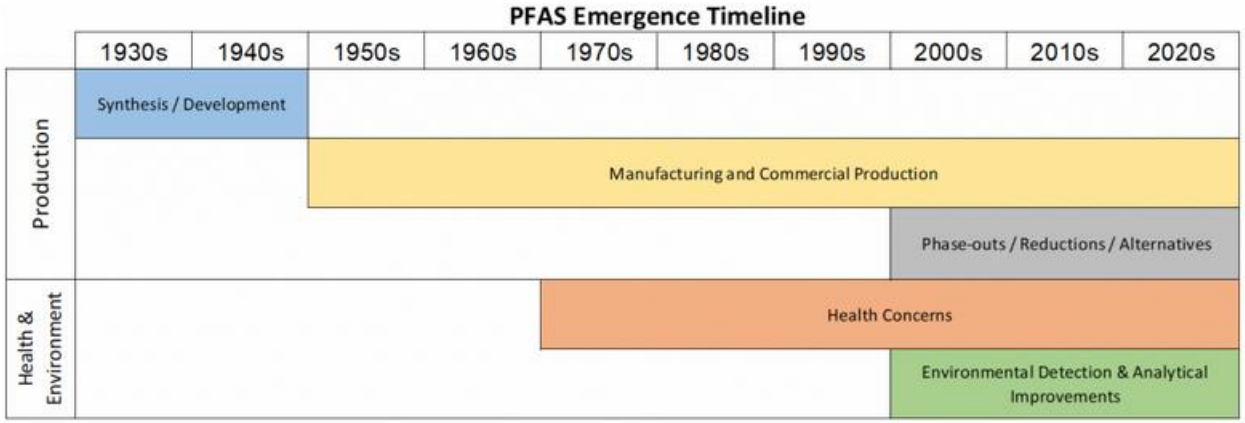


Figure 2-1. General timeline of PFAS emergence and awareness.

Graphic provides general indication of PFAS emergence and awareness by decade. Specific activities and events are described in more detail within this chapter. "Reductions/alternatives" refers to reduction in production/use and includes other PFAS that have replaced legacy chemistry.

- Check out ITRC's website on PFAS:
  - https://pfas-1.itrcweb.org

https://pfas-1.itrcweb.org/2-pfas-chemistry-and-naming-conventions-history-and-use-of-pfas-and-sources-of-pfas-releases-to-the-environment-overview/

PFAS were a requirement!

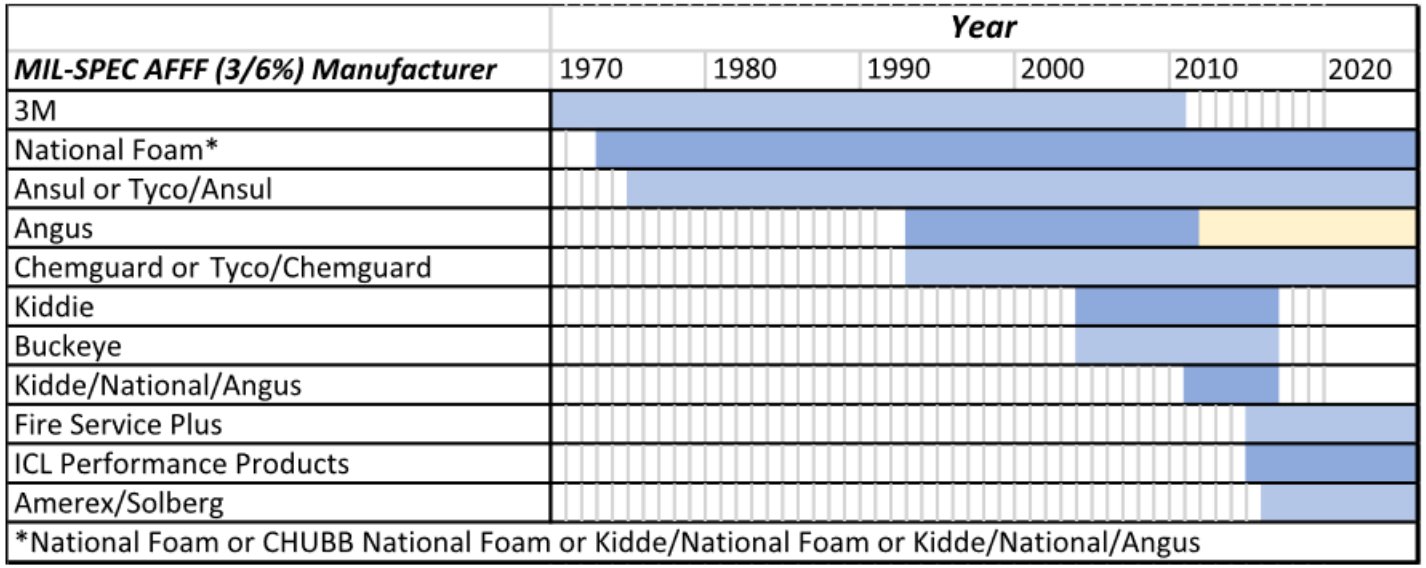


FIGURE 2: Manufacturers of military specifications (MIL-SPEC) aqueous fire-fighting foams (AFFFs) by year. Adapted and updated from Field et al. (2017).

Leeson A, Thompson T, Stroo HF, Anderson RH, Speicher J, Mills MA, Willey J, Coyle C, Ghosh R, Lebrón C, et al. 2021. Identifying and Managing Aqueous Film-Forming Foam-Derived Per- and Polyfluoroalkyl Substances in the Environment. Environ Toxicol Chem. 40(1):24–36. doi:10.1002/etc.4894.

Why now?

- Chemicals that didn’t fit the models used in predictive toxicology.
- We didn’t have the methods to detect effects/bad predictive models.
- So, more and more testing was done with more and more sensitive methods and refinement of predictive models.

What is a PFAS?

A molecule with at least one fluorinated carbon.

Anything with $–CF_3$ or $–CF_2–$

Only those that are commercially relevant and named as “PFAS”

Inclusive + Technical

Restrictive + Legal

What are PFAS?

- Definition has changed over time.

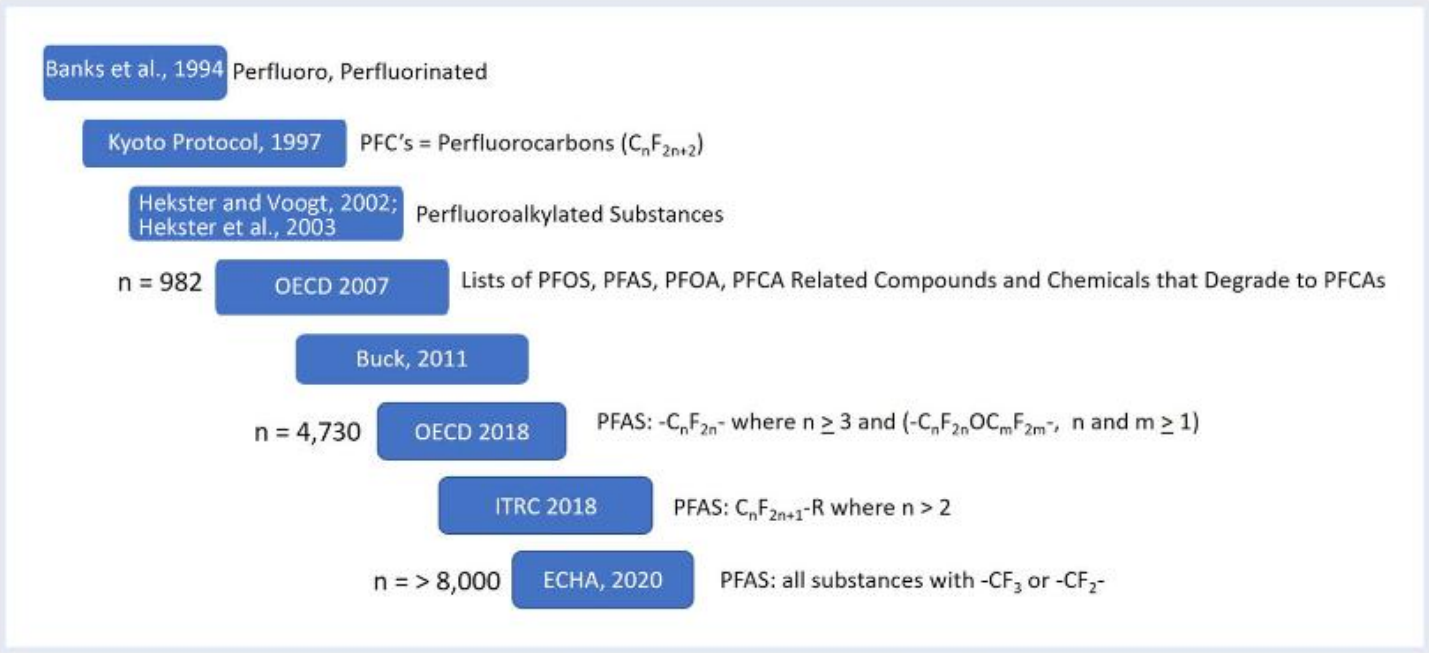


FIGURE 1 The evolution of the term per- and poly-fluoroalkyl substances (PFAS)

Buck RC, Korzeniowski SH, Laganis E, Adamsky F. 2021. Identification and classification of commercially relevant per- and poly-fluoroalkyl substances (PFAS). Integrated Environmental Assessment and Management. 17(5):1045–1055. doi:10.1002/ieam.4450.

Complexity can be massive!

- Development of molecules expanded greatly once the combination of toxicity and persistence has been identified.
  - i.e. move away from PFOA or PFOS.

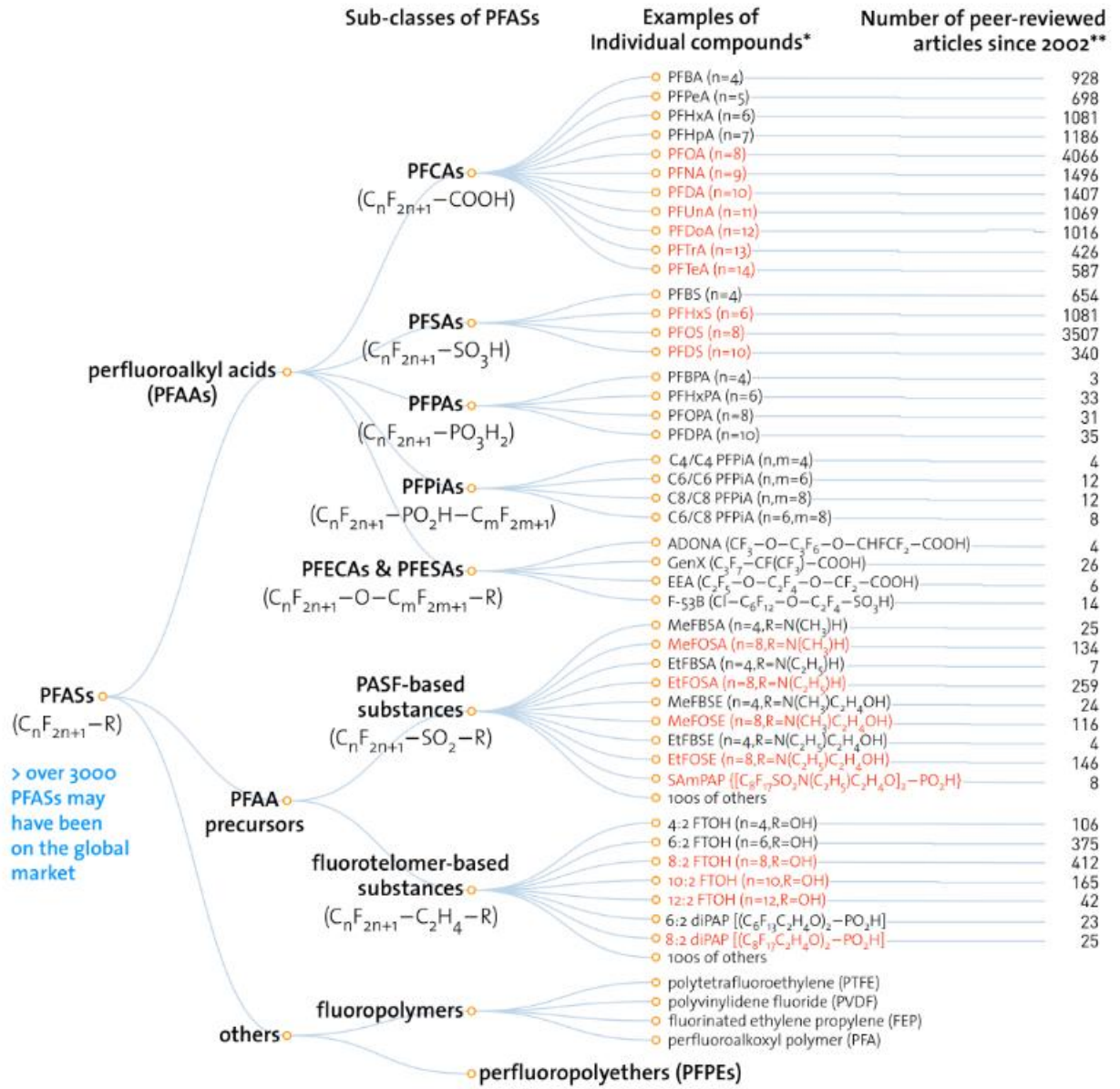


Figure 1. "Family tree" of PFASs, including examples of individual PFASs and the number of peer-reviewed articles on them since 2002 (most of the studies focused on long-chain PFCAs, PFSAs and their major precursors.).

Wang Z, DeWitt JC, Higgins CP, Cousins IT. 2017. A Never-Ending Story of Per- and Polyfluoroalkyl Substances (PFASs)? Environ Sci Technol. 51(5):2508–2518. doi:10.1021/acs.est.6b04806.

Or complexity is manageable.

- All that matters is what we intentionally added and named and can be/is regulated.
- Buck et al. (2021) says 256 PFAS molecules are commercially relevant.
  - Compared to 4730 on OECD “official” list based on one fluorinated carbon definition.

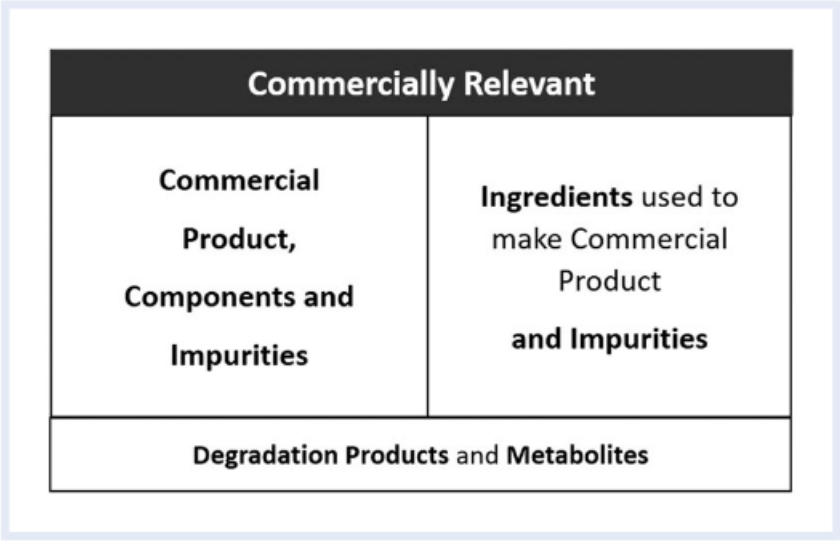


FIGURE 2 Substances included in commercially relevant list

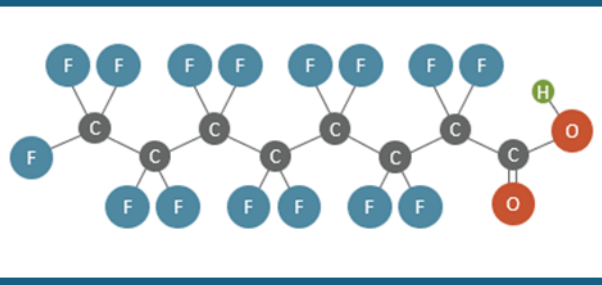
Buck RC, Korzeniowski SH, Laganis E, Adamsky F. 2021. Identification and classification of commercially relevant per- and poly-fluoroalkyl substances (PFAS). Integrated Environmental Assessment and Management. 17(5):1045–1055. doi:10.1002/ieam.4450.

What does this look like at the molecule level?

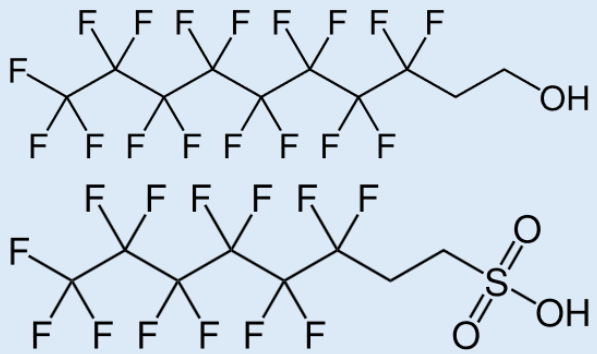
Check me out!

https://pfas-1.itrcweb.org/2-2-chemistry-terminology-and-acronyms/

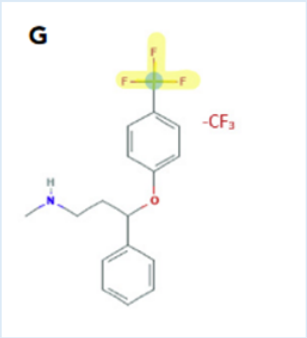
Perfluorocarboxylic acids (PFCAs)



'Precursors' (polyfluorinated)



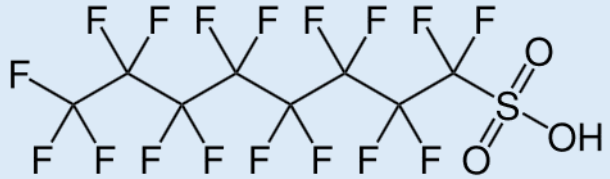
'Whoops...'



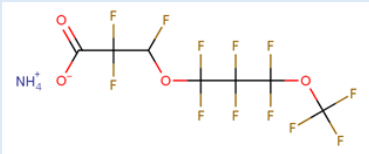
Fluoxetine (Prozac)

Hammel E, Webster TF, Gurney R, Heiger-Bernays W. Implications of PFAS definitions using fluorinated pharmaceuticals. iScience. 2022 Mar 2;25(4):104020. doi: 10.1016/j.isci.2022.104020. PMID: 35313699; PMCID: PMC8933701.

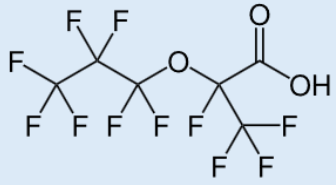
Perfluorosulfonic acids (PFSAs)



'Alternatives'

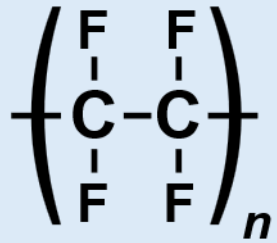


(ADONA)
Ammonium 4,8-dioxa-3H-perfluorononanoate



HFPO-DA (GenX)

Polymers



PTFE (Teflon)

What are the properties of these molecules?

Fluorinated, anionic, surfactants

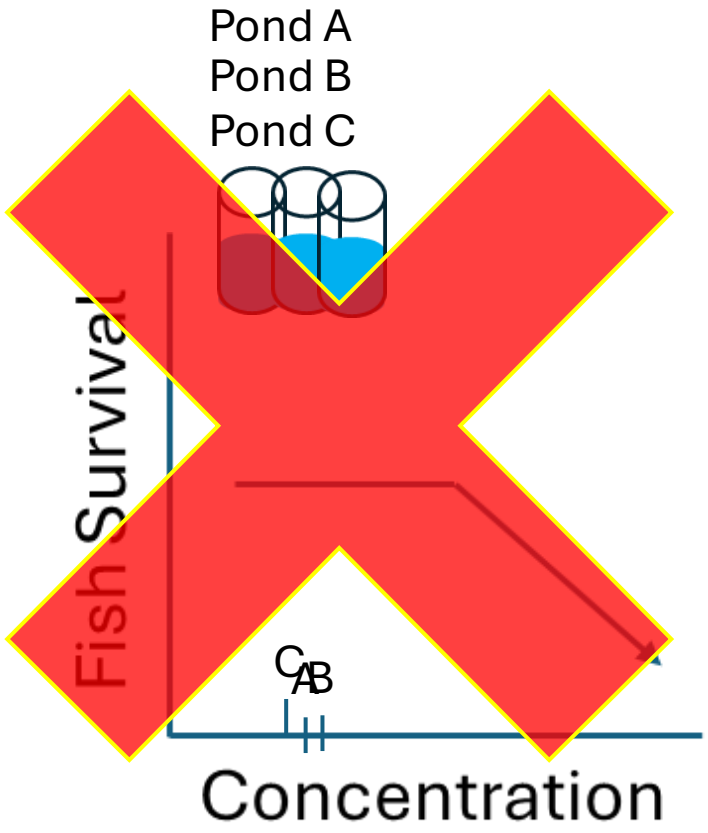
Durable bubbles and oil+water-repellency

Persistent molecules that break our models

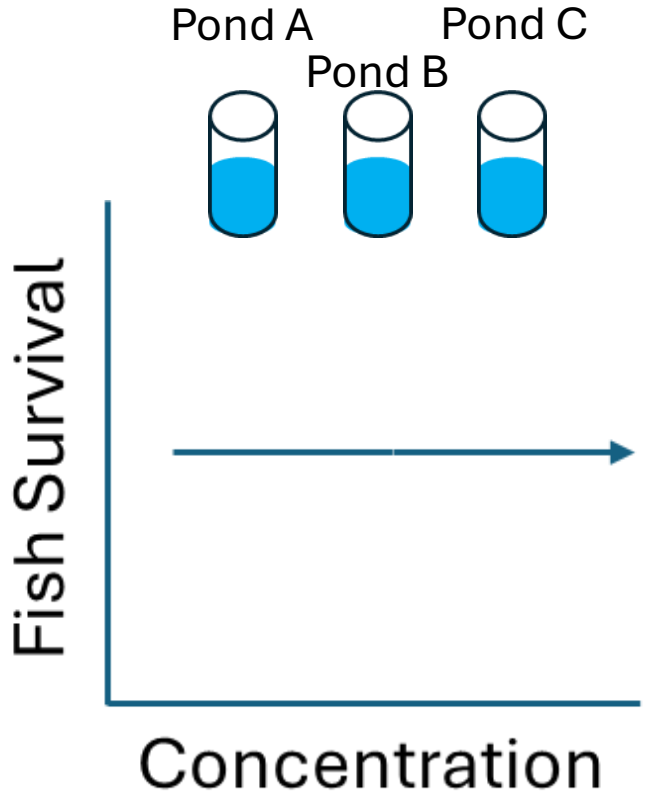
Ok, so it’s weird, who cares?

- Anything catch your eye about this image?

Making exposure zero is not possible.



Make exposure closer to zero?



Make less impactful chemical?

Toxicity of PFAS

- Lab animal and epidemiological data indicate a series of type effects (hazards).

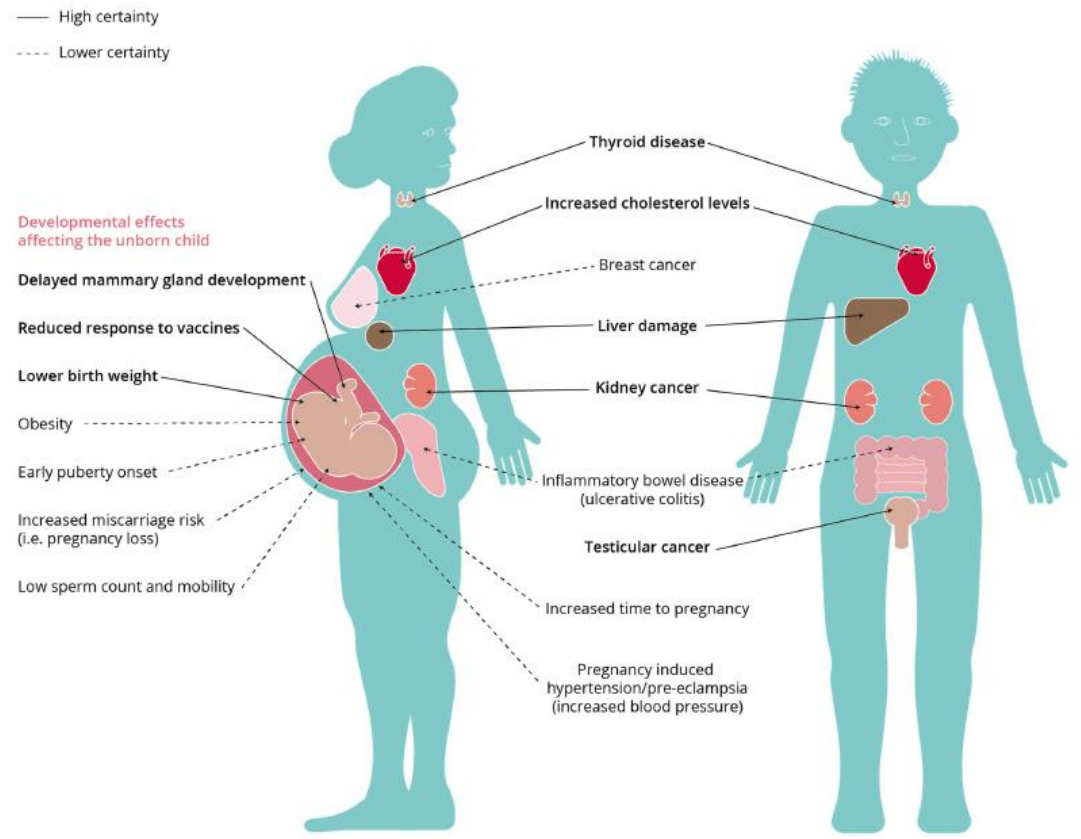


FIGURE 1: Effects of per- and polyfluoroalkyl substances on human health. Used with permission from European Environment Agency (2019). Original sources for this figure: National Toxicology Program (2016), C8 Science Panel (2012), IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2017), Barry et al. (2013), Fenton et al. (2009), and White et al. (2011b).

Toxicity of PFAS

Evidence for cancer

Evidence for non-cancer effects

Summary

EPA is proposing a National Primary Drinking Water Regulation (NPDWR) to establish legally enforceable levels, called Maximum Contaminant Levels (MCLs), for six PFAS in drinking water. PFOA and PFOS as individual contaminants, and PFHxS, PFNA, PFBS, and HFPO-DA (commonly referred to as GenX Chemicals) as a PFAS mixture. EPA is also proposing health-based, non-enforceable Maximum Contaminant Level Goals (MCLGs) for these six PFAS.

Compound	Proposed MCLG	Proposed MCL (enforceable levels)
PFOA	Zero	4.0 parts per trillion (also expressed as ng/L)
PFOS	Zero	4.0 ppt
PFNA	1.0 (unitless) Hazard Index	1.0 (unitless) Hazard Index
PFHxS		
PFBS		
HFPO-DA (commonly referred to as GenX Chemicals)		

Sum exposure = Protective effect threshold

https://www.epa.gov/sdwa/and-polyfluoroalkyl-substances-pfas

Toxicology of PFAS

Absorption → <u>Generally high</u>

Distribution → This is where it gets interesting

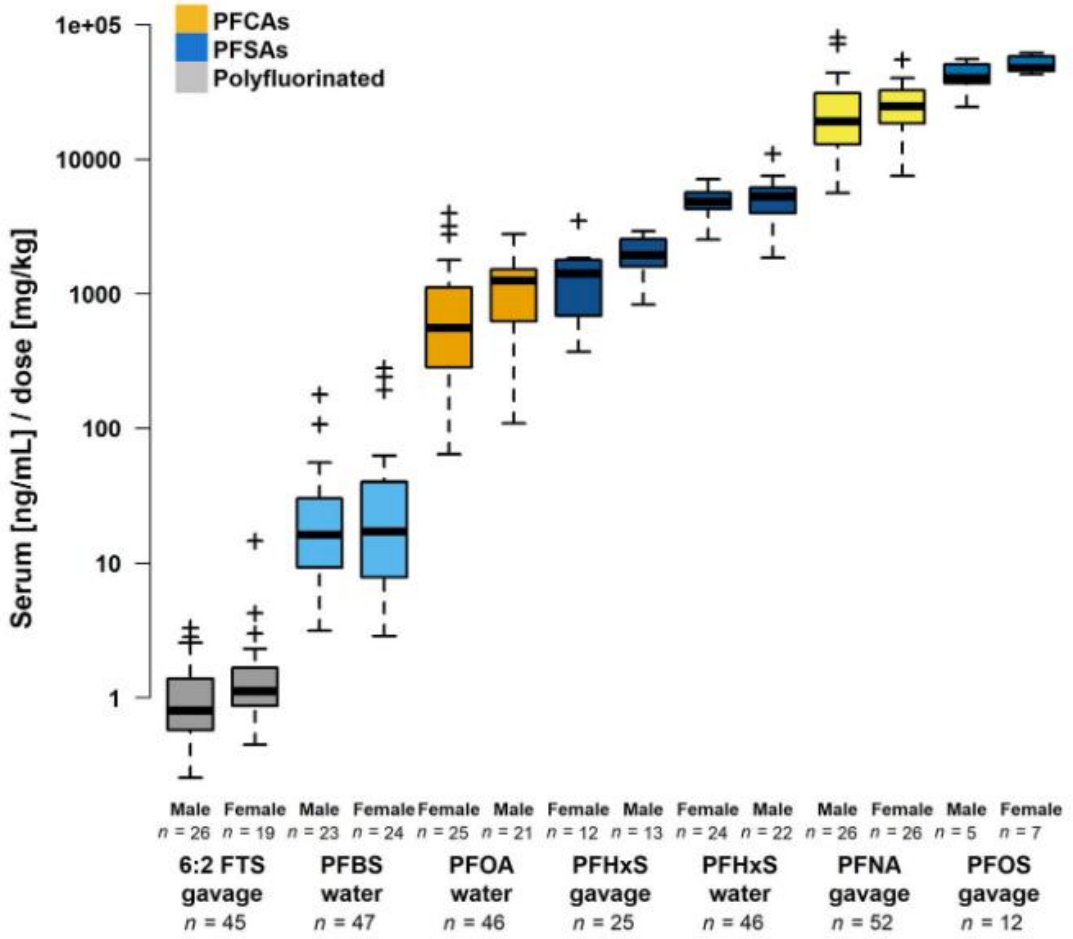
Metabolism → <u>Generally low</u>

Excretion → Interesting again

Toxicology of PFAS

Distribution

Patterns but wide variation

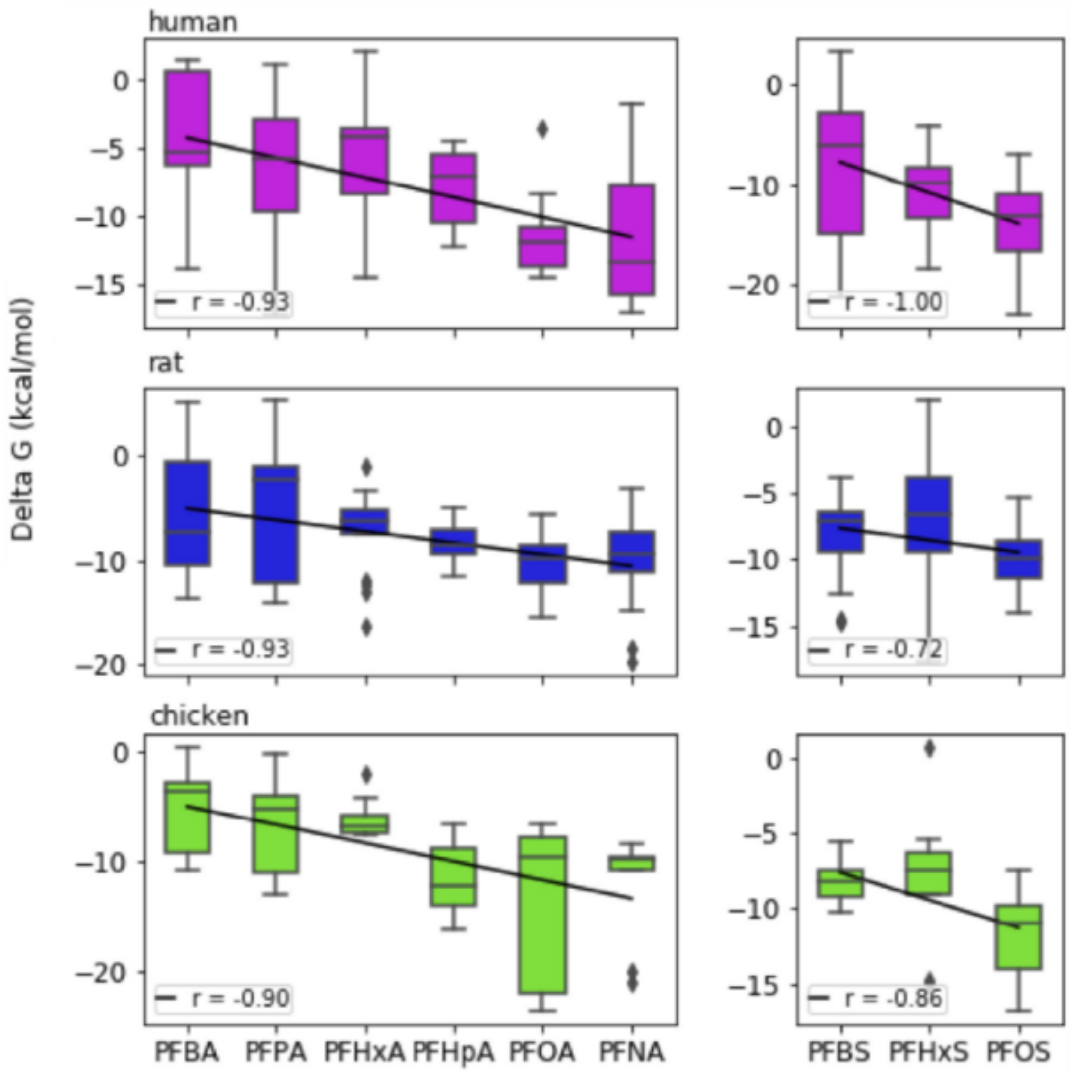


Narizzano AM, Bohannon ME, East AG, McDonough C, Choyke S, Higgins CP, Quinn Jr MJ. 2021. Patterns in Serum Toxicokinetics in Peromyscus Exposed to Per- and Polyfluoroalkyl Substances. Environmental Toxicology and Chemistry. 40(10):2886–2898. doi:10.1002/etc.5151.

Toxicology of PFAS

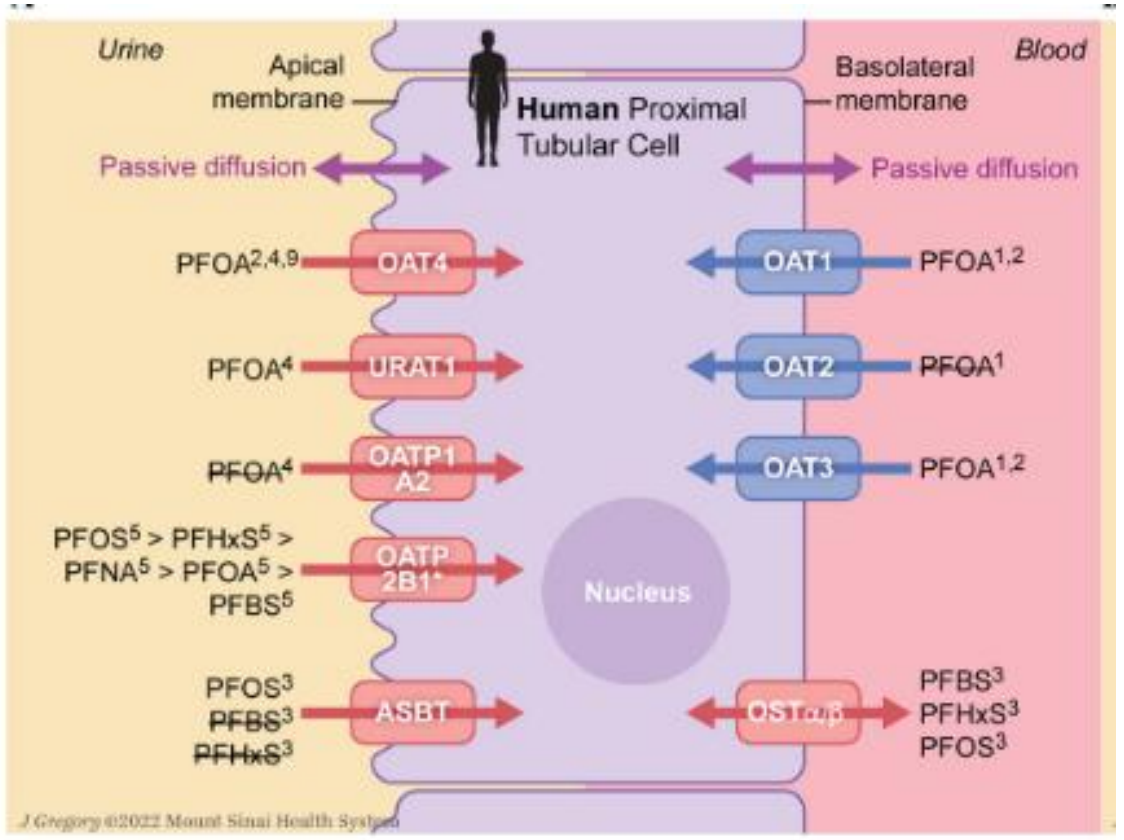
Distribution

Patterns but variability (2x)!



Cheng W, Doering JA, LaLone C, Ng C. 2021. Integrative Computational Approaches to Inform Relative Bioaccumulation Potential of Per- and Polyfluoroalkyl Substances Across Species. Toxicological Sciences. 180(2):212–223. doi:10.1093/toxsci/kfab004.

Toxicology of PFAS



Excretion

Variable recycling!

Niu S, Cao Y, Chen R, Bedi M, Sanders AP, Ducatman A, Ng C. 2023. A State-of-the-Science Review of Interactions of Per- and Polyfluoroalkyl Substances (PFAS) with Renal Transporters in Health and Disease: Implications for Population Variability in PFAS Toxicokinetics. Environ Health Perspect. 131(7):076002. doi:10.1289/EHP11885.

Ecotoxicity of PFAS

- Very mixed signals of sensitivity across taxa
- Reproductive effects most important for risk assessments
- Indirect effects (immune effects) most uncertain and least traditionally utilized in ERAs

Ecotoxicity of PFAS

- Fish/amphibians/aquatic inverts generally have chronic effects above 1 µg/L

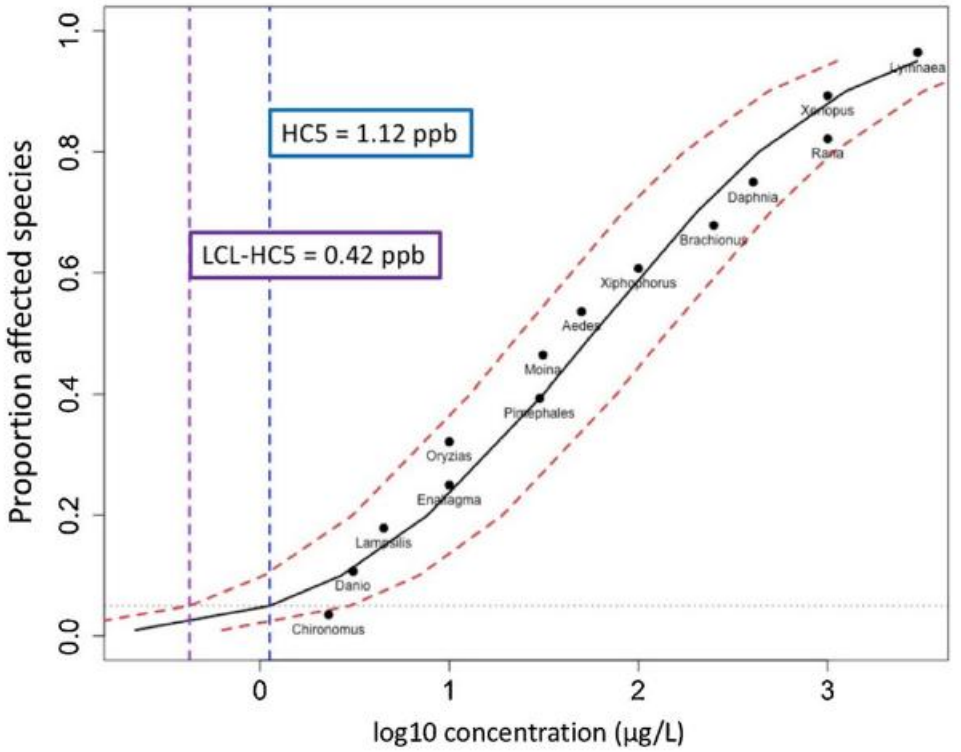


FIGURE 3: Species-sensitivity distribution (SSD) for chronic perfluorooctane sulfonate (PFOS) toxicity data for freshwater species. The SSD was used to estimate the 5% hazardous concentration (HC5) and the 95% lower confidence limit (LCL) of the HC5. Black dotted horizontal line represents the HC5, blue dotted line corresponds to the log10 PFOS concentration at the HC5, purple dotted line is the 95% LCL of the HC5. Species genus names are included for reference.

Salice CJ, Anderson TA, Anderson RH, Olson AD. 2018. Ecological risk assessment of perfluorooctane sulfonate to aquatic fauna from a bayou adjacent to former fire training areas at a US Air Force installation. Environmental Toxicology and Chemistry. 37(8):2198–2209. https://onlinelibrary.wiley.com/doi/abs/10.1002/etc.4162.

Ecotoxicity of PFAS

- Avian reduced chick survivability is main effect driver
- Both lethal after hatch and reduced hatching rate

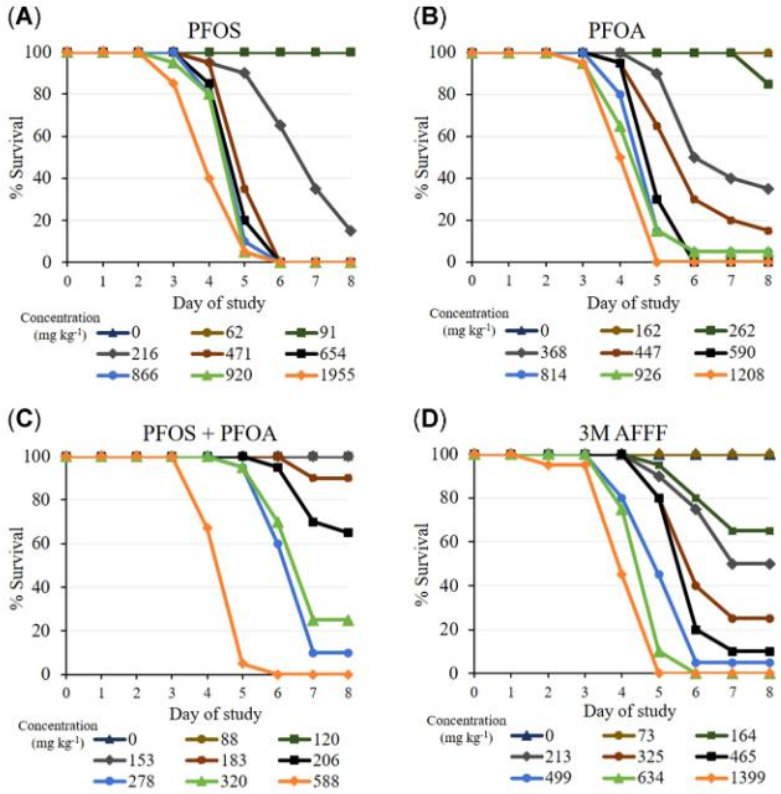


FIGURE 1: Effect of perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), PFOS + PFOA, and 3M aqueous film-forming foam (AFFF) on offspring survivability at day 8 following a 5-d dietary exposure. **(A)** Day 8 survivability of Japanese quail (*Coturnix japonica*) chicks at each concentration of dietary PFOS after a 5-d dietary exposure. **(B)** Day 8 survivability of Japanese quail chicks at each concentration of dietary PFOA after a 5-d dietary exposure. **(C)** Day 8 survivability of Japanese quail chicks at each concentration of dietary PFOS + PFOA after a 5-d dietary exposure. **(D)** Day 8 survivability of Japanese quail chicks at each concentration of PFOS provided by 3M AFFF after a 5-d dietary exposure.

Bursian SJ, Link JE, McCarty M, Simcik MF. 2021. The Subacute Toxicity of Perfluorooctane Sulfonate and/or Perfluorooctanoic Acid and Legacy Aqueous Film-Forming Foams to Japanese Quail (Coturnix japonica) Chicks. Environmental Toxicology and Chemistry. 40(3):695–710. https://onlinelibrary.wiley.com/doi/abs/10.1002/etc.4684.

Transition to more Andrew-centric data/work

Ecotoxicity of PFAS

- Mammals mirror effects of concern in humans, but with higher thresholds

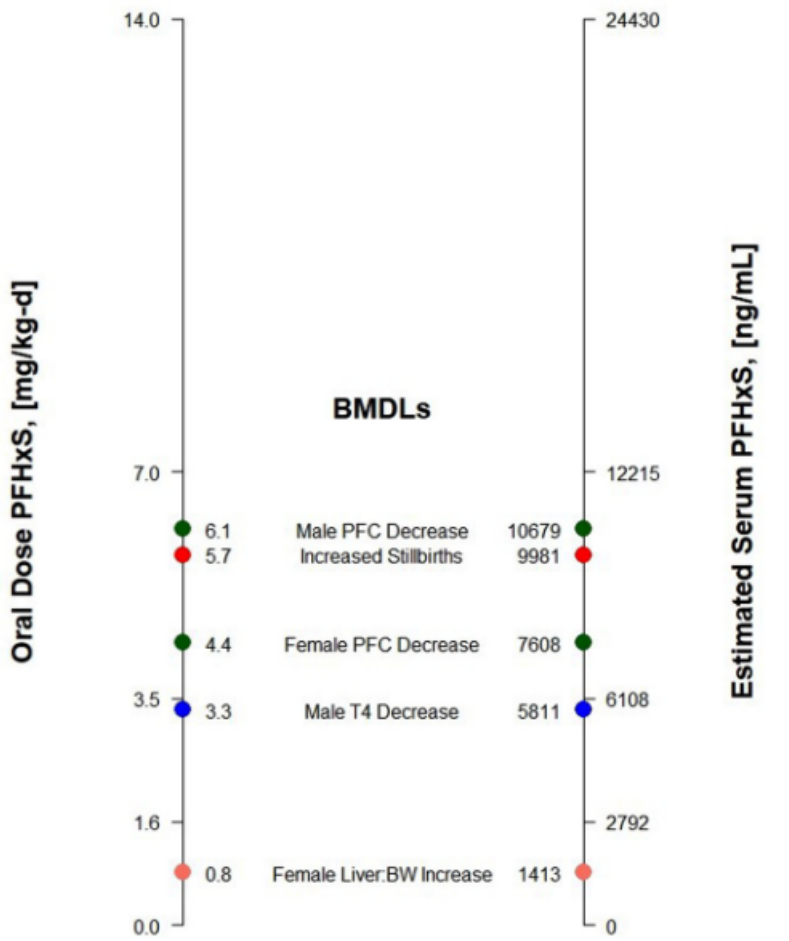
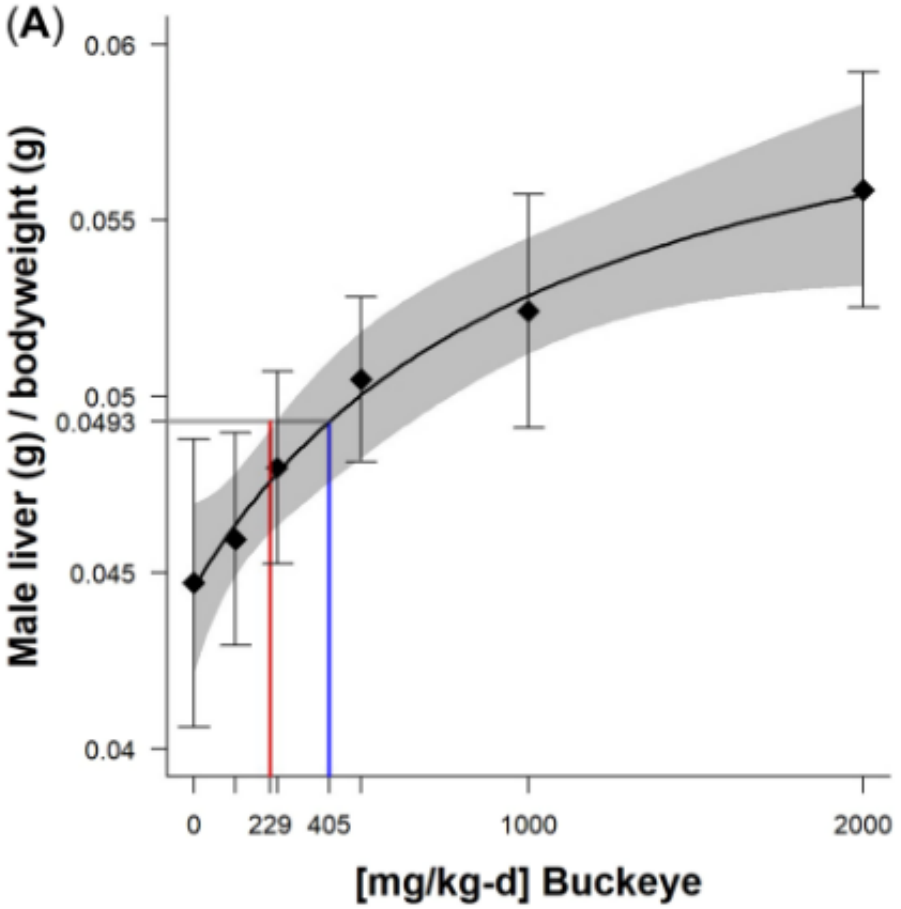


Fig. 4. BMDLs for *Peromyscus* exposed to PFHxS expressed as oral mg/kg-d or estimated serum concentration (ng/mL). To convert oral BMDLs to serum-based BMDLs, we followed the ratio of PFHxS in serum: dose delivered reported by [19]. Dose concentrations are tick-marked, while dots are BMDLs. Each color represents unique effects.

Narizzano AM, Bohannon ME, East AG, Guigni BA, Quinn MJ. 2023. Reproductive and immune effects emerge at similar thresholds of PFHxS in deer mice. Reproductive Toxicology. 120:108421. https://linkinghub.elsevier.com/retrieve/pii/S0890623823000953.

Ecotoxicity of PFAS

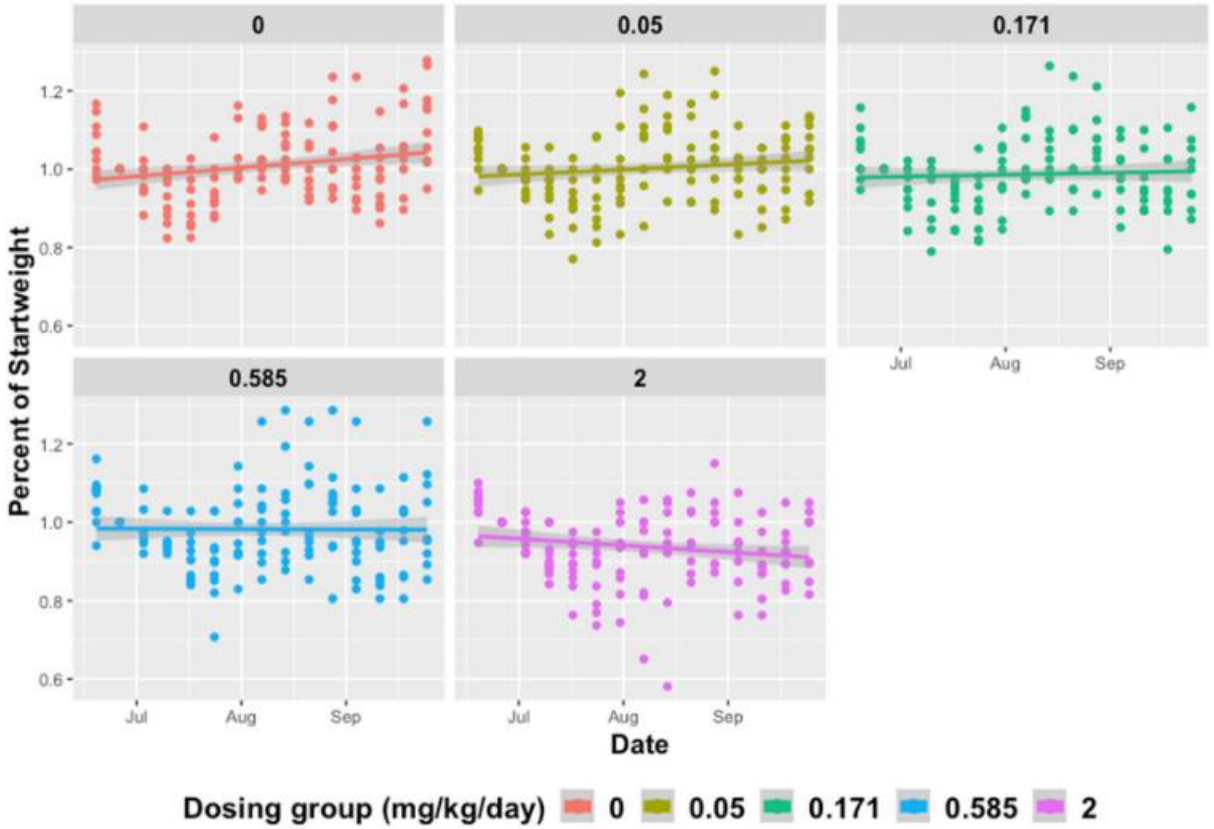
- If PFAS are in products, they still elicit similar effects
- Thresholds, measured by dose of product rise, but align with observations of PFAS alone



East AG, Narizzano AM, Holden LA, Bazar MA, Bohannon ME, Pervitsky D, Adams VH, Reinke EN, Quinn Jr. MJ. 2023. Comparative Toxicity of Seven Aqueous Film-Forming Foam to In Vitro Systems and Mus. Environmental Toxicology and Chemistry. https://onlinelibrary.wiley.com/doi/abs/10.1002/etc.5714.

Ecotoxicity of PFAS

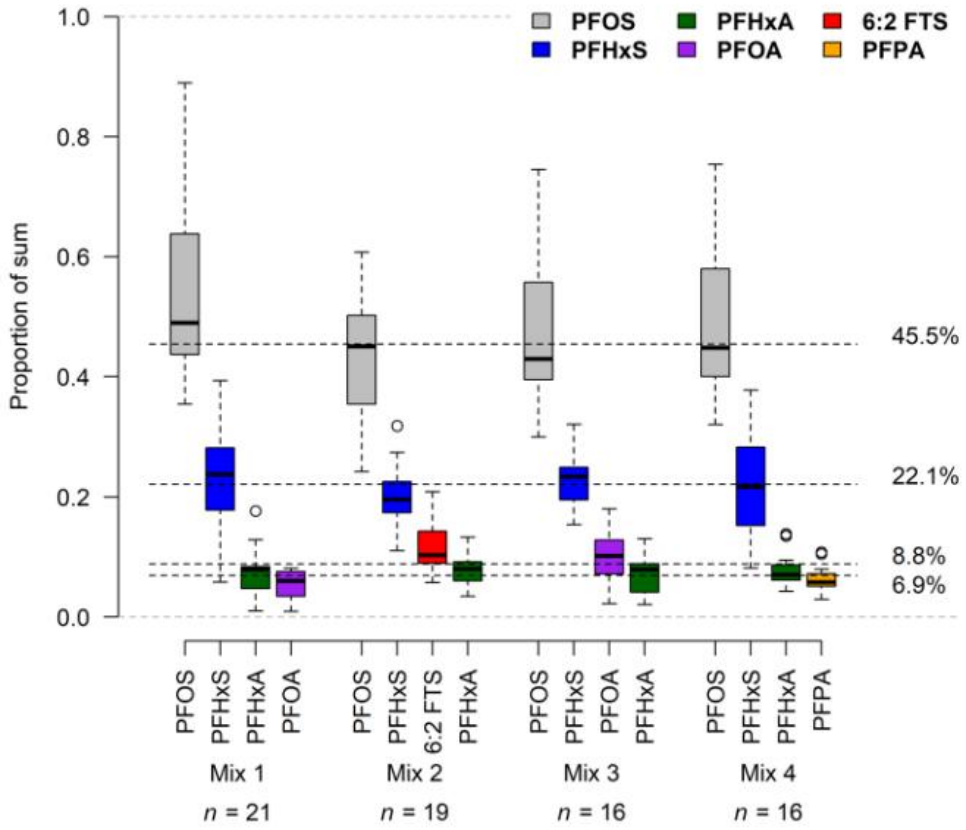
- Terrestrial herp
  - Brown anoles
- Reduced bodyweight is different than other organisms

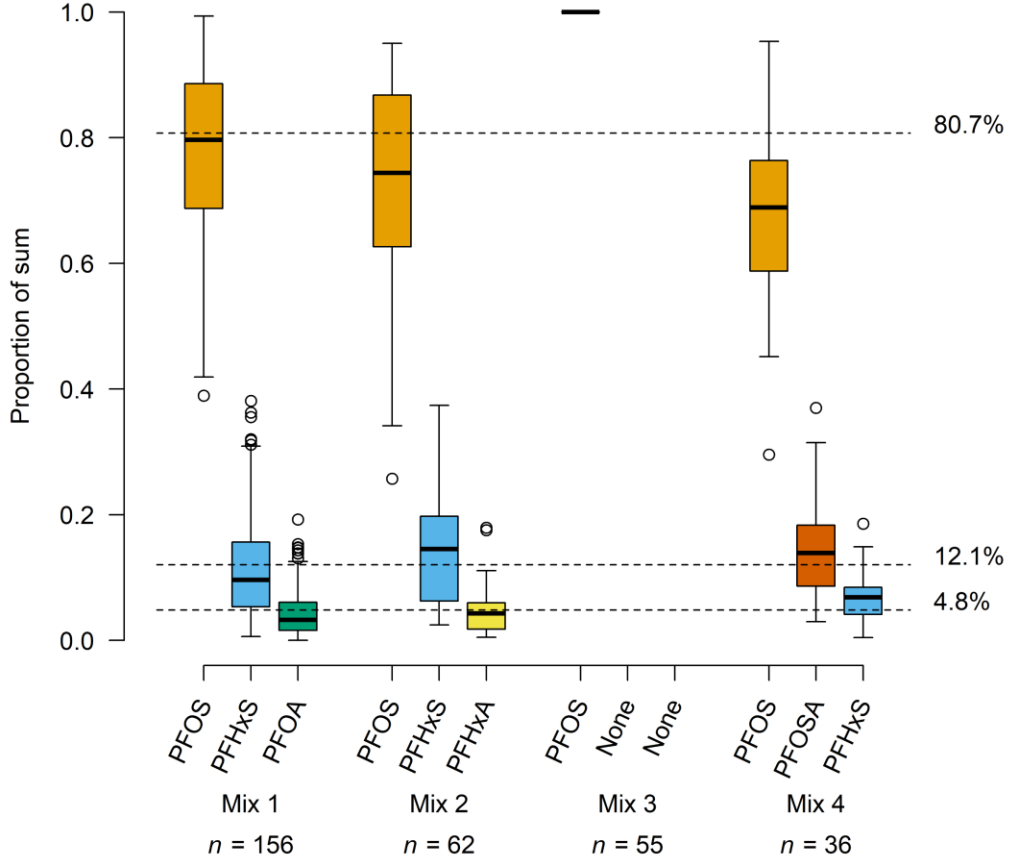


Salice C.J., Interim Report, ER-2627. https://serdp-estcp-storage.s3.us-gov-west-1.amazonaws.com/s3fs-public/project_documents/ER-2627_Interim_Report.pdf

Estimating exposure so we can talk about risk

- What PFAS are relevant?
  - At DoD sites, surface water and soil are dominated by PFOS and PFHxS.



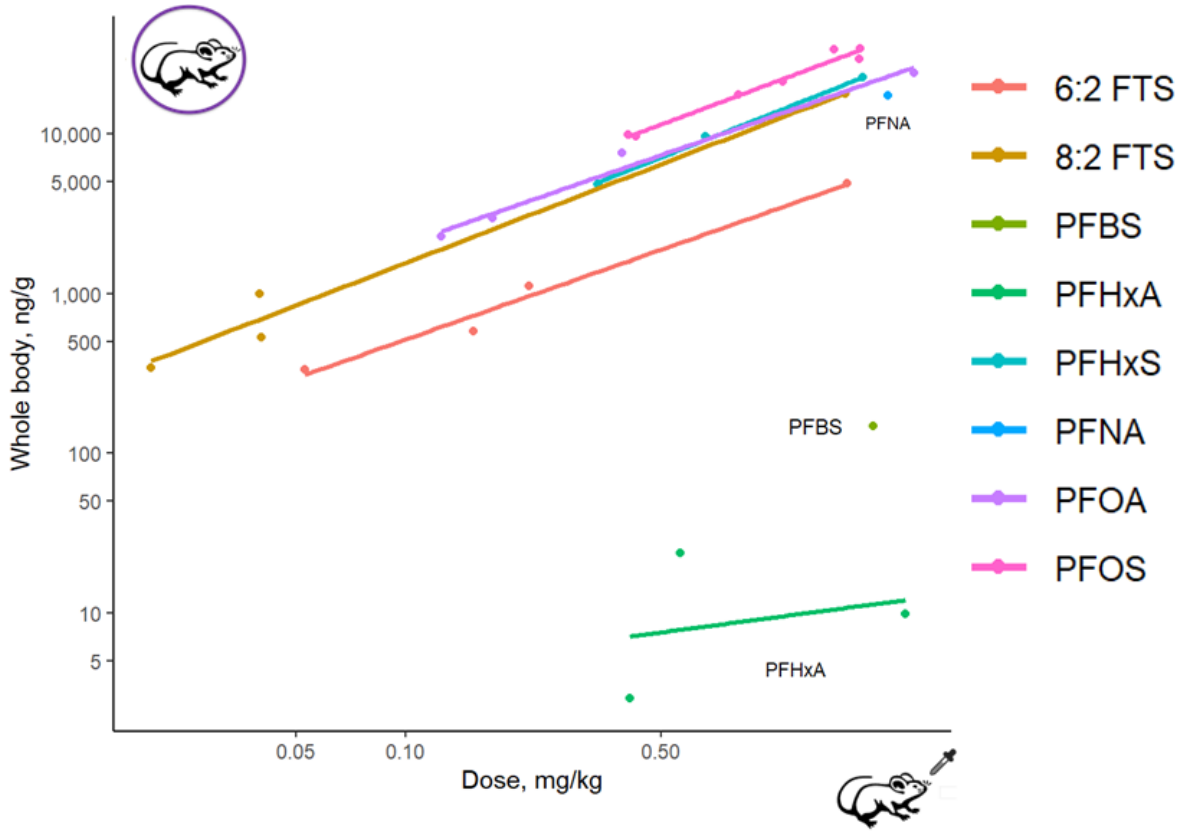


East A, Anderson RH, Salice CJ. 2021. Environmental Toxicology and Chemistry. https://onlinelibrary.wiley.com/doi/abs/10.1002/etc.4893.

East et al., in review. ET&C, 2024.

Do mixtures influence exposure?

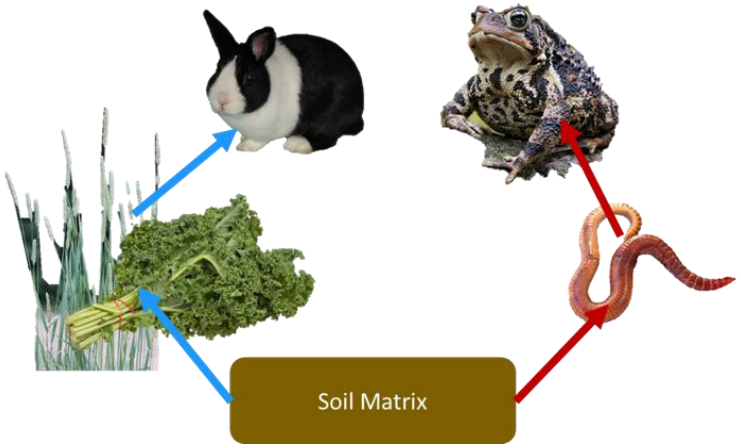
- Additivity is main observation
- Measured whole body concentrations are a function of dose regardless of exposed to single or mixture of PFAS

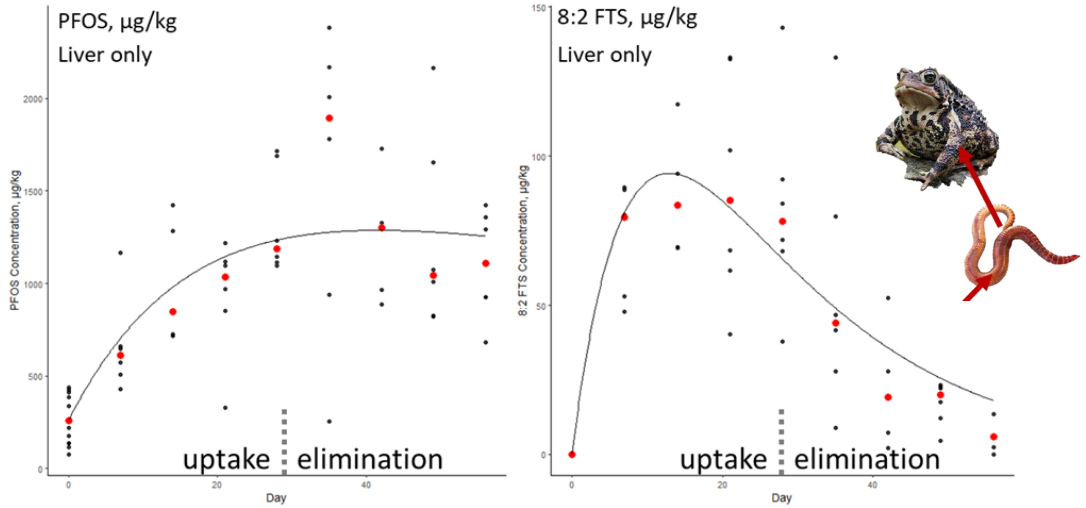


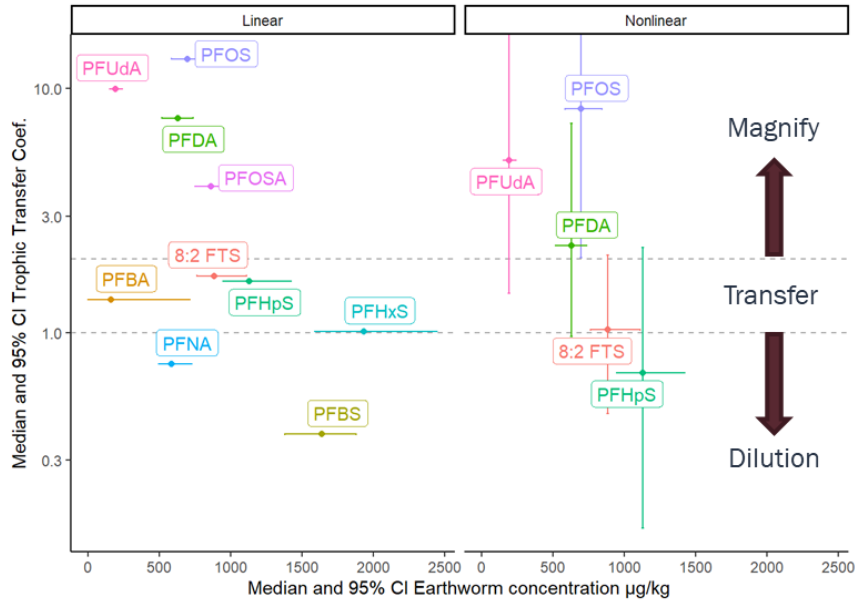
East et al., in prep.

Internal kinetics and trophic transfer

- Trophic Transfer Coefficients
  - Uptake / Elimination = measure of overall affinity of taxa+PFAS combination
  - Increase in TTC with increase in trophic level indicates trophic magnification







Putting it all together?

- Hard to say, ecorisk assessments are still “just” site-by-site per regulations that drive ecorisk assessments.
- Current big picture thinking is that small mammals will drive terrestrial risk (high soil contact, high diet concentrations, sensitive taxa)

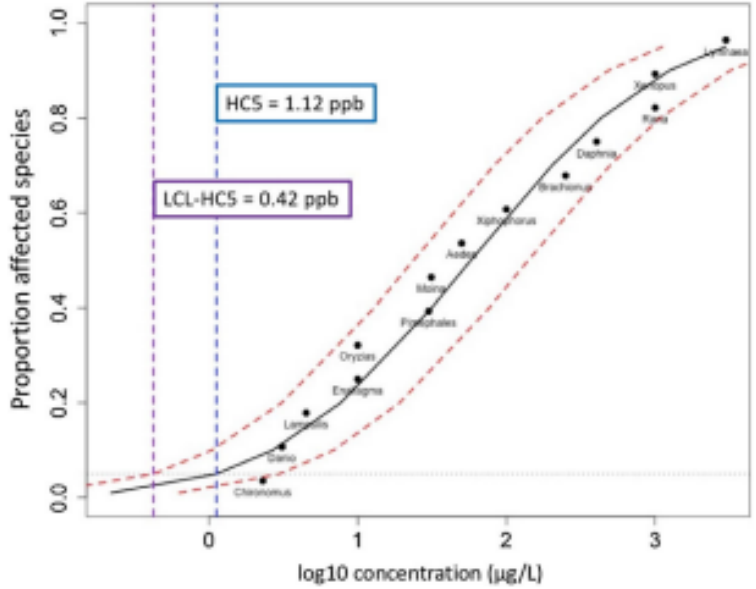


FIGURE 3: Species-sensitivity distribution (SSD) for chronic perfluorooctane sulfonate (PFOS) toxicity data for freshwater species. The SSD was used to estimate the 5% hazardous concentration (HC5) and the 95% lower confidence limit (LCL) of the HC5. Black dotted horizontal line represents the HC5, blue dotted line corresponds to the log10 PFOS concentration at the HC5, purple dotted line is the 95% LCL of the HC5. Species genus names are included for reference.

TABLE 2: Probability of exceeding benchmark toxicity values

Exposure scenario	Location	SSD HC5 (1.12 ppb)	SSD HC5 LCL (0.42)	Qi et al. (2011) (0.6 ppb)	Giesy et al. (2010) (5.1 ppb)
Reference	Flat River	<0.001	<0.001	<0.001	<0.001
Overall—likely	All Cooper Bayou	0.17	0.32	0.26	0.050
Specific location—likely	Weapons Bridge	0.14	0.25	0.21	0.043
High-end—likely	Cooper Confluence	0.23	0.36	0.31	0.09
High-end—unlikely	Upper-Tributary Mack’s Bayou	0.37	0.51	0.46	0.19

C5 = 5% hazardous concentration; LCL = 95% lower confidence limit of the HC5 from the SSD; SSD = species sensitivity distribution for chronic perfluorooctane sulfonate toxicity generated in the present study (Supplemental Data).

Salice CJ, Anderson TA, Anderson RH, Olson AD. 2018. Environmental Toxicology and Chemistry. https://onlinelibrary.wiley.com/doi/abs/10.1002/etc.4162.

Questions?

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