

Lessons Learned From 20 Years Of Study Of The Dioxins: Can It Help Inform EPA In Setting An MCL For PFOS/PFOA?

Dennis Paustenbach, PhD, DABT, FATS

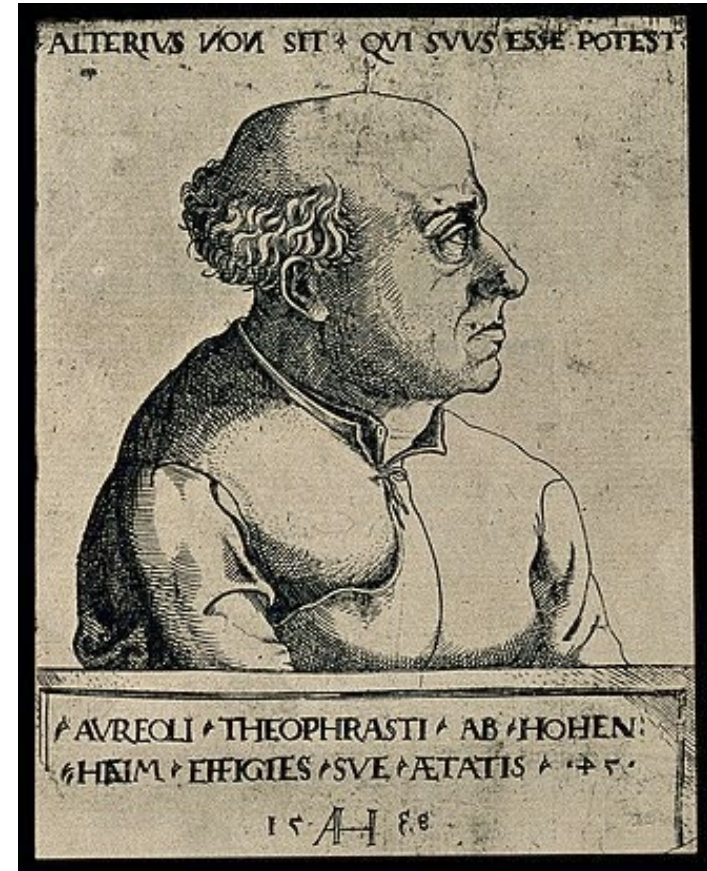
Toxicology Forum

Shubik Lecture

January 22, 2024

Washington DC

Before Proceeding, I Must
Confess That I Am An Old
School Toxicologist... That Is,
To Me, Dose Is Nearly
Everything, Whole **Animal
Studies Are Useful, And Good
Epi Studies Are Invaluable!**



Paracelsus

A Relevant Observation

- Dr. Shubik believed that the Toxicology Forum was a place where scientists within the regulated community (e.g., corporations and groups like DOD/DOE), the regulatory agencies and university professors could talk freely about scientific matters of significance.
- Let me share my views about the historical journey with the dioxins and how it might help inform decision making on the perfluorinated chemicals.

Overview

- PFOS/PFOA.. Scientific and Regulatory Challenges
- Is there something to learn from the dioxin experience?
- Biological half-life in humans and environmental half-life
- Acute and Chronic Toxicity (cancer)
- Epidemiology
- EPA proposed MCL of 4 ppt... and the impact on society
- A possible path forward

Society is Facing A Significant Decision
About How to Regulate PFOS/PFOA In
Drinking Water... Perhaps the Most
Financially Impactful Rulemaking in the
History of the Environmental Revolution
(Which Began in 1962)

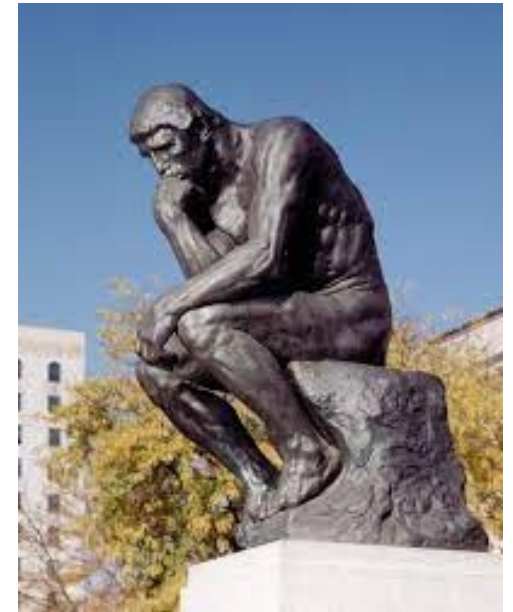
PFAS In The News



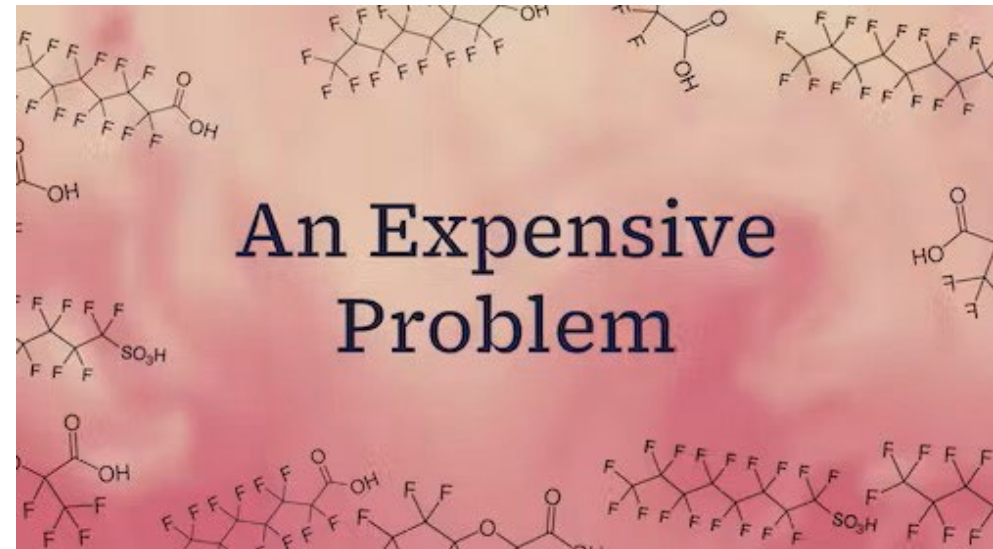
EPA, 2023. Questions and Answers: Drinking Water Health Advisories for PFOA, PFOS, GenX Chemicals and PFBS

Let Me Be Clear...

- U.S EPA needs to promulgate several MCLs for perfluorinated chemicals
- I applaud them for all the work they have invested in this effort; it was a massive undertaking
- But, I am suggesting that this MCL is like no other; thus, requiring great care



Regulating PFAS In
Drinking Water At The
Proposed MCL Of 4 ppt
Could Cost The US Either
Several Hundred Billions
or Trillions (Bloomberg
Law Estimates, 2023)



The Cost Will Impact Many Persons

- A lifetime health advisory of 70 ppt was proposed by EPA in 2016
- American Water Works Association (AWWA) has indicated that the price tag for drinking water to achieve PFOS/PFOA levels of 4 ppt would exceed \$50 billion over twenty years (probably much, much higher)
 - For affected households, it may cost an additional \$80-11,000 annually for filtration systems to address these chemicals.

- EPA. 2023. Questions and Answers: Drinking Water Health Advisories for PFOA, PFOS, GenX Chemicals and PFBS
- TERA Conference. 2023. AWWA Presentation

There will be An Impact On Society

- It will significantly affect the Superfund Program
- Many water providers and firms would be impacted at an MCL of 4 ppt; but few be significantly affected at 70 ppt
- Some companies will not survive 4 ppt MCL
- Personal injury claims could easily reach many billions



- Alston & Bird. 2021. Superfund Cleanup article
- ACC. 2023. Organizations Oppose EPA's Drinking Water Proposal blog post
- Reuters. 2023. Expect more litigation in 2024 article
- Baker McKenzie. 2023. PFAS Litigation Expanding blog post

A Massive Regulatory Challenge

- Fire training facilities
- Fire stations
- Refineries
- DoD sites/Military bases
- Commercial and private airports
- Landfills (leaching from consumer products)
- Biosolids land application
- Rail yards
- Chemical facilities
- Plating facilities
- Textile/carpet manufacturers
- Residential areas with septic systems

The risk that companies will be driven into insolvency has been voiced publicly by Judge Richard M. Gergel of the US District Court for the District of South Carolina, who's overseeing multidistrict litigation against firefighting foam defendants.

At a court hearing in July, Gergel urged plaintiffs and defendants to join together to lobby Congress about the scope of the problem, saying private industry "just doesn't have the capacity to remediate this completely."

U.S. Competitiveness On The Global Stage

U.S. Chambers of Commerce has stated “Many products critical to modern society —including aircraft, automobiles, semiconductors, and medical equipment — cannot be produced without these chemistries as there are no feasible or economic PFAS replacements.

The PFAS Restriction, therefore, would have significant negative impacts on the operations, business models, and supply chain dynamics in those sectors and others.” (2023)

- U.S Chamber of Commerce. 2023. Impacts of the PFAS Restriction on Trade Between the U.S. and the European Union

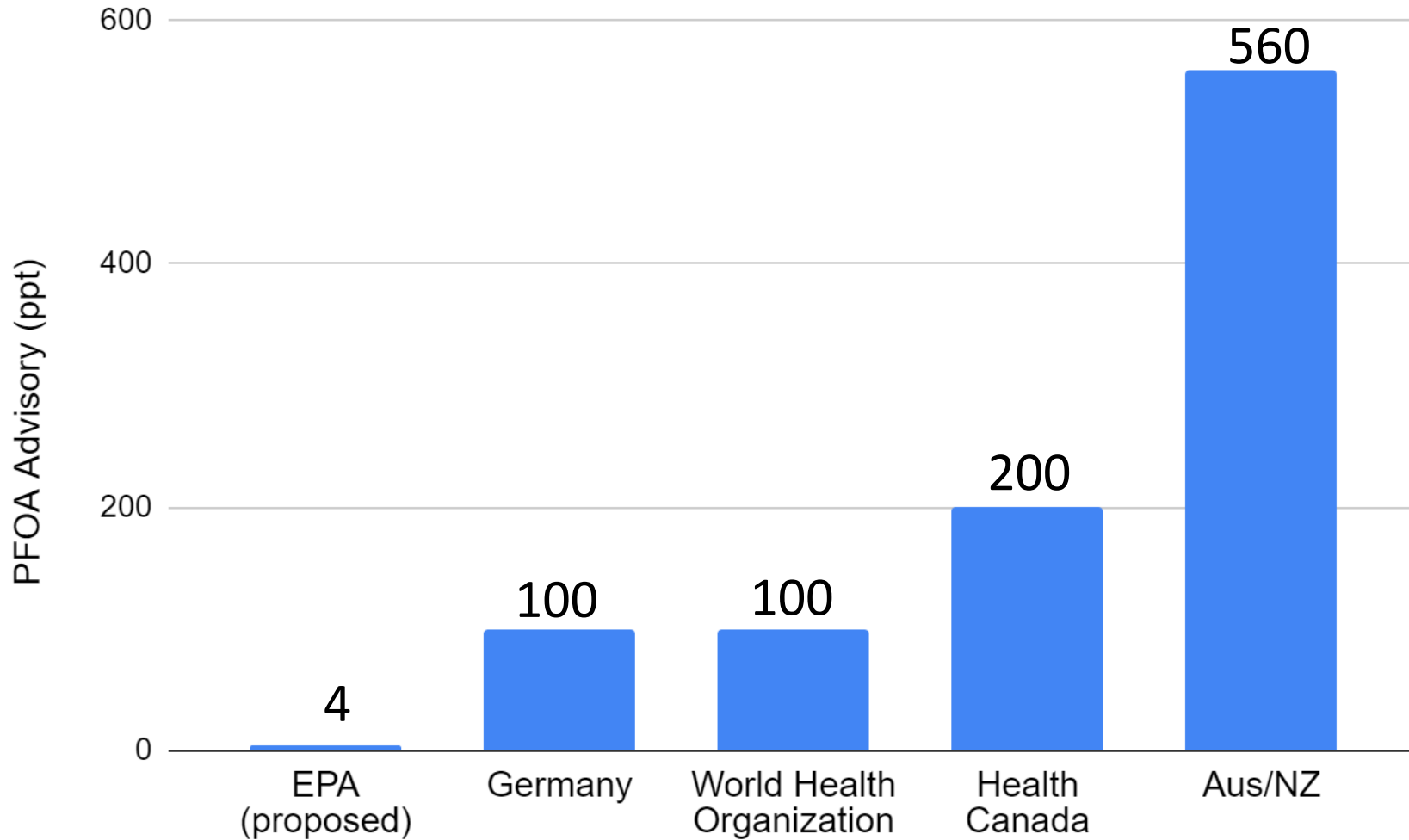
Safe Doses Proposed By Various Nations (They Span A 1,000-Fold Difference)

- US EPA: 0.0000015 $\mu\text{g}/\text{kg}\text{-day}$
- EU: 0.0008 $\mu\text{g}/\text{kg}\text{-day}$
- Canada: 0.02 $\mu\text{g}/\text{kg}\text{-day}$
- Germany: 0.02 $\mu\text{g}/\text{kg}\text{-day}$
- Australia: 0.16 $\mu\text{g}/\text{kg}\text{-day}$



- Burgoon et al. 2023. Reg Toxicol Pharm. 145: 1-12.

Water Guidelines In Other Countries



- Beck, N. 2023. Presentation at TERA Conference
- Dietrich & Griem, 2023. Presentation at TERA Conference

Might The EPA Proposed Maximum Contaminant Level (MCL) Deserve Additional Reflection?

Might A Higher MCL be Adequately Protective of Public Health?

Does History Suggest Caution is Warranted?

Can We Learn From The Dioxin Experience (1985-2010)

My Past

- In 1984, I was assigned to a team to deal with Times Beach, Missouri
- It was the first and only town in America to be purchased by the government due to a toxicant (dioxin)
- From 1985-2005, published 20+ papers on dioxins. Served on several Science Advisory Panels.
- The journey with dioxins/furans should give us pause as we move forward to regulate PFOS/PFOA.

What Are PFAS?

- **Known as the “forever chemicals”**
- A family of over 800-12,000 chemicals
- Used for decades in thousands of applications
- **Environmentally and biologically persistent (relatively)**
- **Found in the blood of all humans, animals, and aquatic species.**

- EPA. 2023. PFAS Explained
- FDA. 2023 PFAS

What Are “Dioxins”?

- **Known as “The Most Toxic Chemical Known to Man”**
- Dioxins and Furans are a family of structurally related chemicals which have a common mechanism of action
- **Environmentally and biologically persistent**
- **Found in the blood of all humans, animals, and aquatic species.**

- WHO. 1999. Dioxins And Their Effects On Human Health
- WHO. 2023. Dioxins

Brief History Of 2,3,7,8-TCDD

- 1899: Chloracne was seen in chlorine workers
- 1962-1970: Agent Orange in Vietnam
- 1978: Kociba rat study identified cancer at very low doses
- 1985 – 2005: A myriad of possible adverse effects were alleged
- 2004: Poisoning of President Yushchenko
- 1980-2015: Debate about toxicity (e.g., cancer) in humans

- White and Birnbaum. 2009. J Environ Sci Health C. 27(4): 197
- Crummett, W. 2003. Decades of Dioxin

Brief History Of PFOA

- 1940's: PFAS production and use in industry begins
- 1960-1980: Mixed results in toxicology studies
- 1981: Concern about developmental effects
- 1987: Rat study identifies a cancer risk at high doses
- 2012: A study in the Faroe Islands suggests decreased effectiveness of vaccinations (but within normal limits)
- 2010-2024: A myriad of possible effects were alleged (irrespective of dose and species)

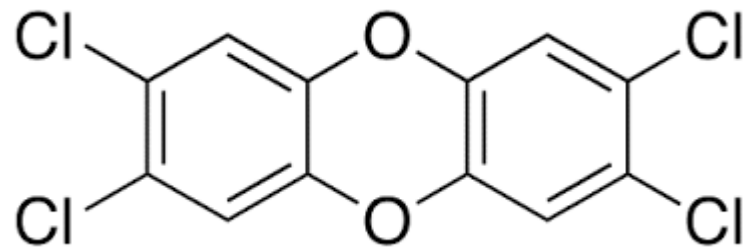
- EPA. 2009. Provisional Health Advisories for PFOA and PFOS
- Grandjean et al. 2012 JAMA. 307(4): 391-397
- Fenton et al. 2021. Environ Toxicol Chem. 40(3): 606-630

You Would Not Expect These Two Classes Of Chemicals To Be Similar, Based On Structure, But In Many Ways, They Are.

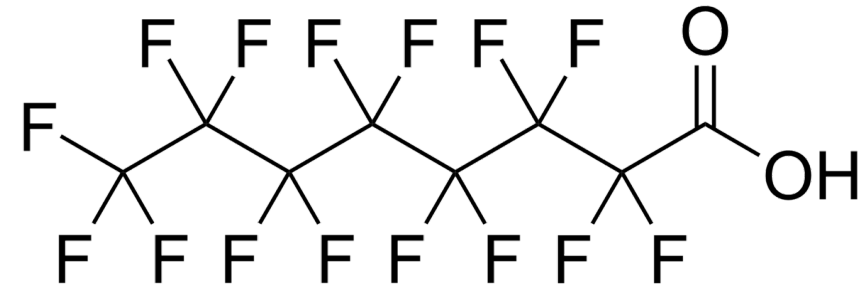
Both Are Environmentally And Biologically Persistent, As Well As Lacking In Human Toxicity At Typical Daily Doses (and perhaps at 100-500-fold higher doses)

Comparing PFAS And Dioxins

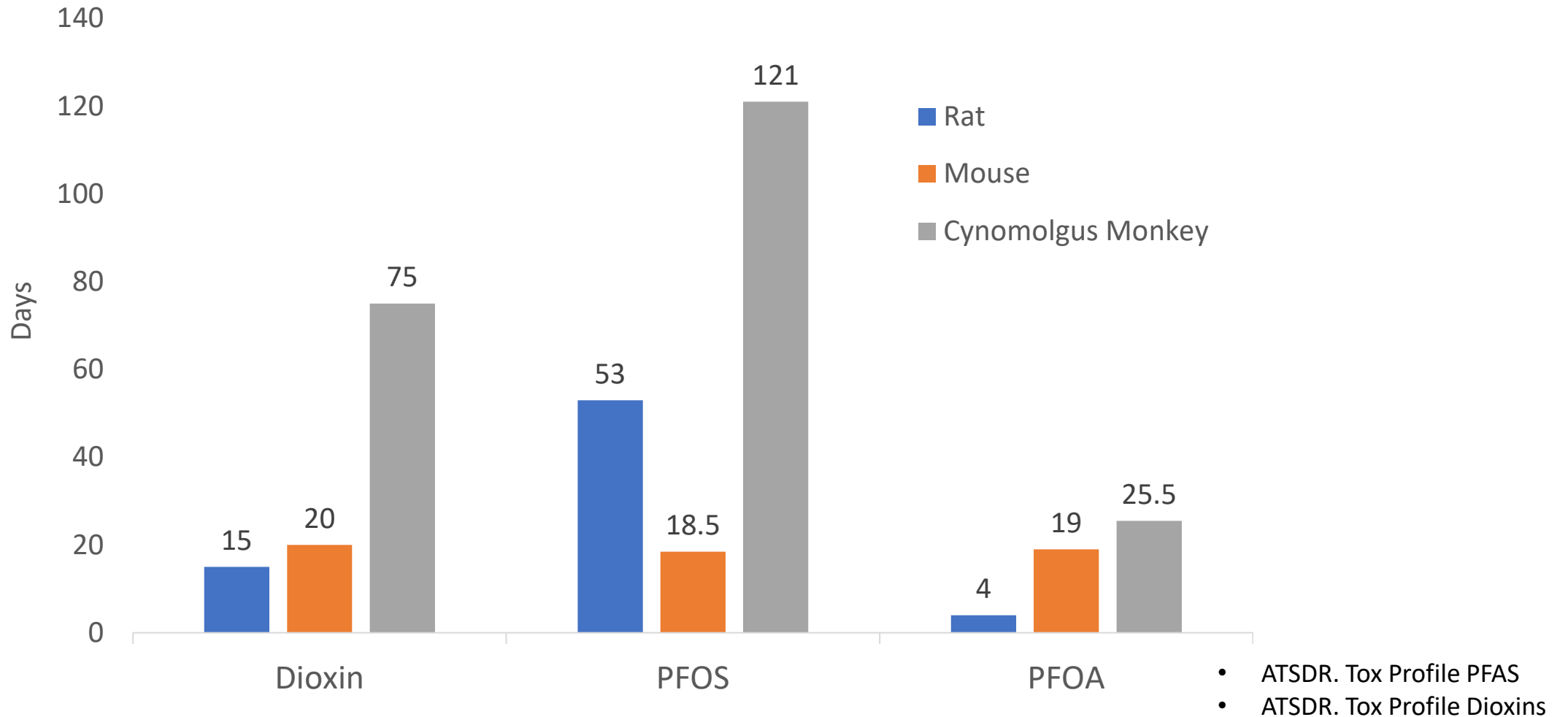
2,3,7,8 TCDD



PFOA



Biological Half-Life In Rodents And Monkeys



Biological Half-Life ($t_{1/2}$) In Humans (dioxin and PFOS/PFOA)

- 2,3,7,8-TCDD [dioxin] = **7.0-8.5 years**
- PFOS = **4 to 5 years**
- PFOA = **0.5 to 15 years (best est. = 1.5 yrs)**

- Dourson and Gadagbui. 2021. Reg Toxicol Pharm. 126: 1-14
- Wisconsin Dept of Health Services. 2019. PFOS

Acute Toxicology (LD₅₀)

2,3,7,8-TCDD (μg/kg)

Mouse: 35 μg/kg

C57B16 mice: 110 μg/kg

Rat: 30 μg/kg

Long-Evans rats: 13 μg/kg

Guinea Pig: 2 μg/kg

Hamster: 5051 μg/kg (oral)

Rabbit: 115 μg/kg (oral)

PFOS (μg/kg)

Mouse: 579,000 μg/kg

Rat: 252,000 μg/kg

PFOA (μg/kg)

Mouse: <187,000 μg/kg

Rat: 555,000 μg/kg

Lethal Dose (LD) For Humans (2,3,7,8 TCDD)

- The most toxic chemical known to man has never killed anyone; even when they tried.
- LD probably 100-10,000-fold higher than in animals.

- Kociba and Schwetz. 1982. Drug Metab Rev. 13(3): 387-406
- Crummett, W. 2003. Decades of Dioxin

The Hallmark Of Exposure Was Chloracne

- Disfiguring skin ailment
- Almost Permanent



<http://news.bbc.co.uk/1/hi/world/europe/4035789.stm>

Lethal Dose (LD) For Humans (PFOA and PFOS)

- LD for PFOA in man is unknown (apparently, very low toxicity)
- LD for PFOS in man is unknown (apparently, very low toxicity)

- EPA. 2017. Technical Fact Sheet – PFOS and PFOA
- Stahl et al. 2011. Environ Sci Eupo. 23: 1-52

Cancer Hazard (Dioxin)

- The Kociba rodent study surprised toxicologists (1976)... it was highly potent
- Later animal studies showed it to be carcinogenic via ingestion in many species
- But, no human study clearly showed it to be carcinogenic at any dose (no consensus will be reached on this topic)

- Kociba et al. 1978. Toxicol Appl Pharm. 46(2): 279-303
- NTP. 2021. Report on Carcinogens

Cancer Hazard (PFOS/PFOA)

- ATSDR noted that at the highest dose “The incidence of hepatocellular carcinoma was not significantly increased” (2021)
- The 3M Butenhoff study and the DuPont study were negative for the most part (but the NTP concluded differently)
- Most epidemiology studies illustrated little or no cancer risk (no consensus will be reached on this topic)

- ATSDR. 2021. Tox Profile PFAS
- Butenhoff et al. 2012. Toxicology. 293(1-3): 1-15
- Steenland and Winquist. 2021. Environ Res. 194: 1-28

Human Epidemiology for POFA/PFOS (2022)

- **Steenland and Winquist (2021):** Performed a review of 16 cohort (or case-cohort) studies, 10 case-control studies (4 nested within cohorts and 6 non-nested), 1 cross-sectional study and 1 ecological study.
- They concluded that “overall, the evidence for an association between cancer and PFAS remains *sparse*.”
- A couple of studies suggested a possible increased risk for kidney cancer; but usually not statistically significant.

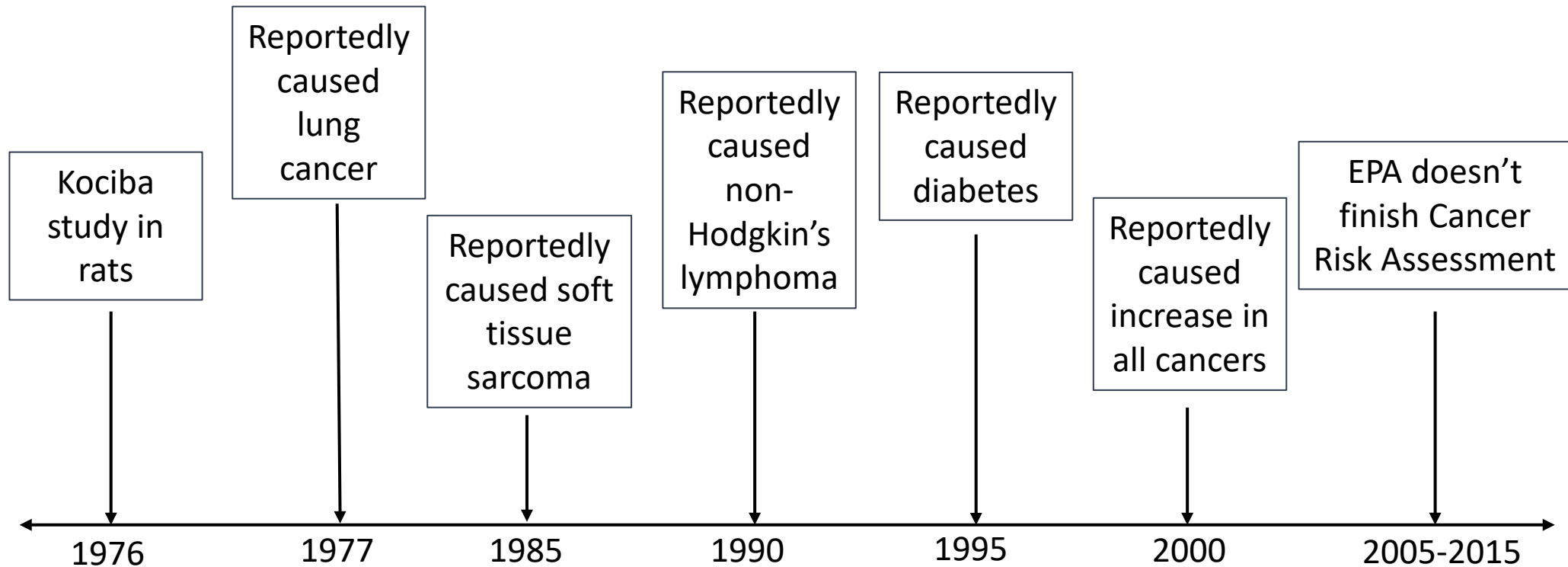
- Steenland and Winquist. 2021. Environ Res. 194: 1-28

Mode Of Action Of Dioxins And PFOS/PFOA In Rodents

- Wasting syndrome is seen with both TCDD and longer-chain PFAS
- Dioxins work through AhR
- Both seem to produce the downregulation of lipogenesis in rodents.
 - For PFOA and PFOS, many believe this is due to activation of PPAR α in rodents (inhibit fatty acid metabolism and lipid synthesis)
 - Humans respond differently from rodents to PFOS/PFOA (PPAR α does NOT cause cell proliferation; as it does in rodents)

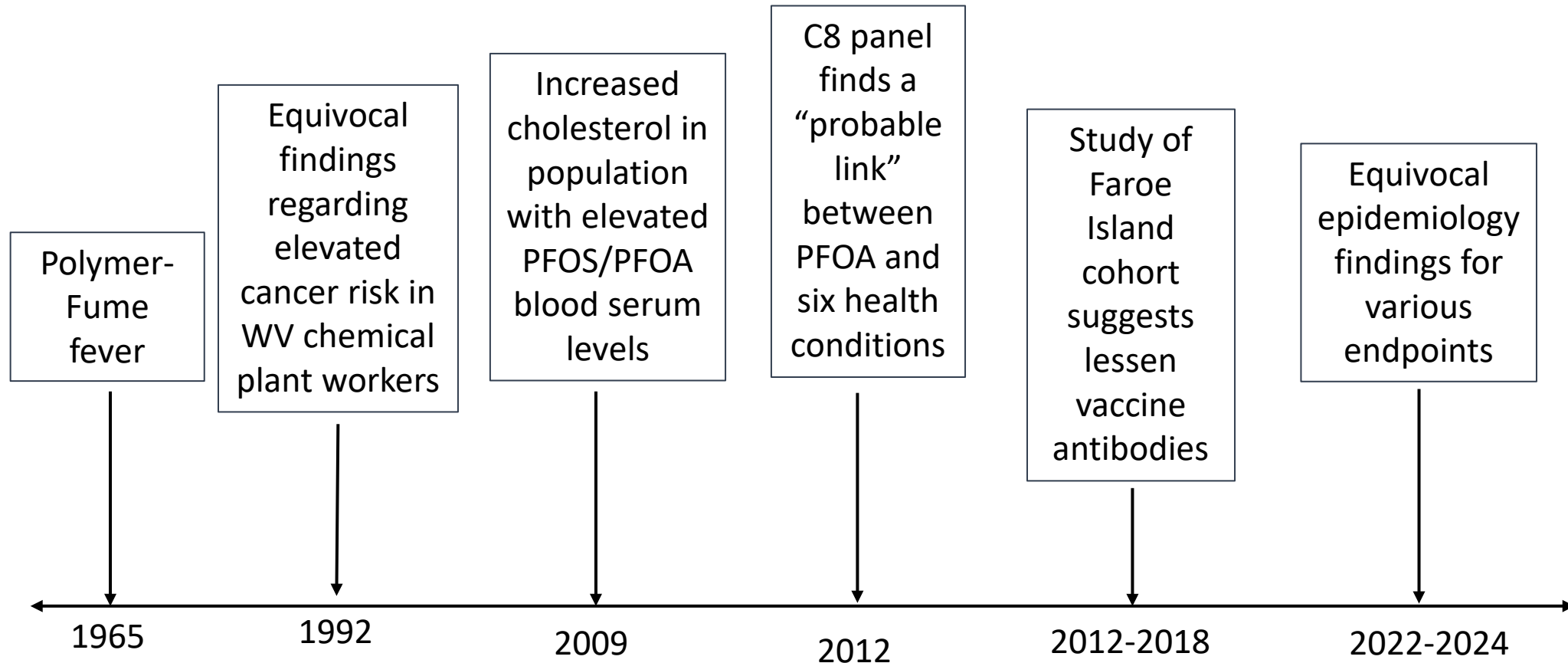
- Tuomisto et al. 1999. Pharmacol Biochem Behav. 62(4): 735-742
- Andersen, ME. 2023. Presentation at TERA Conference

Dioxins: The Epidemiology Journey



- Crummett, W. 2003. Decades of Dioxin
- ATSDR Tox Profile Dioxins

PFOS/PFOA: The Epidemiology Journey



Learning from History

- When animal and human studies yield inconsistent results across several biological endpoints, history tells us that we are probably looking at an artifact



Dinosaur



Elephant

- Marshall et al. 2023. *Altern Lab Anim.* 51(2): 102-135
- Akhtar. 2015. *Camb Q Health Ethics.* 24(4): 407-419

Persistent Chemicals Tend to Have Similar Toxicity Profiles

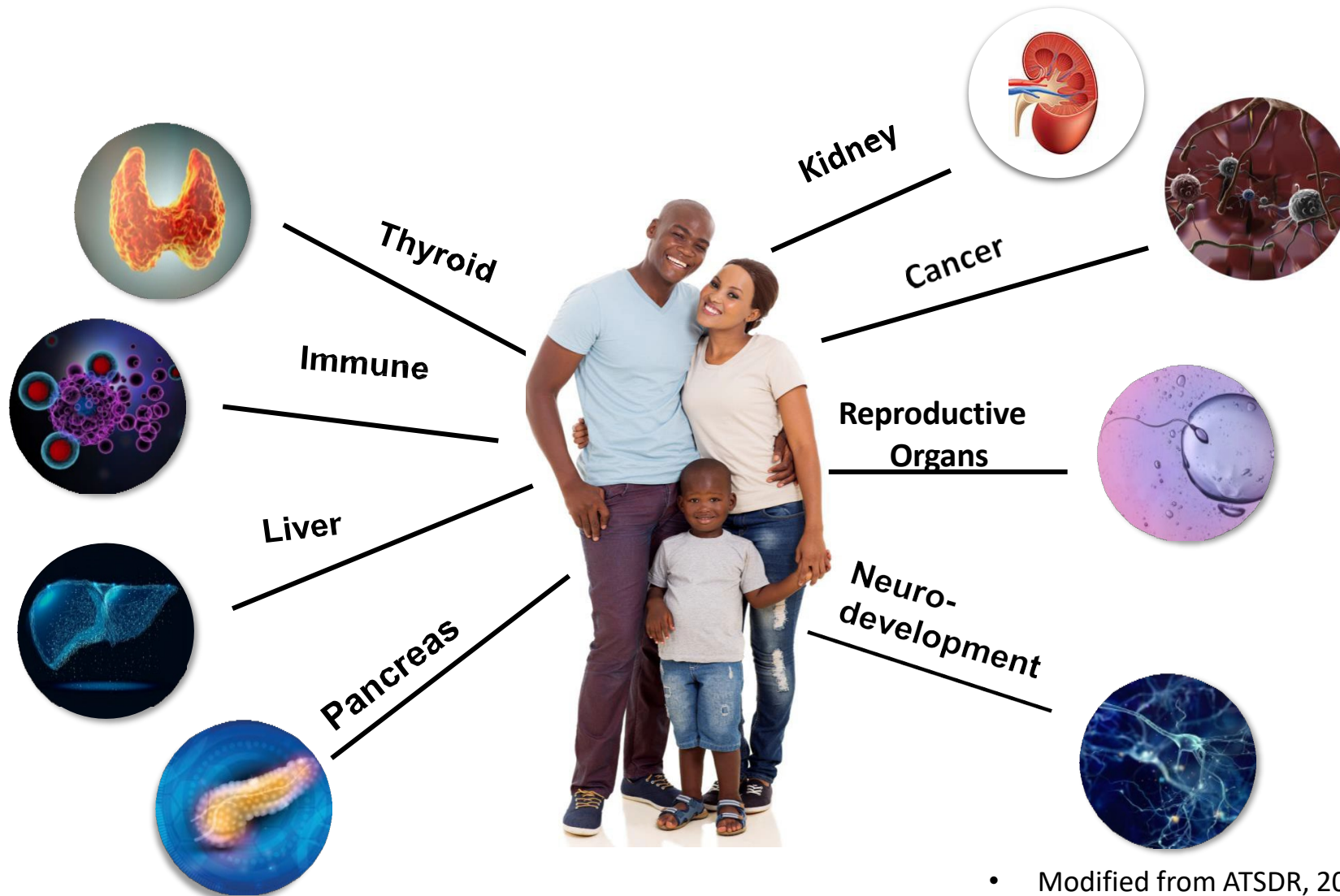
- DDT: No known lethal dose (No clear increased cancer risk in humans)
- PCB: No known lethal dose (No clear increased cancer risk in humans)
- Deca BDE: No known lethal dose (No clear increased cancer risk in humans)
- HCBD: No known lethal dose (No clear increased cancer risk in humans)

Note: The similarity is that they are all fundamentally non-genotoxic, highly lipid-soluble and poorly metabolized.

Dioxins and PFAS, not surprisingly, generate lively debates with respect to toxicity, cost/benefit, risk management and risk communication

- Berthold et al. 2023. PLoS One. 18(11): 1-20
- Tuyet-Hanh et al. 2010. Int J Environ Res Public Health. 7(5): 2395-2406

What The Public Has Seen And Read For Several Years (Dose and Species Are Rarely Discussed)



Such Broad Claims are usually Unjustified.. Chemicals Normally Affect One Or Two Target Organs (Always Dependent On Dose And Duration)

- Inhaled Benzene ➡ acute myelogenous leukemia
- Inhaled Chromium 6 ➡ lung cancer
- Inhaled Vinyl Chloride ➡ angiosarcoma of the liver
- Inhaled BCME ➡ lung cancer

- McHale et al. 2012. Carcinogenesis. 33(2): 240-252
- OSHA. 2024. Hexavalent Chromium
- Sherman. 2009. J of Hepatology. 51(6): 1074-1081
- CDC ToxFAQs for Bis(chloromethyl) Ether

One Can't Help But Think That ... Dioxins and the PFOS/PFOA Are Similar

- Uneven acute toxicity across species
- Humans and rodents appear quite different regarding toxicity
- Relatively long biological half-life
- Wasting syndrome seen at high doses in some animals
- Appear to be recognized in humans as fatty acids
- Very weak or no signal for carcinogenicity in humans
- Weak genotoxin or lacking genotoxicity

- Abraham. 2023. Environ Health Perspect. 131(1): 1-2

Can We Improve On Risk Communication?

“PFAS are linked to multiple health risks including cancer, thyroid disorders, developmental and reproductive complications and decreased immune function.”

- Jackson Hole Newspaper
(Jan. 16, 2024)

■ Local

Town request: Don't put your old ski wax in trash

By KATE READY
JACKSON HOLE DAILY

“Forever chemicals” leeching into our water supply and food chain and creating a health risk are popping up elsewhere: inside ski wax.

With that in mind, the Town of Jackson is suggesting a few ways to safely dispose of old ski wax instead of just tossing it in a trash can.

“Teton County Integrated Solid Waste and Recycling accepts ski wax with PFAS at its hazardous waste collection facility, which will open for appointments beginning in April,” the town press release said. “Currently, Skinny Skis is accepting old ski wax for disposal at its shop in downtown Jackson. Skiers who drop off their old wax may even receive a discount on the purchase of new PFAS-free ski wax.”

Per- and polyfluoroalkyl substances — man-made chemicals known as “PFAS” — are referred to as “forever chemicals” because the chemical bonds that help them repel oil and water also prevent them from degrading in nature or bonding with other particles to disintegrate through natural cycles, according to a town press release.

PFAS have been manufactured since the 1940s and are commonly found not only in ski wax but also a variety of con-

sumer goods, including waterproof and stain-resistant fabrics, nonstick pans, firefighting foam, food packaging and cosmetics.

If old ski wax is dumped in the trash, PFAS can seep into groundwater in landfills, the town warned. That's why the town is highlighting options to turn in ski wax locally, year round, to help limit “forever chemicals” in Jackson and its surrounding ecosystem.

Ski wax containing PFAS rubs off onto snow, which contaminates soils, streams, and groundwater when it melts. In Wyoming, PFAS have been identified in six water bodies. In the Green River, for example, they are consumed by rainbow trout.

PFAS are linked to multiple health risks including cancer, thyroid disorders, developmental and reproductive complications and decreased immune function.

“Skiers and snowboarders who wax their skis or boards face higher risks of exposure to PFAS when they use wax that contains PFAS,” the press release said. “One study found professional ski waxers in Norway had up to 25 times as many PFAS in their blood as the general population.”

To help limit PFAS at the source, it's recommended that people switch to fluoro-free ski wax, available at most ski shops.

When Did The Word “Linked or Associated” Become Equivalent With “Caused”?

I Think It Started With 2,3,7,8-TCDD In 1982. The C8 panel used the words “probable link” for cancer and PFAS (2012).

- ITRC. 2023. PFAS

Society And Its Agencies Can Make
PFOS/PFOA The Most Economically
Impactful Regulatory Action Of the
Past 40 years... or not.

The Original (2016) EPA Drinking Water Guideline for PFOS/PFOA was 70 ppt. EPA then proposed an MCL of 4 ppt for each one (2023).

- Rockefeller. 2023. First Federal PFAS blog
- EPA. 2024. NPDWR

A Recent U.S. Drinking Water Survey

- Over 10,000 water purveyors will be evaluated
 - Data on about 2,000 were released
 - Only six had Hazard Indices over 1.0
 - Only a few had drinking water over 70 ppt for PFOS/PFOA
 - 219 systems reported water values over 4 ppt for PFOS/PFOA
- Small Systems May Bear The Brunt Of PFAS Treatment Costs Under SDWA Rule, 2024 (Jan. 8, 2024)
 - TERA. Presentation by AWWA (2023)
 - The Waterloop Podcast: First Data For PFAS In Water Systems Released By EPA (Aug. 29, 2023)

“EPA assumed that high compliance costs could be managed by the largest municipalities and water utilities with significant operating budgets.”

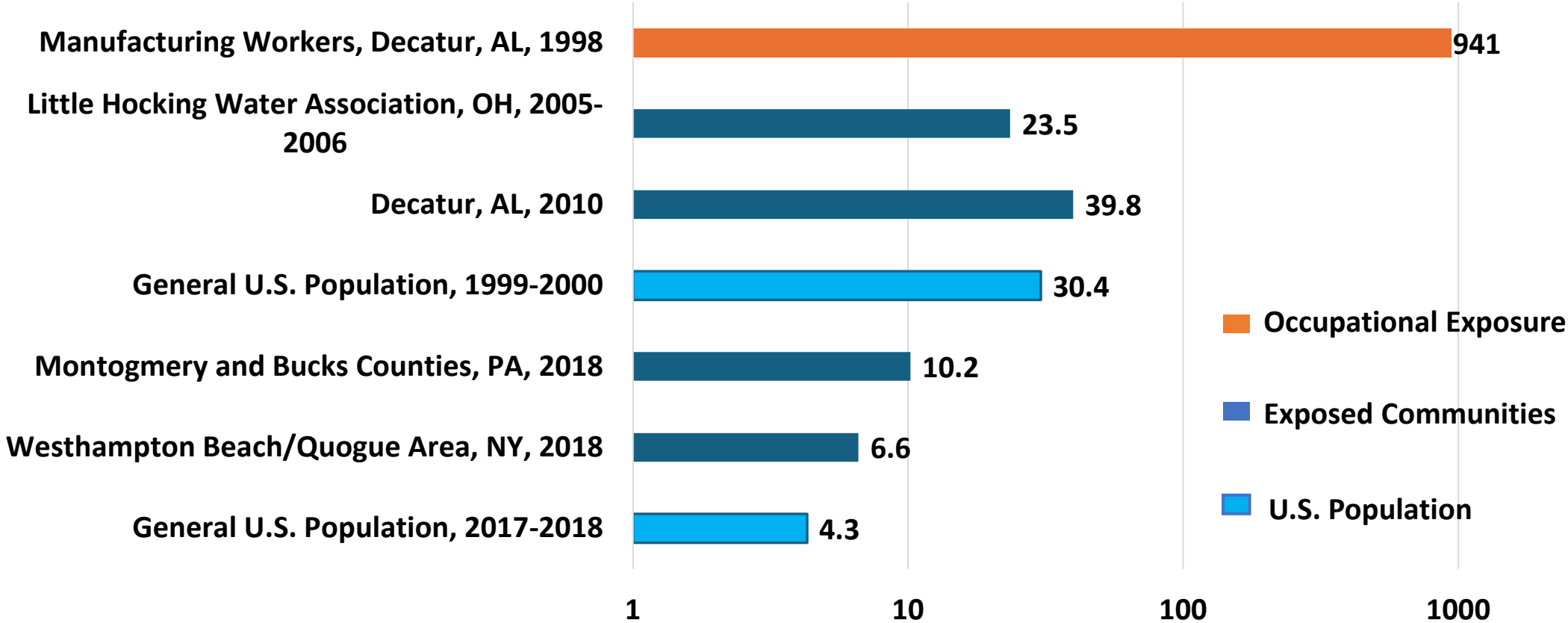
The greatest economic burden from the EPA’s proposed ruling will fall on small, disadvantaged communities and small water systems

- Small Systems May Bear The Brunt Of PFAS Treatment Costs Under SDWA Rule, 2024 (Jan. 8, 2024) (Chad Seidel quoted)

PFOS/PFOA Exposure Assessment May Not Be Receiving Sufficient Attention....

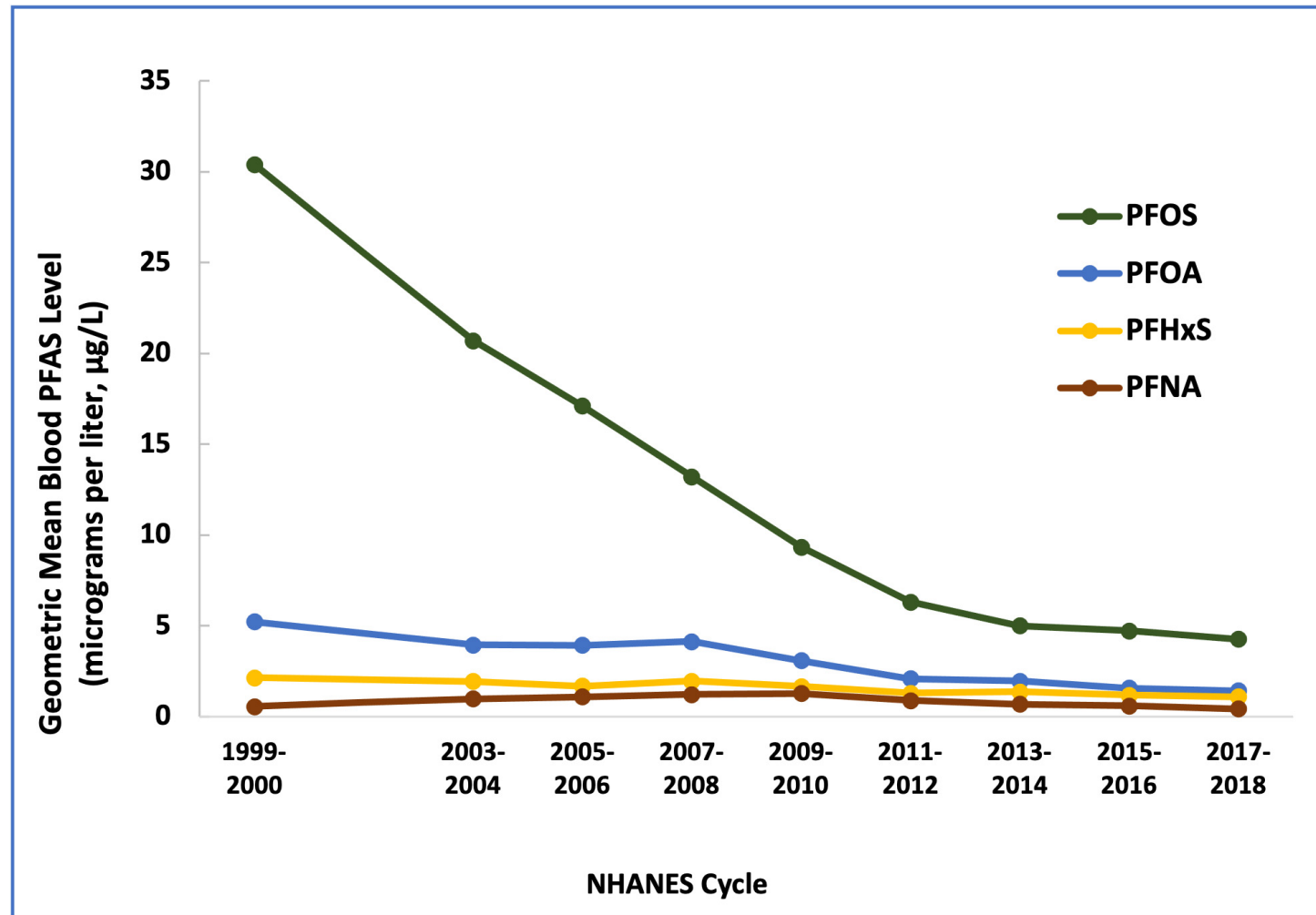
- Keep in mind, perhaps 60%-70% of intake of PFOS/PFOA appears to be due to seafood. As much as 80-90% of chemical intake is not related to water. This is termed a source apportionment analysis.
- Not much tap water is ingested by humans. For most households, at least 90% of treated water is used in dishwashers, washing machines, car washing, toilets, showers, and watering lawns/garden
 - Christensen et al. 2017. Environ Res. 154: 145-151
 - EPA Exposure Factors Handbook
 - EPA. 2022. Technical Fact Sheet: Drinking Water Health Advisories for Four PFAS (PFOA, PFOS, GenX chemicals, and PFBS)

Blood Concentrations ($\mu\text{g/L}$) In U.S. (PFOS)



• ATSDR. 2024. PFAS in the U.S. Population

Blood Levels Of The Most Common PFAS In People In The United States Over Time



- ATSDR. 2024. PFAS in the U.S. Population

Possible Outcomes of MCL at 4 ppt

- Because, as much as 80-90% of the intake of PFOS/PFOA is from seafood or other sources, it is plausible that if every water purveyor achieves the MCL of 4 ppt, the typical concentration of these chemicals in the blood may not measurably decrease in the coming years.
- Serious adverse effects on domestic and international commerce, without any measurably positive impacts on public health.
- One cannot rule out a lessening in blood concentrations due to inadequate information on exposure.

One Thought...

Set a MCL of 100 ppt in 2024 (the current World Health Organization Guideline)... with a Mandated “Re-evaluation” in 2029?

Then, if in 2029, based on Blood Level Data and New Epidemiology Data, the Agency could Lower the MCL to 50 ppt or less, if necessary

Phased-In Approach For Dioxins

(Was Proposed and/or Used In Germany In The 1990s)

- 1970s-1980s: Aerial emissions were high (sometimes over than 100 ng/m³)
- 1990: They proposed an aerial emissions limit of about 4 ng/m³ (based on my memory)
- 1998: Lowered goal to 1 ng/m³ (based on my memory)
- 2005: Concluded that more stringent regulations were not needed (significant amounts of money were not invested on excessive engineering controls)

A Myriad of Risk Management Challenges

- How does one weigh the precautionary principle vs. objective risk assessment?
- How much emphasis should be placed on toxicology or epidemiology studies that are murky or equivocal?
- How do you put a value on the possible vs. plausible vs. likely health benefits to society (or lack thereof)?
- How does one attempt to address “what we don’t know, about what we don’t know”? For example, will such an aggressive MCL damage our most valued industries? Will such an MCL drive some firms out of the U.S. marketplace?
- Will such an MCL improve Public Health?

Closing Thoughts

There May Be Lessons to be Learned
From 20 Years of Scientific and
Regulatory Initiatives Focused on the
Dioxins....Before We Finalize Our
Decisions Regarding the PFAS chemicals

The End

Disclosure

- Twenty years ago, I published a paper illustrating the aerial transport of PFOA
- I have had no involvement since then (until Dr. Dourson asked me to speak at his conf in Oct. 2023)
- I have not been retained as an expert in litigation. However, I was retained in December 2023 to discuss the possible impact of personal injury litigation on the industry.

