A toxicologist's perspective of the health risks of perfluoroalkyl substances (PFAS)

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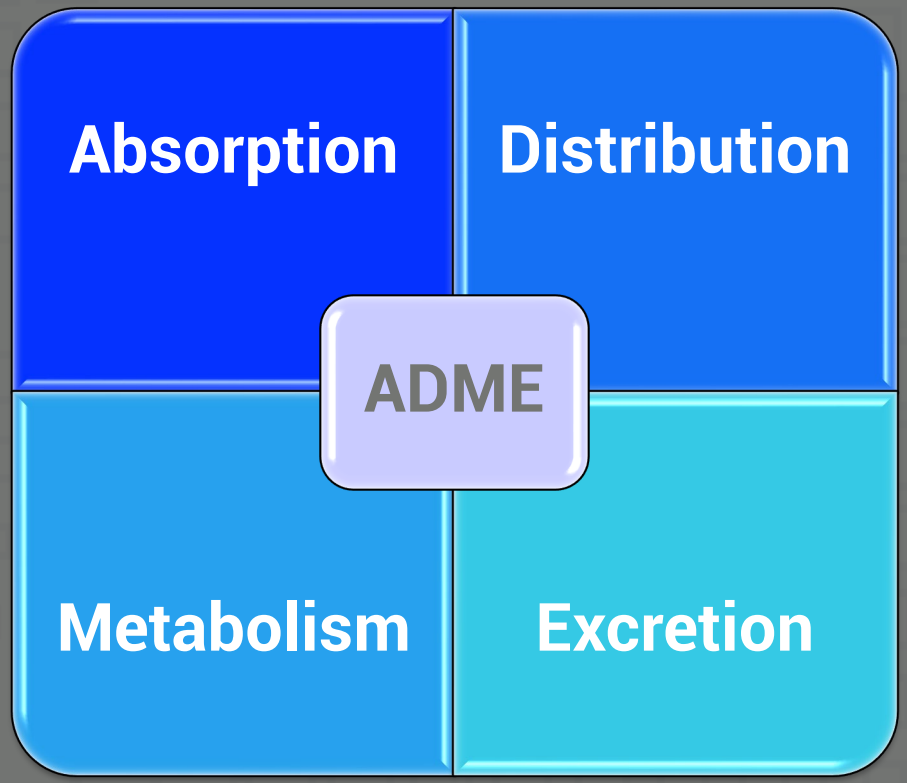
Polyfluoroalkyl and Perfluoroalkyl Substances

- Carbon-fluorine bonds
  - Categorized by number of carbon side chains, **Short- and Long-Chained**
  - Reason for environmental persistence
- Applications
  - Non-stick, waterproof, soil/stain/oil-resistant properties
  - Medical devices
  - Food packaging
  - Upholstery, Carpet, Clothing

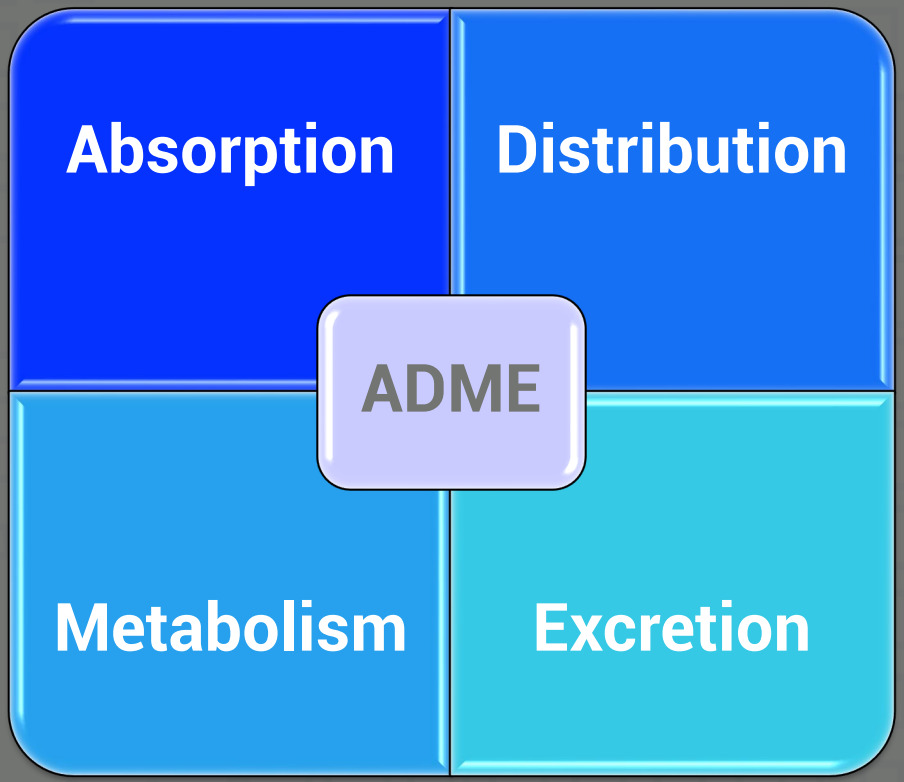
PFAS Toxicology

- Absorption
  - Primary route of exposure is oral intake; complete absorption
- Distribution
  - Binds proteins (not lipids); distributed to liver, kidney, spleen; somewhat to testes and brain.



PFAS Toxicology

- Metabolism
  - Minimal metabolism of PFOS or PFOA due to strong C-F bond
  - Precursor chemicals (fluorotelomers and derivatives) are biotransformed into PFAS
  - PFAS metabolism in humans is different from PFAS metabolism in rodents
    - ❖ Impact on development of toxicity values

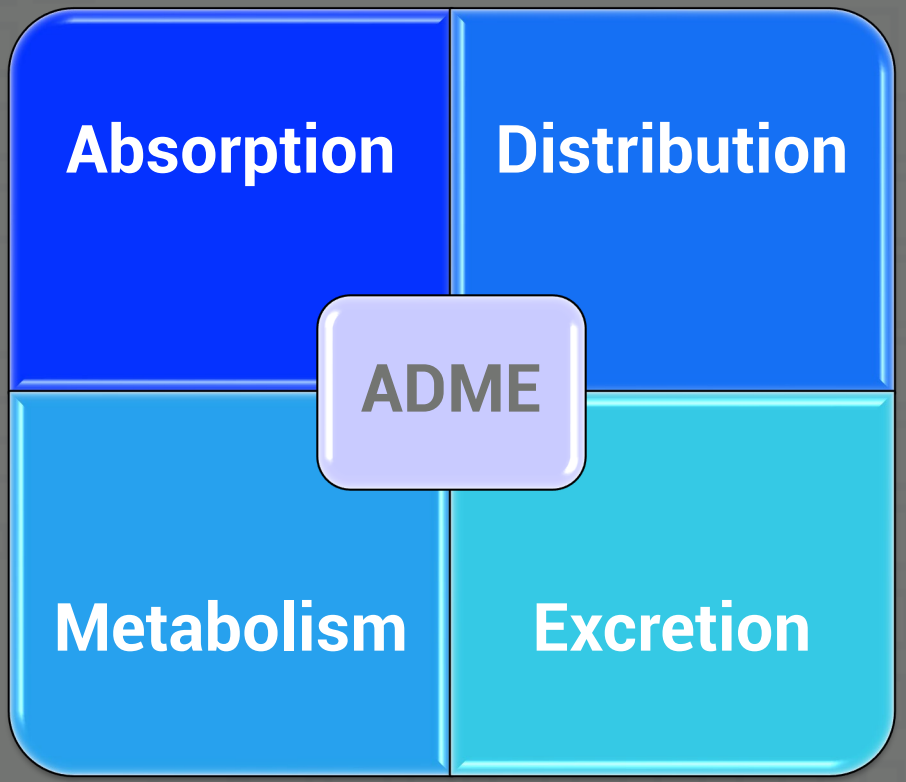


PFAS Toxicology

> Excretion

- Half lives (blood): generally longer for sulfonates than carboxylates, increase with chain length for carboxylates, and are shorter for branched isomers.

PFOS: 5.4 years	PFOA: 2.3 years
PFHxS: 8.5 years	PFHxA: 32 days
PFBS: ~35 days	PFBA: 80 hours



Health effects of PFAS

- Cancer
- Liver toxicity/Lipid Metabolism
- Reproductive/Development
- Endocrine modulation
- Immunotoxicity

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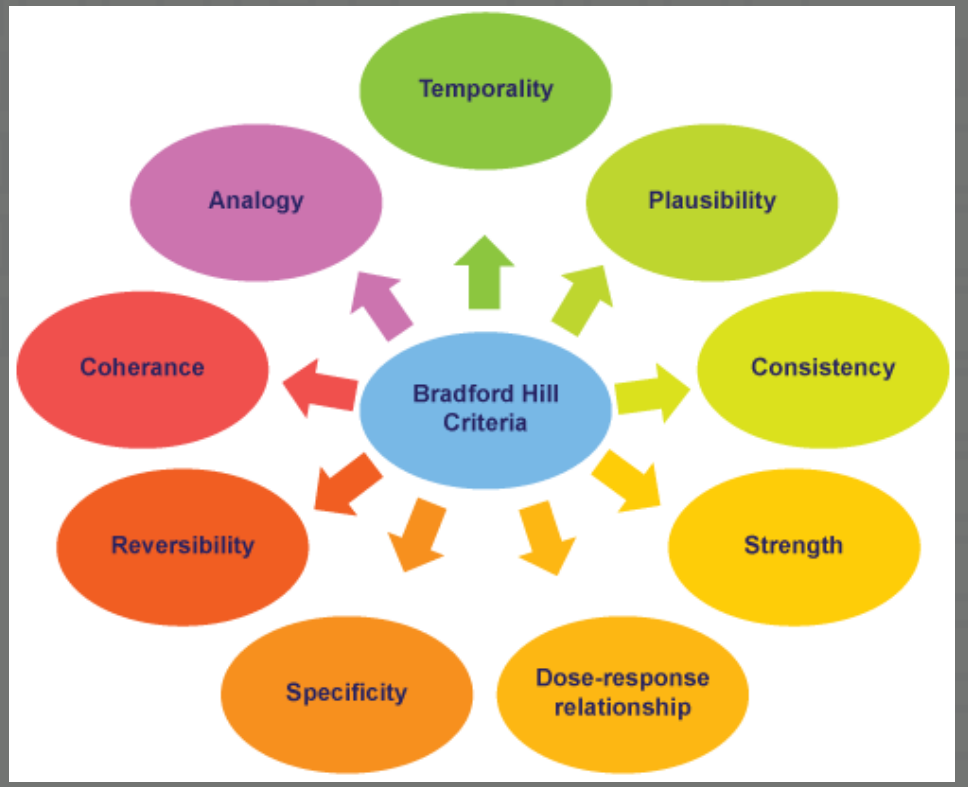
PFAS Carcinogenicity (Animal Data)

- USEPA reports suggestive evidence that PFOA and PFOS may cause liver, testicular, and pancreatic cancers based on *animal data*
- Cancer endpoints based on two rat studies where PFOA was found to be "weakly tumorigenic" *(Butenhoff et al., 2012; Biegel et al, 2001).*
- Proposed Mechanism:
  - Combined activation of the xenosensor nuclear receptors, PPARα, CAR, and PXR in rats (Elcombe et al. 2010, 2012)

Human PFOA cancer link not well supported by studies

- Results from studies of two occupational cohorts in Minnesota (3M) and West Virginia (DuPont) do not support an increased risk of kidney and testicular cancers.

- Chang et al. (2014) applied Bradford-Hill Criteria and found that kidney or testicular cancer associations are likely due to chance, confounding, and/or bias.



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*References available upon request

PFAS exposure and the case for increased cholesterol levels in humans

> Hypothesis:

Populations exposed via drinking water to PFAS resulted in increased serum cholesterol and ultimately an increased risk of cardiovascular disease.

Mechanism of PFAS Liver Toxicity/Modulation

- PFAS are activators of receptors that regulate lipid metabolism in humans and animals
  - PFCA induced peroxisome proliferation resulted in liver cell hypertrophy and increased liver weight *in rats* (Kudo et al. 2000).
- PPARα activity was higher in response to carboxylates (e.g., PFOA) compared to sulfonates (e.g., PFOS).
  - PFBS < PFOS < PFHxS < PFBA < PFHxA < PFOA.

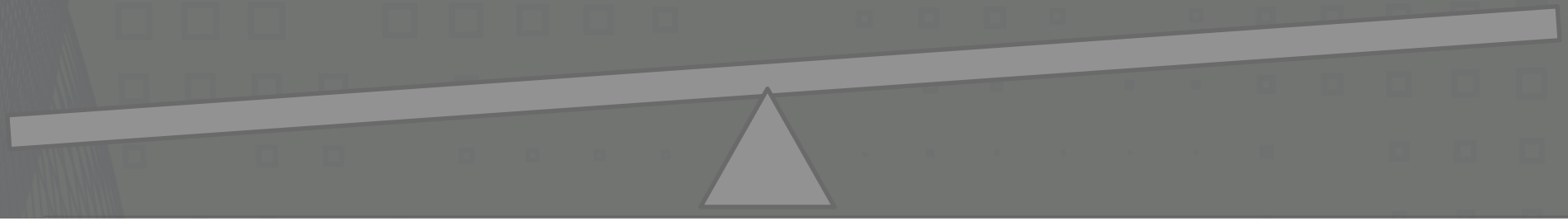
*PPAR = Peroxisome proliferator-activated receptors

Evidence supporting PFAS exposure and increased cholesterol

PFAS activate lipid metabolism receptors in humans and animals

Positive associations between PFAS exposure and increased cholesterol and triglycerides in rodents

Limited epidemiological evidence suggests a similar effect amongst PFAS-exposed humans.



Evidence refuting PFAS exposure and increased cholesterol

PFAS activate lipid metabolism receptors in humans and animals

Positive associations between PFAS exposure and increased cholesterol and triglycerides in rodents

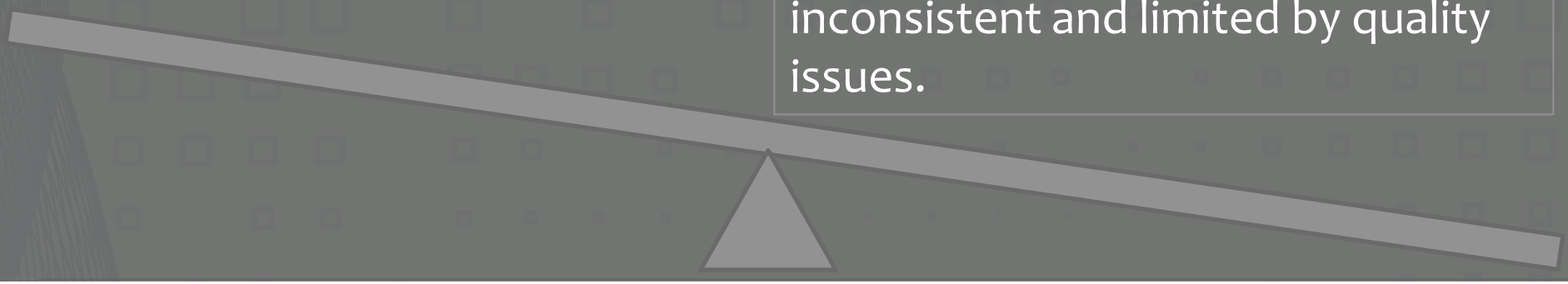
Limited epidemiological evidence suggests a similar effect amongst PFAS-exposed humans.

The elimination time for PFOA and PFOS in humans is substantially longer than in rodents

PPAR-α is expressed in human liver tissue at ~10% of rodent levels

Humans and other primates are less responsive to PPAR-α agonists compared with rodents

Epidemiology studies are inconsistent and limited by quality issues.



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Proposed mechanisms of developmental effects

- PFOS and PFOA can cause reproductive and developmental effects in rodents
  - Total litter loss, reduced pup weight
  - Upregulations of xenoreceptors (androstane, pregnane X) (Bjork et al. 2011; Elcombe et al. 2010, 2012)
- Placenta shares biological features, including transporter proteins, with PFAS target organs kidney and liver (Blake and Fenton, 2020)
  - PFAS is known to pass readily from mother to developing fetus
- Maternal PFAS exposure has been linked to hypertensive pregnancies and pre-eclampsia in humans (Blake and Fenton, 2020)

Health effects of PFAS

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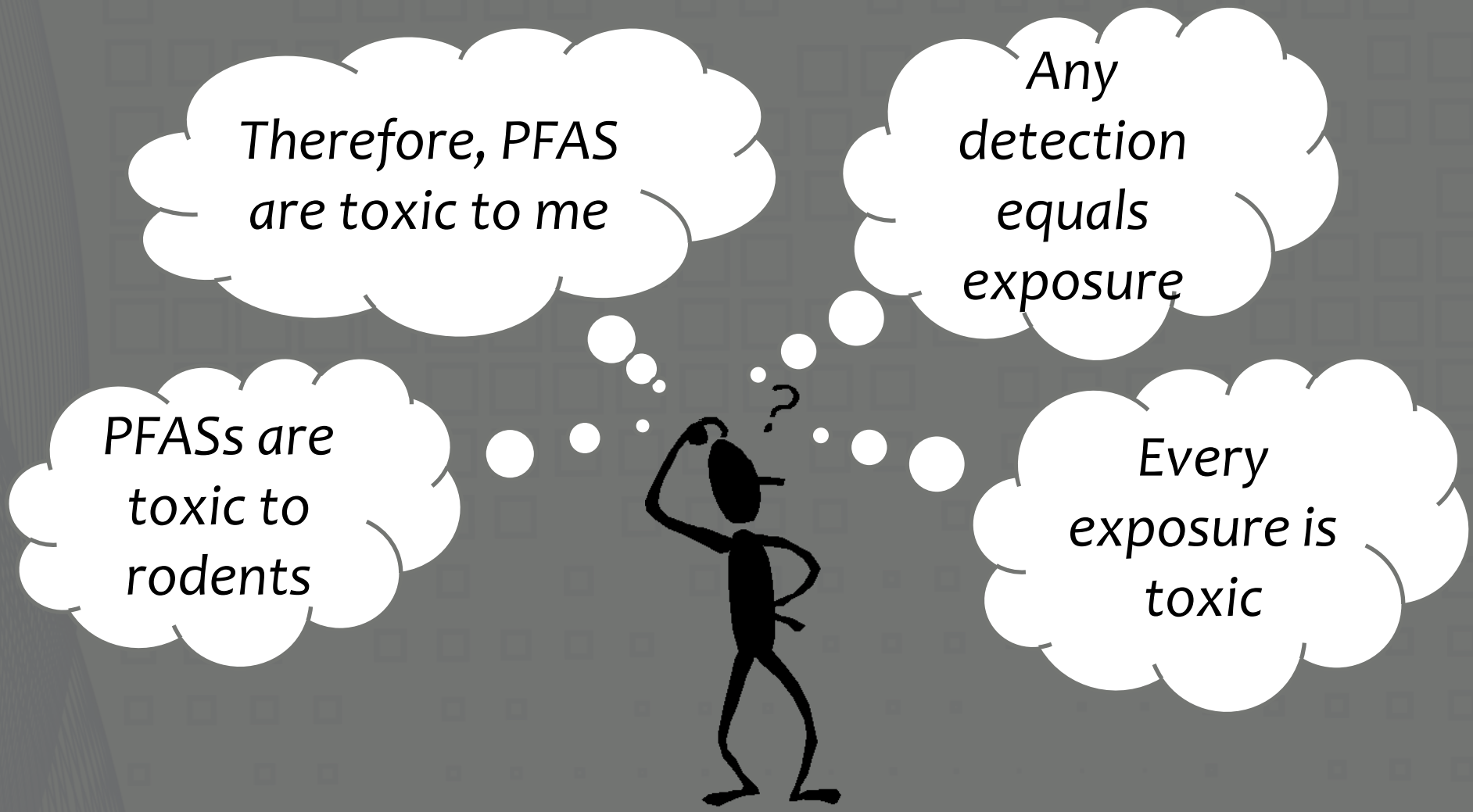
Proposed mechanism of thyroid hormone modulation

- Competitive binding to the thyroid hormone plasma transport protein transthyretin (TTR) that will alter/decrease the free thyroxine (T4) in blood *in animals* (Weiss et al. 2009)
- The binding potency of the fluorinated chemicals was 12-300 times lower than for thyroxine itself
  - PFHxS > PFOS/PFOA > PFHxA > PFBS.
- PFBA and FTOHs had no effect
- Humans expected to be less sensitive to T4 modulation

Perceived risk versus actual risk



Toxicological profiles are NOT equivalent for PFAS

Study Type*	PFOA	PFHxA
Reproductive/ Developmental	3 mg/kg/d M 10 mg/kg/d F	100 mg/kg/d M&F
2-year Chronic Toxicity	1.3 mg/kg/d M 1.6 mg/kg/d F	15 mg/kg/d M 30 mg/kg/d F
Carcinogenicity	Leydig cell tumor, liver adenoma, pancreatic tumor 300ppm diet 14.2 mg/kg M 16.1 mg/kg F	No carcinogenicity at maximum tolerated doses 100 mg/kg/d M 200 mg/kg/d F

*NOAELs

Take-home messages

- PFAS are completely absorbed orally and by inhalation (not dermal)
- PFAS are not metabolized
- Precursor chemicals (fluorotelomers and derivatives) are potentially biotransformed into PFAS
- Relatively high concentrations of short- and long-chain PFAS have been measured in human tissues (lung, liver, kidney, spleen)

Take-home messages

- PFAS are a broad class of chemicals and proposed toxicity factors for PFAS vary widely. Thus, not all PFAS are equally toxic and should be addressed on a chemical-specific basis.
- Liver toxicity, thyroid hormone modulation, and reproductive/developmental effects of PFAS have been documented in animals, but have not been well demonstrated and/or well studied in humans.

Take-home messages

- Most of the epidemiology studies are cross-sectional which means that a causal relationship cannot be evaluated.
- The associations between PFOA and increased cholesterol in humans contradict the results from animal studies, which generally suggest that PFOA exposure in humans *decreases* cholesterol levels.
- The evidence for PFAS exposure and the increased risk of cardiovascular disease does not meet internationally accepted causation criteria.

Thank you!

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