Perspectives on PFAS Health Effects

Stephen Zemba, PhD, PE (in MA)
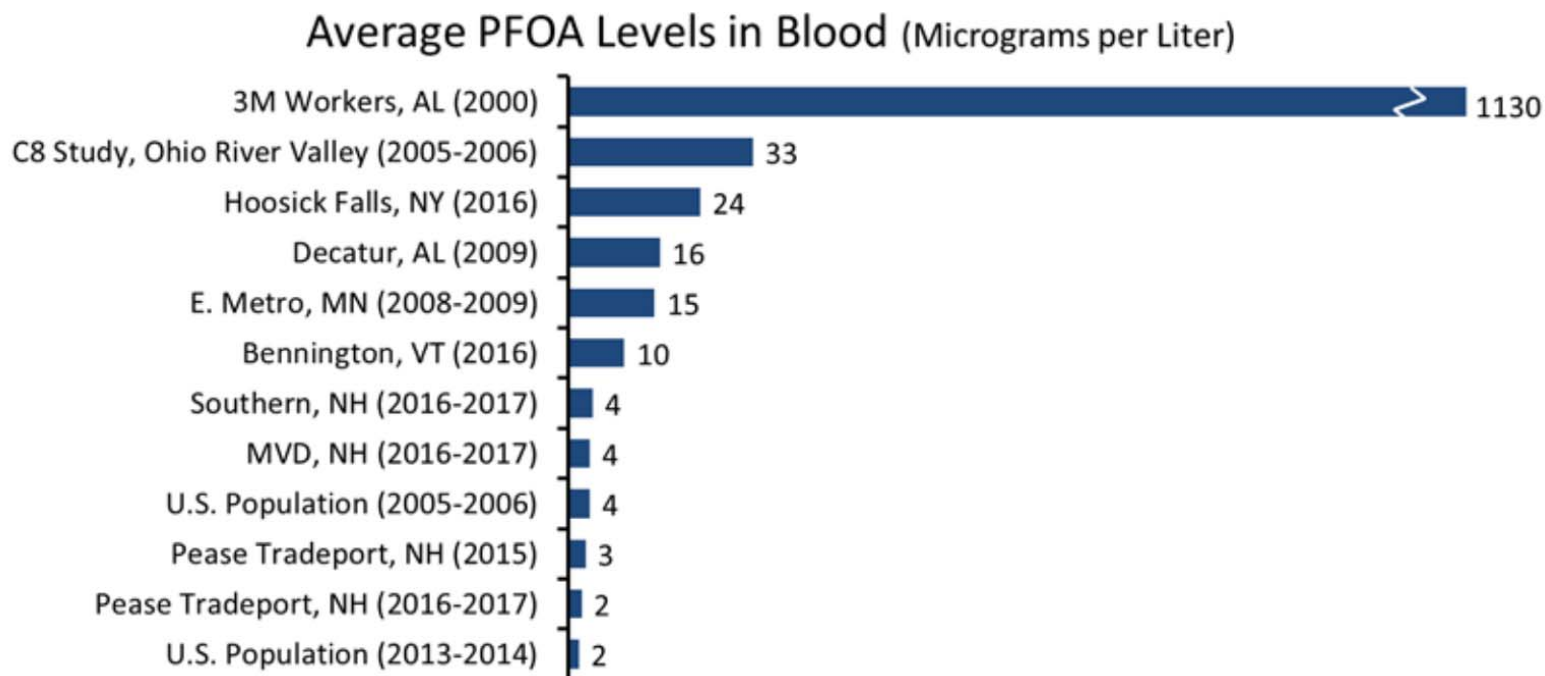
NEWWA 2022 Annual Conference

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Lifetime Health Advisories (LHAs)

- Authorized by Safe Drinking Water Act
- For contaminants without MCLs for which health effects are known or suspected
- Not legally enforceable, but can be highly influential
- Not openly peer reviewed or subject to public comment
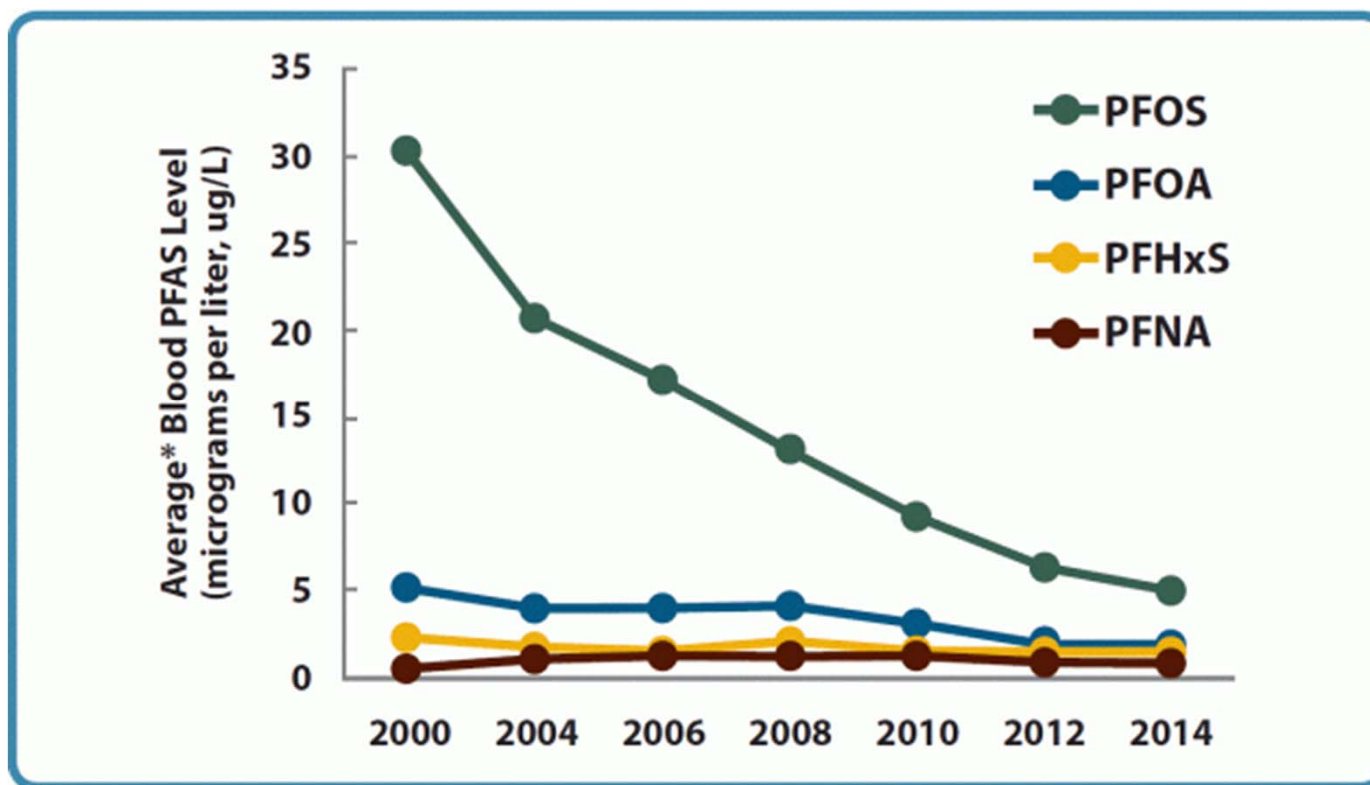- Available for ~200 contaminants

PFAS LHAs (in ng/L = ppt)

PFAS	2009	2016	2022
PFOA	400	70	0.004
PFOS	200		0.02
GenX	-	-	10
PFBS	-	-	2000

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PFOA Levels in Blood (µg/L)

Average PFOA Levels in Blood (Micrograms per Liter)

Location	Level
3M Workers, AL (2000)	1130
C8 Study, Ohio River Valley (2005-2006)	33
Hoosick Falls, NY (2016)	24
Decatur, AL (2009)	16
E. Metro, MN (2008-2009)	15
Bennington, VT (2016)	10
Southern, NH (2016-2017)	4
MVD, NH (2016-2017)	4
U.S. Population (2005-2006)	4
Pease Tradeport, NH (2015)	3
Pease Tradeport, NH (2016-2017)	2
U.S. Population (2013-2014)	2

- Exposure to PFOA and PFOS in water elevates levels in blood
- Bioconcentration over time ~100-fold

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PFAS Levels in Blood Serum (µg/L)

- PFOA background levels decreased from 5 µg/l in late 1990s to present 2 µg/l
- PFOS background levels decreased from 31 µg/l in late 1990s to present 4.3 µg/l

https://www.atsdr.cdc.gov/pfas/pfas-in-population.html

What We Know about Health Effects (EPA 5/9/2022)

Current peer-reviewed scientific studies have shown that exposure to certain levels of PFAS may lead to:
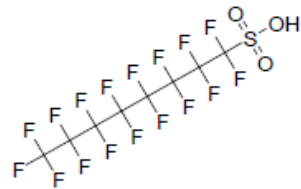
- Reproductive effects such as decreased fertility or increased high blood pressure in pregnant women.
- Developmental effects or delays in children, including low birth weight, accelerated puberty, bone variations, or behavioral changes.
- Increased risk of some cancers, including prostate, kidney, and testicular cancers.
- Reduced ability of the body's immune system to fight infections, including reduced vaccine response.
- Interference with the body's natural hormones.
- Increased cholesterol levels and/or risk of obesity.

- Which PFAS?
- Points of departure?
- Dose-response data?
- Key studies?
- Animal studies v. human epi studies?
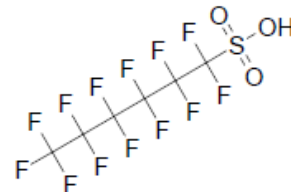- Relevance of animal models?

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https://www.epa.gov/pfas/our-current-understanding-human-health-and-environmental-risks-pfas
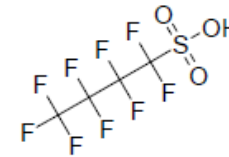
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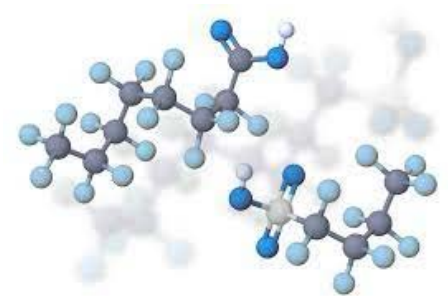
Examples of Some PFAS
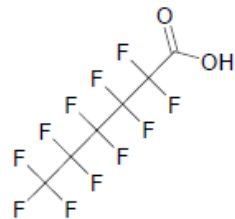
Sulfonic Acids

Perfluorooctane sulfonic acid
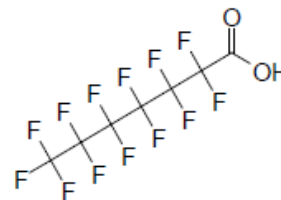
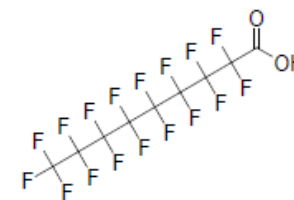Perfluorohexane sulfonic acid

Perfluorobutane sulfonic acid

Carboxylic Acids
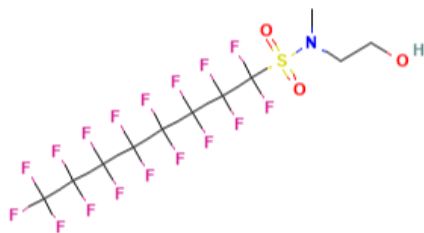
Perfluorohexanoic acid

Perfluoroheptanoic acid

Perfluorononanoic acid

Replacement PFAS

NMeFOSE
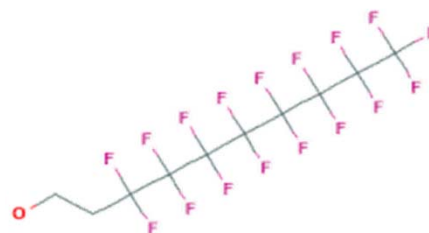
8:2 Fluorotelomer alcohol

GenX

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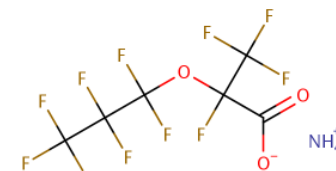
PFAS Risk Assessment

- Numbers of PFAS: Scope of concern for risk assessment?
  - # PFAS on EPA's CompTox website: 5,070
  - # PFAS on analytical lists: 20 to 30 or so
  - # PFAS with established toxicity data: 2 to ~6 depending on sources
- Considerations for the greater PFAS universe
  - Differentiate compounds based on structure/properties, e.g., short-chain v. long-chain, straight v. branched chains
  - Toxic Equivalency Factor schemes
  - Precursor PFAS
  - Lump "similar" PFAS together
  - Use the TOP Assay

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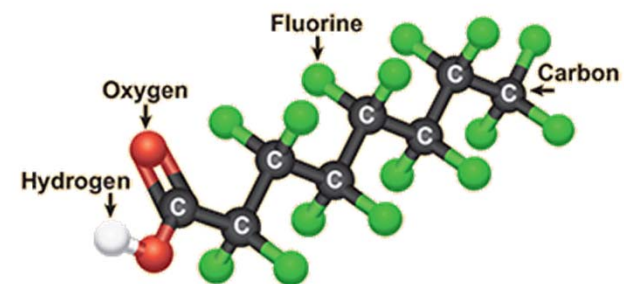
Risk Assessment / Toxicity Data Basics

- Categories of Health Effects
  - Cancer – characterized by Potency Slope Factors & Unit Risk Factors
  - Non-Cancer (neurological, hepatic, reproductive, developmental, etc.) – characterized by Reference Doses and Concentrations
- Sources of Toxicity Information
  - Human data
    - Workplace exposure
    - Epidemiological studies
  - Laboratory animal studies

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C8 Panel Studies

Dupont Washington Works Wood County, WV
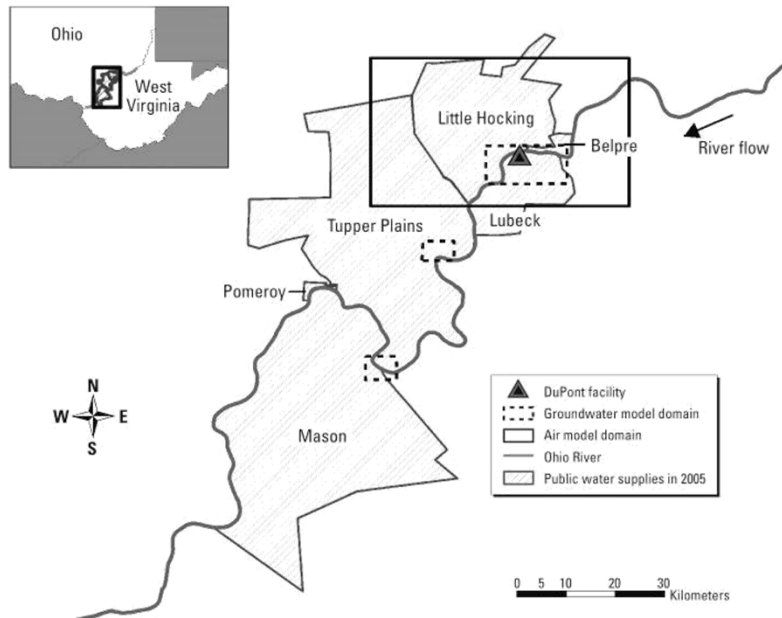
- "Probable links" between PFOA exposure and:
  - Diagnosed high cholesterol
  - Ulcerative colitis
  - Thyroid disease
  - Testicular and kidney cancers
  - Pregnancy-induced hypertension

- No correlations with:
  - Birth defects
  - Miscarriages and stillbirths
  - Preterm birth and low birth weight
  - Liver disease
  - 19 other cancers and 11 other non-cancer effects

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http://www.c8sciencepanel.org/prob_link.html

2016 Lifetime Health Advisory (LHA) of 70 ng/L

Animal Lab Dose	→	Equivalent Human Dose	→	Reference Dose	→	Incremental Exposure	→	Drinking Water Level
LOAEL 1,000,000 ng/kg-d		200 × ↓ Metabolism 5,300 ng/kg-d		300 × ↓ Safety 20 ng/kg-d		5 × ↓ Background 4 ng/kg-d		3.2 L/day, 59 kg 70 ng/L
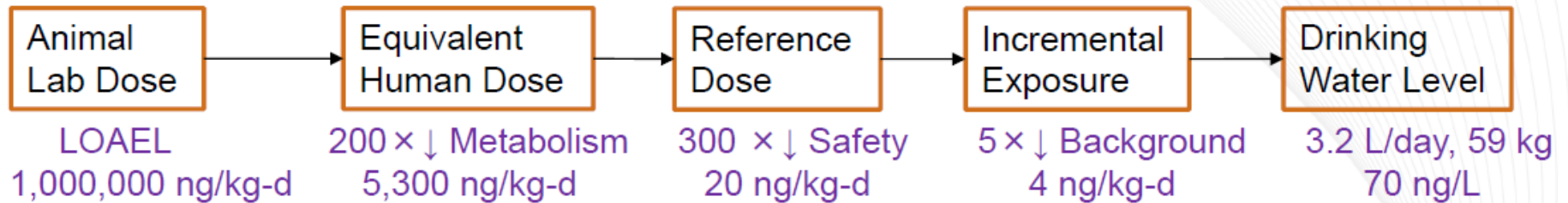
Regulatory Authority	Receptor	Chemical	Reference Dose (ng/kg-d)	Background Exemption	Exposure Rate (l/kg-d)	Risk-Based Concentration (ng/l = ppt)
U.S. EPA LHA	Nursing mother	PFOA + PFOS	20	80%	0.054	70
VT DOH	Nursing infant	PFOA + PFOS	20	80%	0.175	20
TX CEQ	Small child	PFOA	12	0%	0.041	290
		PFOS	23			560

Background Exemption = 100% - Relative Source Contribution

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Key Considerations in Animal Studies

- What constitutes a health effect?
  - Actual damage?
  - Non-permanent differences?
- How to account for animal/human differences?
  - Some animal endpoints may be irrelevant
  - Elimination of PFAS considerably faster in rodents
  - Peroxisome Proliferator-Activated Receptor (PPAR)
    - 10 times more important to rodents
    - What health effects depend on PPAR?

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Relative Source Contribution

- Relative Source Contribution (RSC) = allowable % of acceptable exposure via drinking water
- EPA defaults to an RSC = 20% -- many states have adopted this value, also
- EPA's 2016 LHA alloted 80% of exposure to non-drinking water "background"
  - Background = 80% ×20 ng/kg-day × 70 kg = 1,120 ng/day
- NJ's *former* 40 ppt (ng/l) PFOA groundwater standard was based on doubling of exposure via drinking water
  - Background = 40 ng/l × 2 l/d = 80 ng/day
- Gebbink et al. (2015) PFAS exposure estimates for a 70 kg adult

Gebbink et al data	Low	Intermediate	High
Exposure (ng/day)	9	48	343

- Data suggest that RSC values could be justifiably higher

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NH Application of Multigenerational Model for PFOA

4.0 µg/L PFOA at time of delivery

1.1 µg/L PFOA after one year breastfeeding

20.6 µg/L PFOA at 1 year

6.6 µg/L PFOA at 7 years

4.0 µg/L PFOA at time of delivery

3.6 µg/L PFOA steady state as adult

3.6 µg/L PFOA steady state as adult

Based on PFOA drinking water concentration of 0.012 µg/L

Adult blood:water ratio = 300

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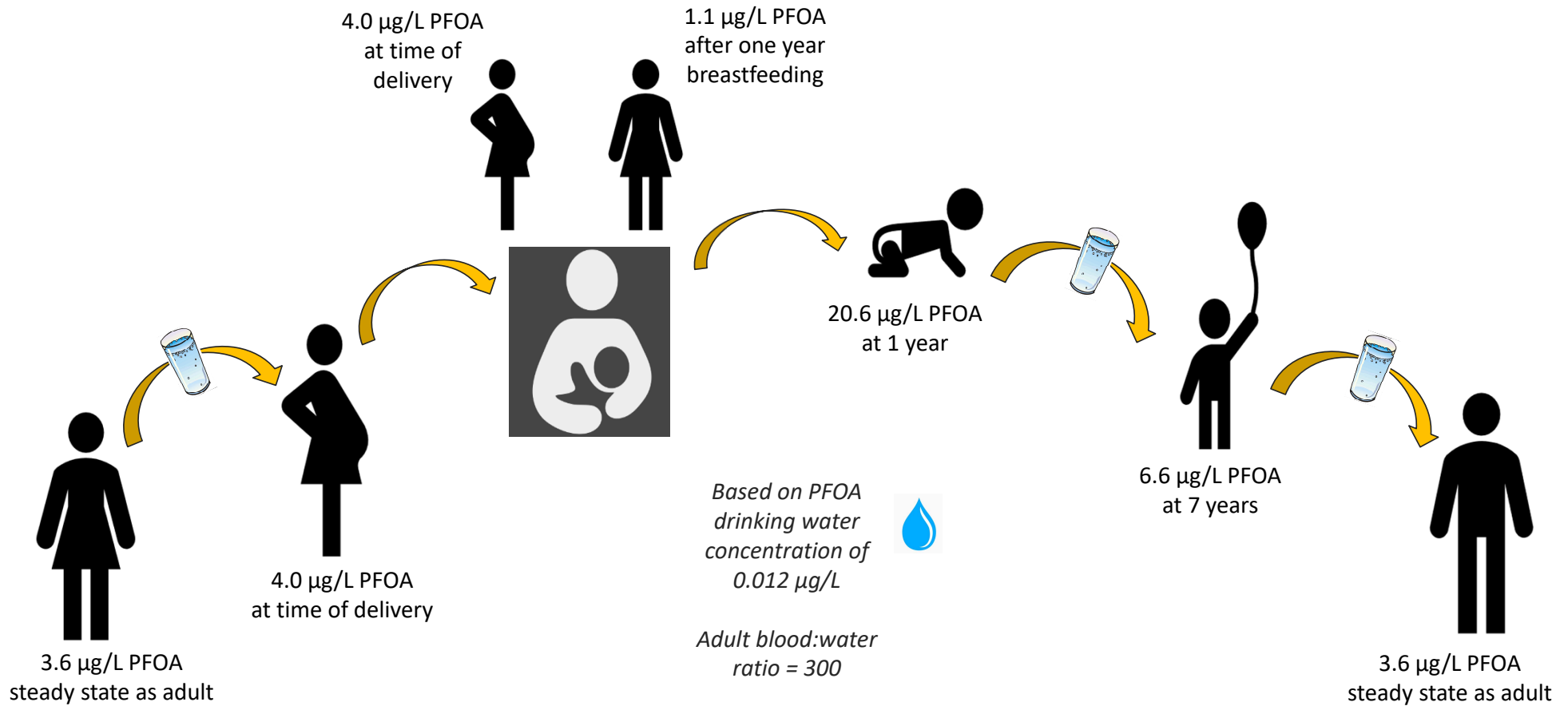
PFAS in Human Serum

- Current models/data indicate PFAS in serum highest in infants (basis of NH MCLs, figure at right)

- Critical health effect: Immune system development

Estimated Exposures to Perfluorinated Compounds in Infancy Predict Attenuated Vaccine Antibody Concentrations at Age 5-Years

Philippe Grandjean,[*,a,b] Carsten Heilmann,[c] Pal Weihe,[d] Flemming Nielsen,[b] Ulla B Mogensen,[e] Amalie Timmermann,[b] and Esben Budtz-Jørgensen[e]

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Figure: https://www4.des.state.nh.us/nh-pfas-investigation/wp-content/uploads/June-PFAS-MCL-Technical-Support-Document-FINAL.pdf

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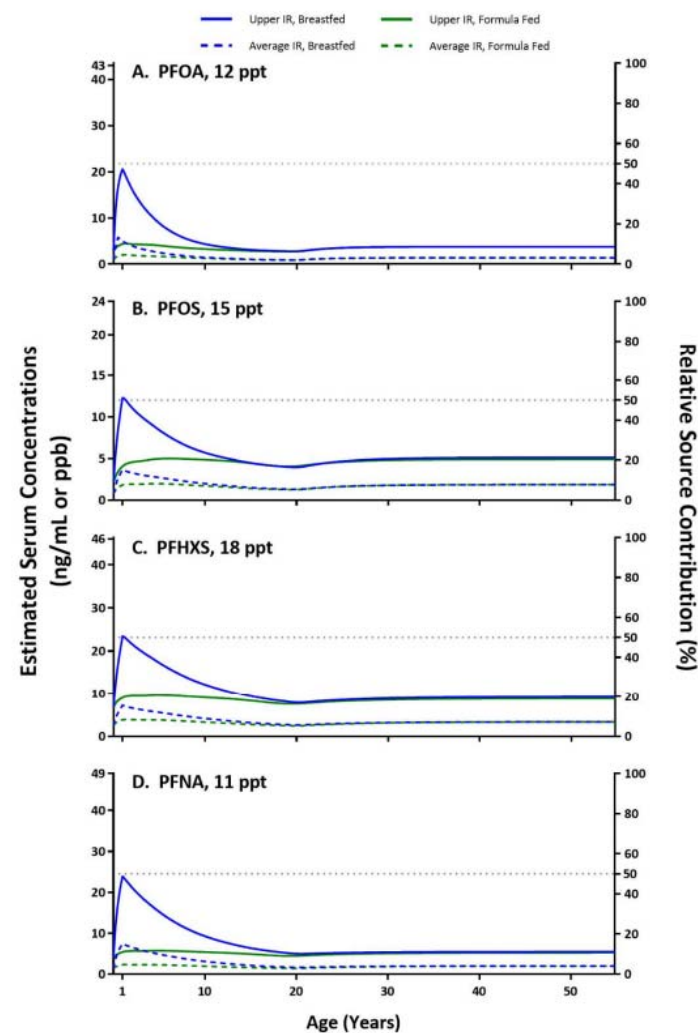
Shift to Immunotoxicity / Epidemiology (PFOA)

Table 15. Summary of Endpoints and Studies Considered for Dose-Response Modeling and Derivation of Points of Departure for All Effects in Humans and Rodents

Endpoint	Study Reference and Confidence	Strain/Species/Sex	Notes
Immune Effects			
Reduced Antibody Concentrations for Diphtheria and Tetanus	Grandjean, (2012, 1248827); Grandjean, (2017, 3858518); Grandjean, (2017, 4239492); Budtz-Jørgensen (2018); Medium confidence	Human (male and female children)	Effect was large in magnitude and generally coherent with epidemiological evidence for other antibody effects. BMD modeling performed by study authors.
Reduced immunoglobulin M (IgM) Response	Loveless et al., 2008, 988599; DeWitt et al., 2008, 1290826; Medium confidence	C57BL/6N mice (females), Crl:CD-1(ICR)BR mice (males)	Functional assessment indicative of immunosuppression. Immune effects were consistently observed across multiple studies

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Shift to Immunotoxicity / Epidemiology (PFOA)

Table B-1. BMDs and BMDLs for Effect of PFOA at Age Five Years on Anti-tetanus Antibody Concentrations at Age Seven Years

BMR	Estimated without control for PFOA		Estimated with control for PFOA	
	BMD (ng/mL)	BMDL (ng/mL)	BMD (ng/mL)	BMDL (ng/mL)
5%	0.52	0.16	0.67	0.17[a]

[a] Value on which POD is based for immunotoxicity related to tetanus.

- POD = Point of Departure; BMDL = Benchmark Dose Lower Limit
- BMDL = Concentration in Serum
  - Typical in U.S. adults = 2 ng/mL at present
    - 5 ng/mL in late 1990s
- If Infant serum:Adult serum ratio = 5, implies 10 ng/mL in infants at present
- Implication: Infant exposures to PFOA > BMDL

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Thoughts/Perspectives on PFOA/PFOS LHAs

- Maximum Contaminant Levels (MCLs) for PFOA and PFOS will likely be proposed at reliable detection limits

- Significance of endpoints
  - Tetanus in the U.S. (2001 to 2008)
    - 233 total cases (29 per year)
    - 26 total deaths (3 per year)
  - Diphtheria in the U.S. (1996 to 2018)
    - 14 total cases (<1 per year)
    - 1 death

- Epidemiological studies are based on high-end environmental exposures – target exposure levels imply widespread adverse effects on immune system development across the population

https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6012a1.htm
https://www.cdc.gov/vaccines/pubs/pinkbook/dip.html
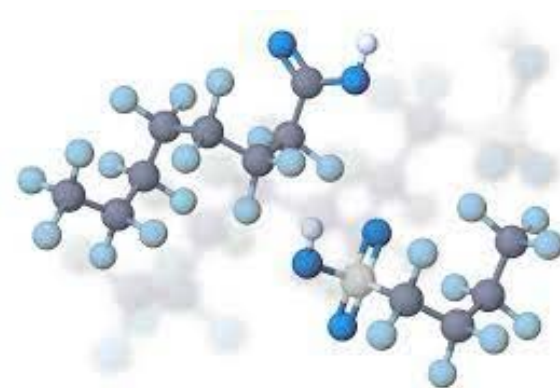
PFAS Exposure and COVID-19 ?

Statement on Potential Intersection between PFAS Exposure and COVID-19:

CDC/ATSDR understands that many of the communities we are engaged with are concerned about how PFAS exposure may affect their risk of COVID-19 infection. We agree that this is an important question.

CDC/ATSDR recognizes that exposure to high levels of PFAS may impact the immune system. There is evidence from human and animal studies that PFAS exposure may reduce antibody responses to vaccines (Grandjean et al., 2017, Looker et al., 2014), and may reduce infectious disease resistance (NTP, 2016). Because COVID-19 is a new public health concern, there is still much we don't know. More research is needed to understand how PFAS exposure may affect illness from COVID-19.

- Deductive Logic
  - PFAS exposure weakens the immune system development
  - Increased susceptibility to contracting COVID-19 and/or fighting it off
- How strong is the evidence? Is there a dose-response relationship?

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ATSDR website, https://www.atsdr.cdc.gov/pfas/health-effects/index.html, accessed July 9, 2020

Do PFAS cause Cancer?
(and does it matter)

- Evidence of PFAS carcinogenicity from C8 Panel studies and animal studies is inconsistent and/or inconclusive
- Results of local health studies have been negative or inconsistent
  - Hoosick Falls, NY (2017) – only lung cancer statistically elevated (lung cancer not otherwise linked to PFAS)
  - Merrimack, NH (2018) – no significantly different cancer rates, including cancers associated with PFOA
  - Washington and Dakota Counties, MN (2018) – overall cancer rate same as statewide
- In 2016, issue was somewhat moot as the risk for a 70 kg person drinking 2 L/day water with 70 ppt PFOA for 70 years is **0.14 per million** (1.4×10^{-7}) (potency 0.07 kg-d/mg)
- New evidence for PFOA carcinogenicity is discussed in the 2021 EPA "Approaches" document – could lead to an MCLG of 0?

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GenX in North Carolina – 2017 Evaluation

- "In July 2017, DHHS set a provisional health goal of 140 nanograms per liter (ng/L) or parts per trillion (ppt) for GenX in drinking water. This is a level of GenX in drinking water below which no adverse health effects would be expected over a lifetime of consumption."

- "NCDHHS is currently reviewing EPA's human health toxicity assessment for GenX chemicals. The current provisional drinking water health goal will likely be replaced by EPA's national health advisory level for GenX in drinking water when that becomes available, which is expected in spring 2022."

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https://epi.dph.ncdhhs.gov/oee/a_z/genx.html

GenX in North Carolina – Details of 2017 Evaluation

- Pre-2017 Preliminary Assessment: 71,000 ng/L
  - Used European Chemical Agency RfD = 10,000 ng/kg-d
  - Based on exposure of a bottle-fed infant
    - 7.8 kg weight
    - 1.1 L/d consumption
    - 100% RSC (all exposure from formula)

- 2017 Revision: 140 ng/L
  - Revised RfD = 100 ng/kg-d
  - Based on exposure of a bottle-fed infant
    - 7.8 kg weight
    - 1.1 L/d consumption
    - 20% RSC (up to 80% "background" exposure)

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https://files.nc.gov/ncdeq/GenX/DEQ-GenX%20FAQ%2008212017%201.pdf
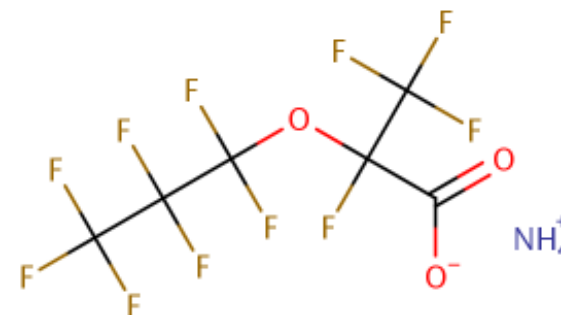
US EPA 2022 Toxicity Assessment for GenX

- RfD = 3 ng/kg-d
- Exposure to lactating mother drinking water at 0.0469 L/kg-d
- RSC = 20%
- Health Advisory Level = 10 ng/L (rounded)

Agency / Time	Reference Dose (RfD) (ng/kg-d)	Relative Source Contribution (RSC) Allotted to Drinking Water	Safe Drinking Water Criterion (ng/L = ppt)
NH DHHS pre-2017	10,000	100%	71,000
NH DHHS 2017	100	20%	140
US EPA 2022	3	20%	10

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Ecological Risk Assessment Under Development

- Relevant to Ambient Water Quality Criteria
- DoD-sponsored guidance provides:
  - Info on 18 PFAS (PFOS & PFOA focus)
  - Aquatic toxicity criteria for PFOS & PFOA
  - Biotransfer and bioaccumulation factors
  - Foodweb methodology
  - Toxicity reference values
- Take-home points
  - Some PFAS (*e.g.*, PFOS) bioaccumulate
  - Human health may outweigh ecotoxicity
  - Key receptors may be small mammals and birds with limited habitat ranges

GUIDANCE DOCUMENT

Guidance for Assessing the Ecological Risks of PFASs to Threatened and Endangered Species at Aqueous Film Forming Foam-Impacted Sites

SERDP Project ER18-1614

JANUARY 2020

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Distribution Statement A
This document has been cleared for public release

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https://www.serdp-estcp.org/content/download/49882/491435/file/ER18-1614%20Guidance%20Document.pdf

Thank you!

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ITRC Technical Resources for PFAS

https://www.itrcweb.org/Team/Public?teamID=78

- Fact sheets
- Web-based Technical and Regulatory Guidance Document
- On-line Training Materials