PFAS, Toxicology and Risk

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December 6, 2023

ESAA PFAS Symposium

Outline

- What do we know about PFAS and human health?
- What we don’t know or understand about PFAS and health risk?
- What factors do we need to consider when evaluating PFAS exposures and toxicity?
- PFAS science and toxicity limits/guidelines – are we on the right track for protecting human health?

What do we know about PFAS and human health?

PFAS bind to proteins and accumulate in organs that are highly perfused with blood (animals), fatty membranes (plants)

Some differences between humans and rodents in metabolism that impacts extrapolation of data

Mimic fatty acids in the body, impact cholesterol synthesis in liver – affects cell membranes and fatty acid metabolism

Some PFAS may be peroxisome proliferators

Dose, PFAS chain length and functional groups appear to influence effects

Range of potential adverse effects reported in literature

- **International Agency for Research on Cancer (IARC)** announced December 1, 2023 that PFOA has been classified as a Group 1 Carcinogen, and PFOS as Group 2B – more information to be released in 2024 as supporting information
- PFAS are non-genotoxic. IARC suggests mechanism involves epigenetic changes and immunosuppression

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What we don’t know about PFAS

TOXICITY DATA

Only available for some PFAS

Potential animal vs. human differences

Some mechanisms lack consensus

HUMAN DATA

Only available for some PFAS

Mechanisms unclear for some effects

Often based on serum concentrations

PRECURSORS

Environmental transformation and mobility

Biotransformation in the body

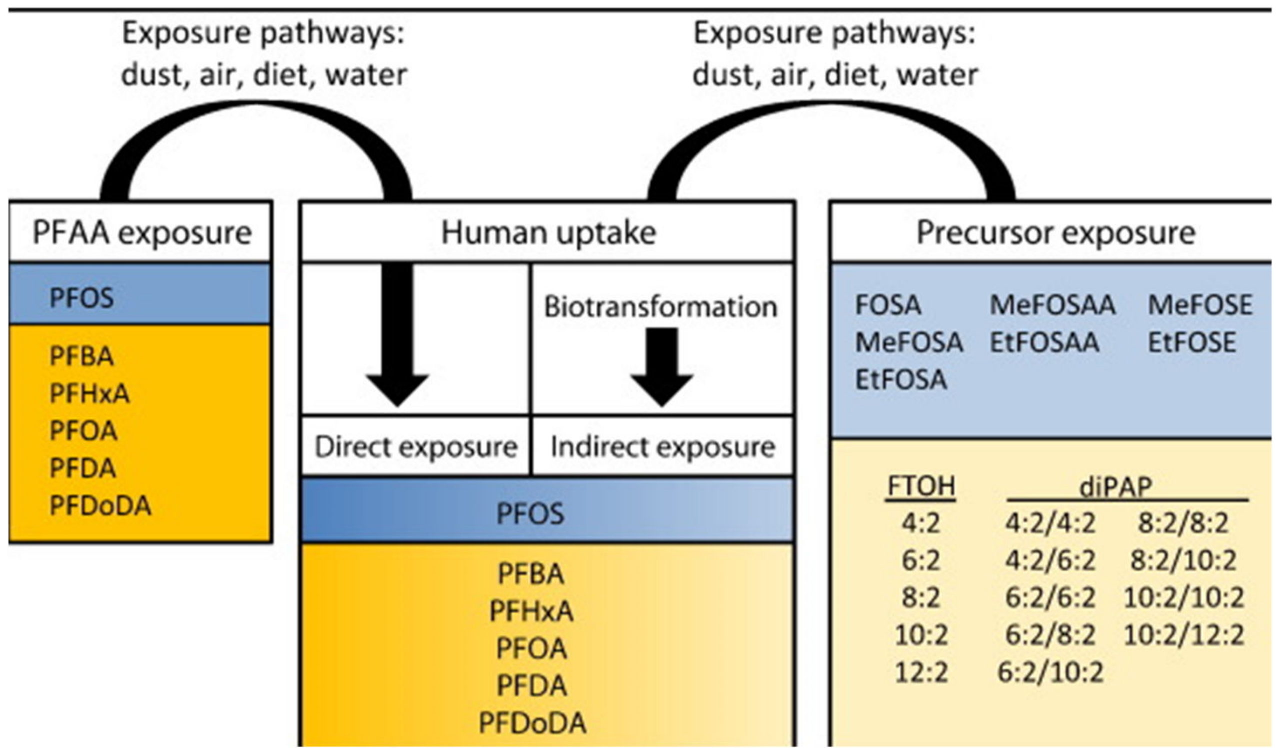
METHODS

Key to exposure assessment

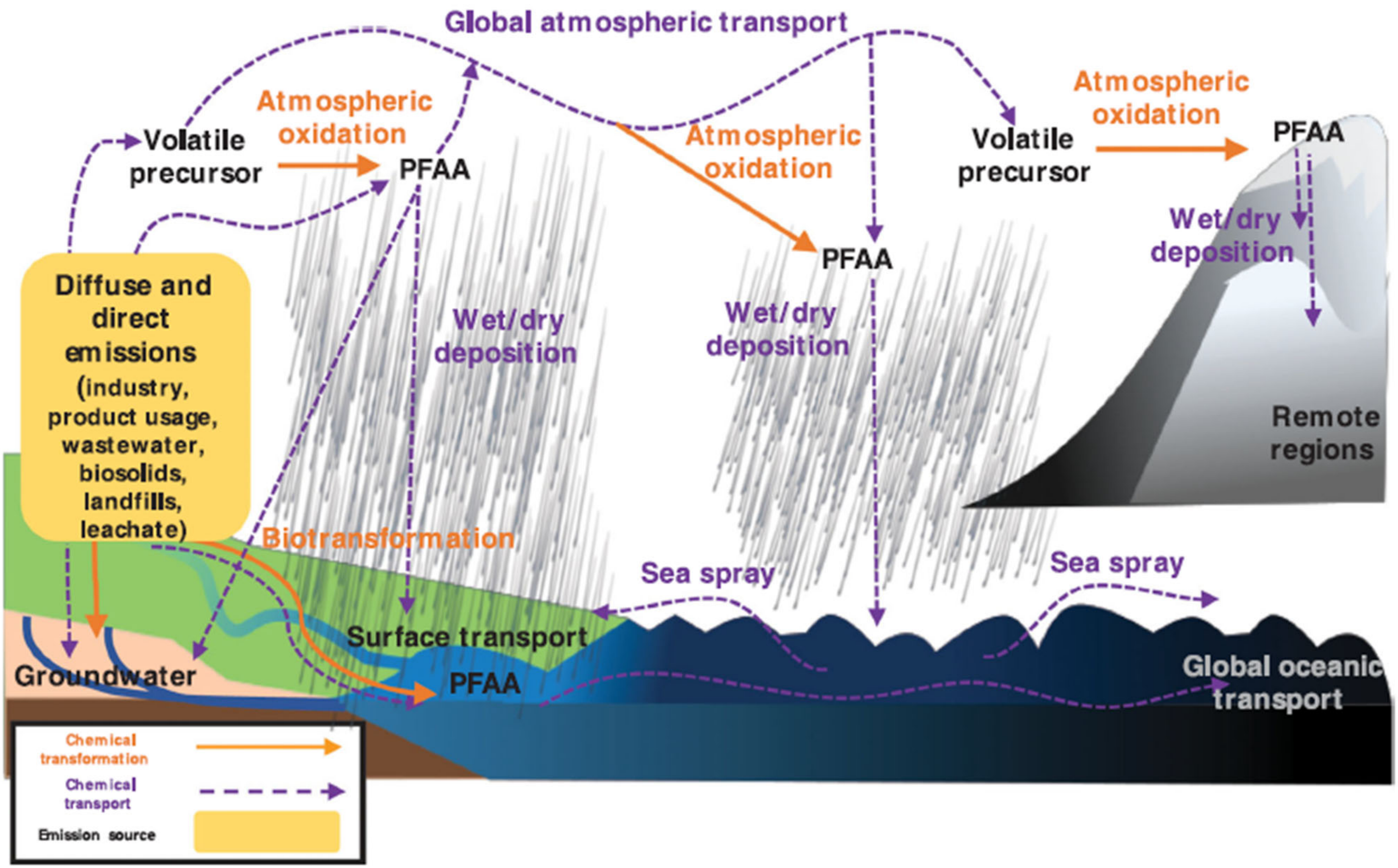
Standardization lacking in some media

Why do precursors matter?

- Precursors can also be **biotransformed** in biota/mammals to longer-chain PFAS
- Limited or no toxicity information for many PFAS/precursors on their own or in combination
- Where do precursors come from?
  - Substitutes for long-chain
  - Textiles
  - Consumer products and pharmaceuticals
  - Packaging
  - ?



Gebbink et al. (2015)



Conceptual Model of PFAS Emission Sources and Transport Pathways (De Silva et al. 2021)

Issues related to Contaminated Site Risk Assessment

- Some guidelines and screening-levels are available
  - Limited and continually shifting
- Existing and draft toxicity reference values are based on a variety of endpoints and assumptions
  - Range of values – lack of consensus
- Many PFAS and precursors of relevance do not have guidelines, screening values or TRVs
  - No guidance on how to include in assessment
- Potential for background exposures at individual receptor and broader regional levels
  - Risk characterization challenge

Guidelines and Toxicity Values

- Current Health Canada Perfluorooctanoic acid (PFOA) guideline (2018)

$$\text{Maximum acceptable concentration (MAC)} = \frac{\text{TDI (0.000021 mg/kg bw)} \times 70\text{ kg} \times 0.2}{1.5\text{ L/day}}$$

$$= 0.0002\text{ mg/L} \quad (0.2\ \mu\text{g/L or } 200\text{ ng/L})$$

- **Tolerable Daily Intake (TDI):** based on incidence of hepatocellular hypertrophy (enlarged liver cells) in rats, adjusted for differences in toxicokinetics (animals vs. humans), and overall uncertainty
- Body weight, Allocation Factor (the 0.2), and ingestion are fairly consistent across jurisdictions

Toxicity Reference Values (TRV)

$$TRV = \frac{\textbf{Point of Departure} \text{ (unit per kg body weight/day) x } \textbf{(Exposure Adj.)}}{\textbf{Uncertainty Factor}}$$

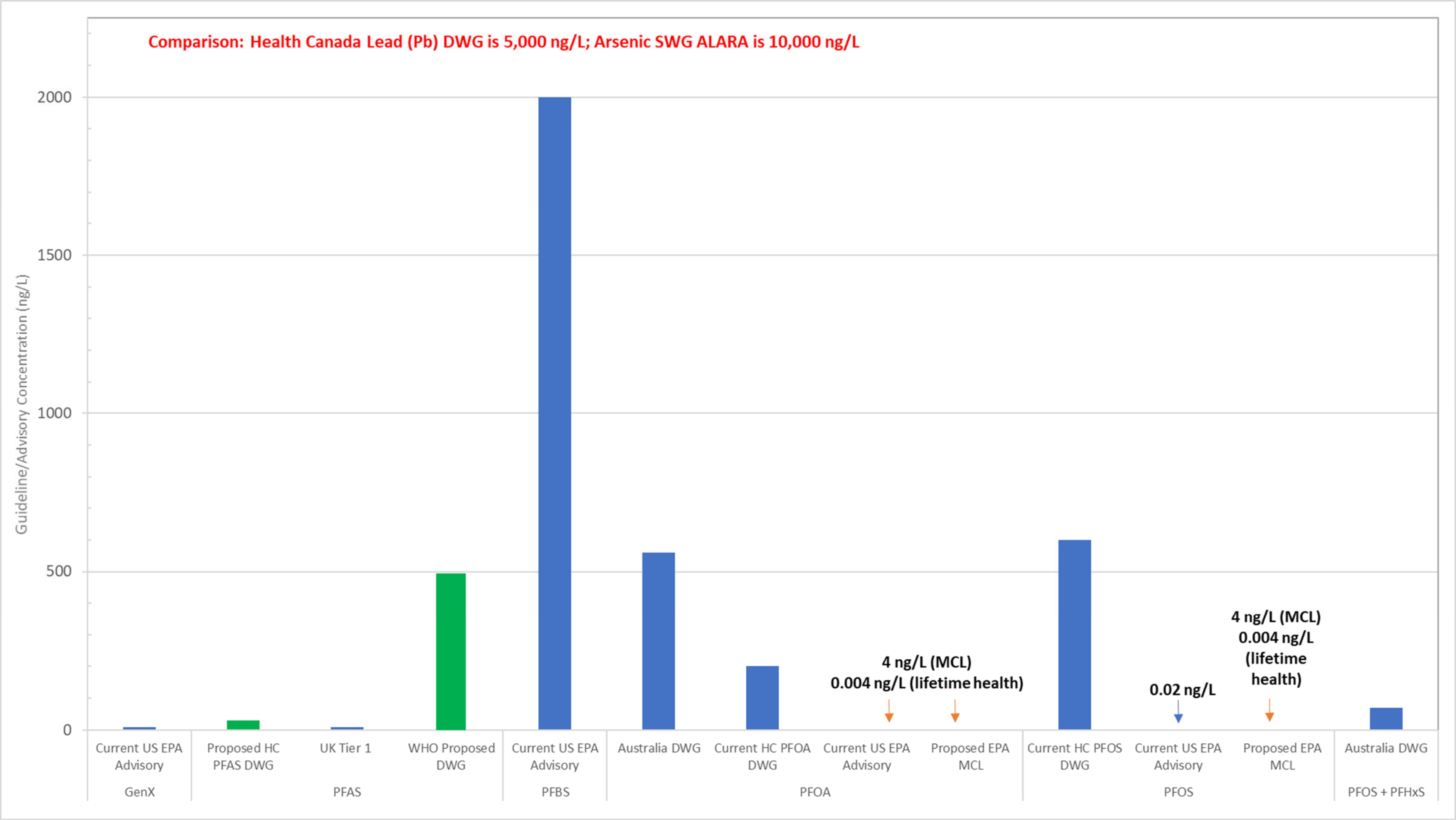
TRV: Can be in form of TDI, Acceptable Daily Intake, Reference Dose

POD: threshold effect level – no observed or low rate of observed adverse effects from studies; Might be estimated from pharmacokinetic models or back-calculated from human data

Exposure adjustment – adjust from animal or occupational type exposures to exposure relevant to humans, general population

Uncertainty Factors – can range from 1 to 3,000; considers things like:

- Species differences (i.e. rodents to humans)
- Intraspecies differences (how different people are from each other)
- Type of POD used (effect vs. no-effect)
- Pharmacokinetics and pharmacodynamics
- Database uncertainty



Examples of Drinking water guidelines – mixture of toxicity (blue), analytical (orange) and treatment achievability (green) basis in ng/L (or parts per trillion)

PFAS mixtures

- PFAS can occur as mixtures in the environment, homes and consumer products
- Most toxicity data are for single PFAS rather than mixtures
- No scientific consensus on how to assess combined effects of PFAS
  - Additivity?
  - Potential for non-additive effects?
  - Relative potency?
  - Other?

Lack of data regarding effect and mechanisms for individual and mixtures of PFAS limits ability to assess as a group

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Summary

- PFAS are a health and environmental issue
- Lack of weight of evidence or consensus on many things - We are far from having a complete understanding of PFAS
- Toxicity values and approaches to environmental guidelines constantly changing
- Public health management must be a **balance** of the precautionary principle and the weight of evidence, costs, technological and practical challenges of PFAS measurement and treatment

Thank you

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Resources

- Agency for Toxic Substances and Disease Registry (ATSDR). 2021. Toxicological Profile for Perfluoroalkyls. US Department of Health and Human Services. https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf
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