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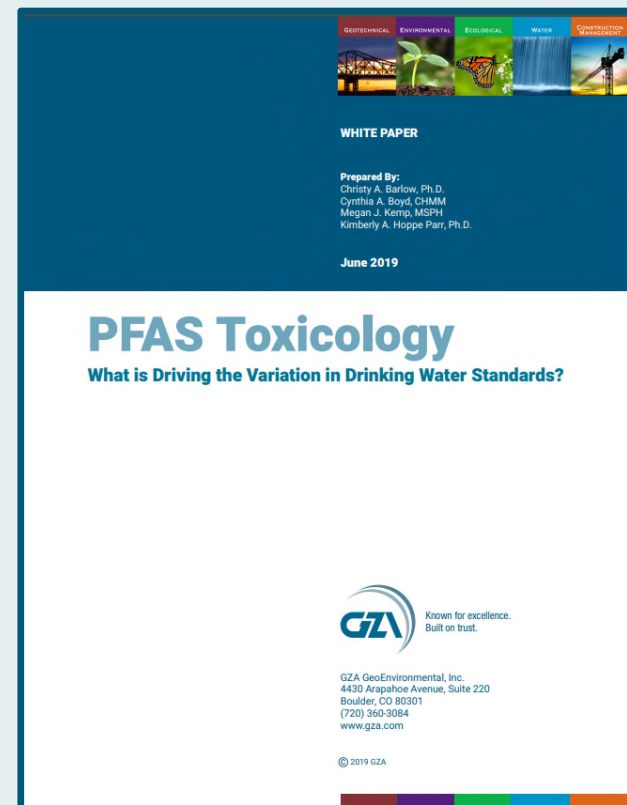
# PFAS Toxicology - What is Driving the Variation in Drinking Water Standards

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# Overview for Today

- Toxicological Effects
- Variation in Standards
- Root Cause of Uncertainty
- Considerations



# Per- and Polyfluoroalkyl Substances (PFAS)

- A large family of synthetic organic compounds that contain multiple fluorine atoms
  - Man-made
  - Persistent
  - Accumulate over time

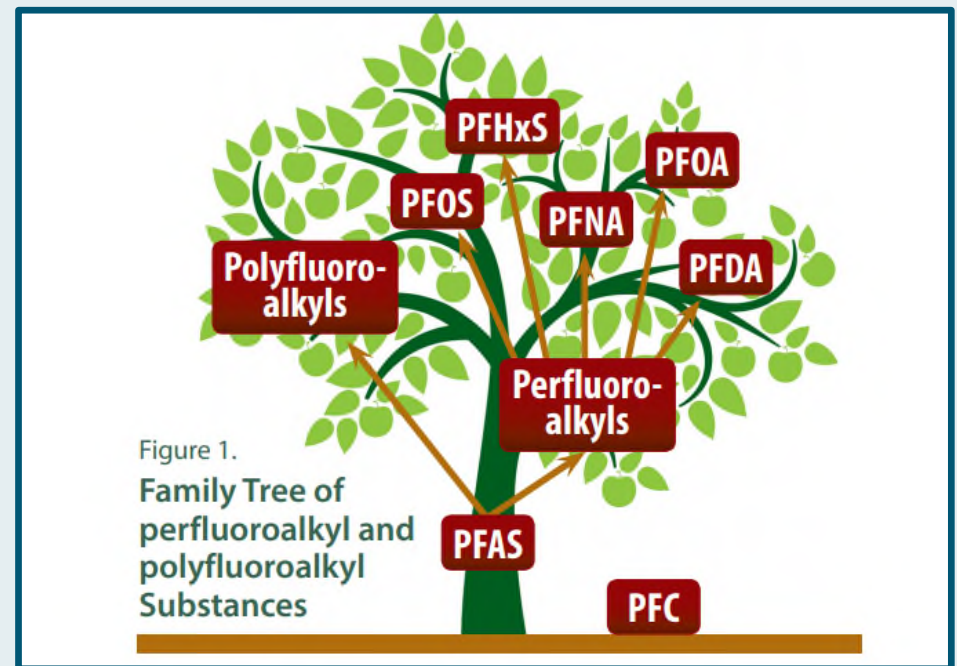


Image Source: ATSDR

# Chemical Properties of PFAS

- Thousands of diverse compounds
  - Long vs. Short Chain
  - Linear vs. Branched
  
- Strong C-F bond
  - Thermal stability
  - Chemical stability (low reactivity)
  
- Hydrophobic and lipophobic
  - Nonreactive
  - Non-stick

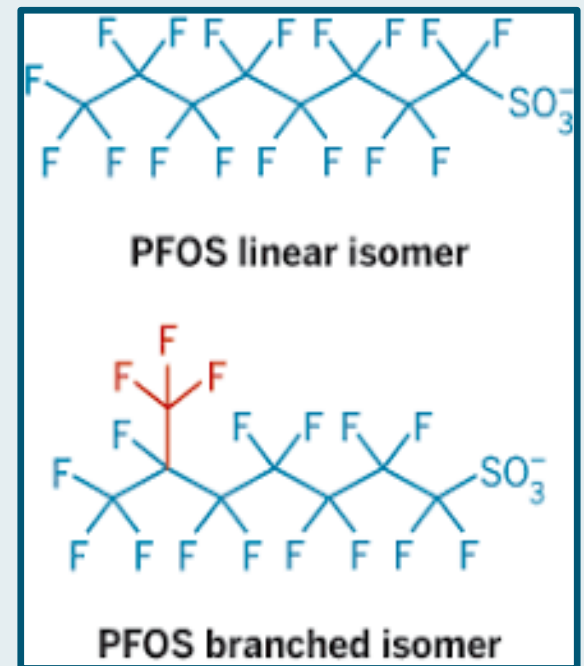


Image Source: [www.esaa.org](http://www.esaa.org)

# Exposure Pathways

- Occupational → Inhalation
- General Public → Ingestion
  - Drinking water
  - Eating contaminated food
  - Consumer products  
(hand to mouth transfer)

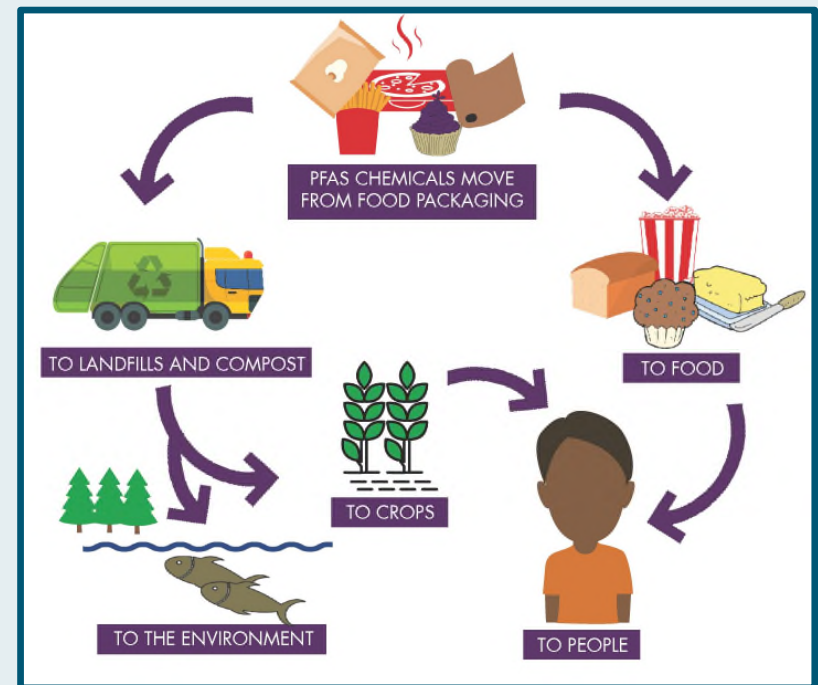
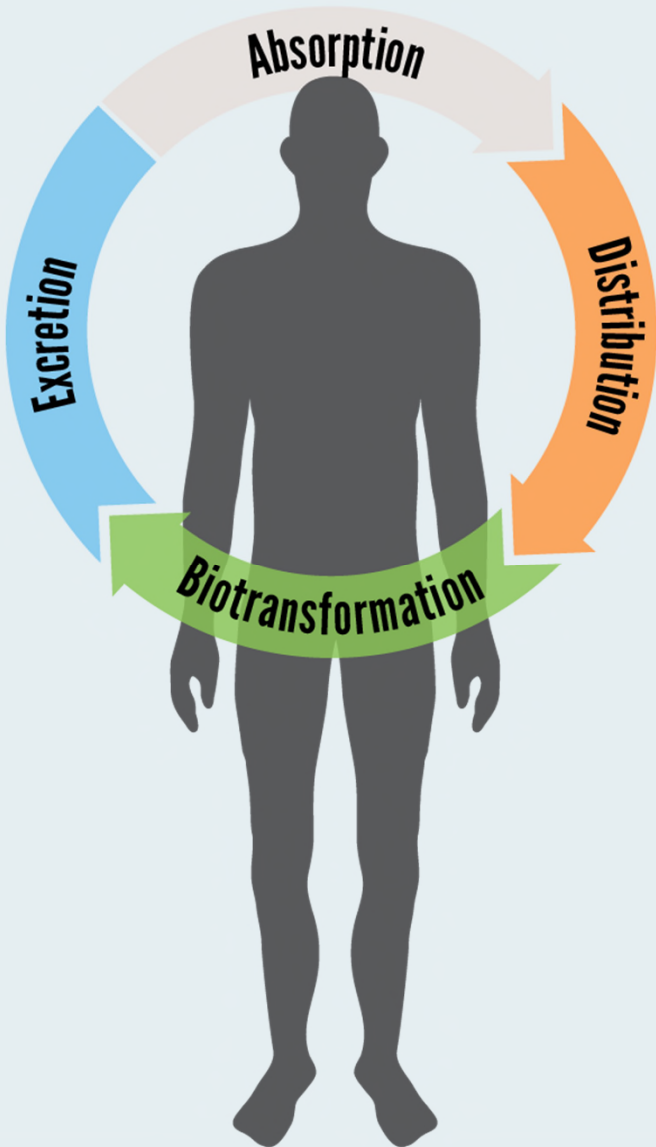


Image Source: Michigan DEQ website

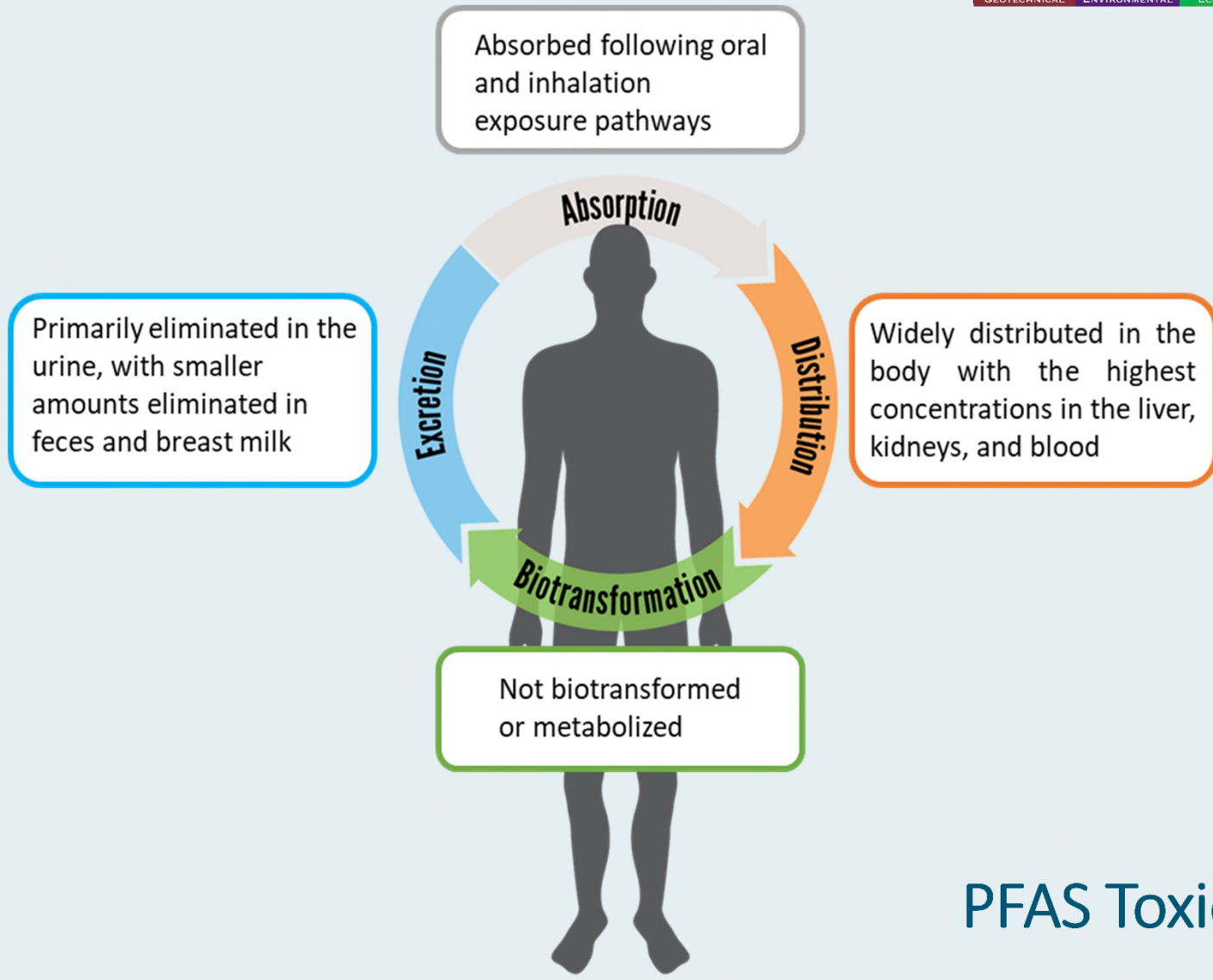


## Toxicokinetics

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Do various PFAS compounds affect the body differently?

- Chain length
- Chemical composition
- Structural differences



# PFAS Toxicokinetics

# Are there differences between PFAS?

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- Distribution: long-chain lengths that contain a sulfonate group do not pass the placental barrier as readily
- Excretion: chemical composition, chain length and branching impact the excretion rates of the PFAS compounds



- In general, long-chain PFAS take YEARS where short-chain takes DAYS to WEEKS



# Observed Human Health Effects

— High certainty  
 - - - Lower certainty

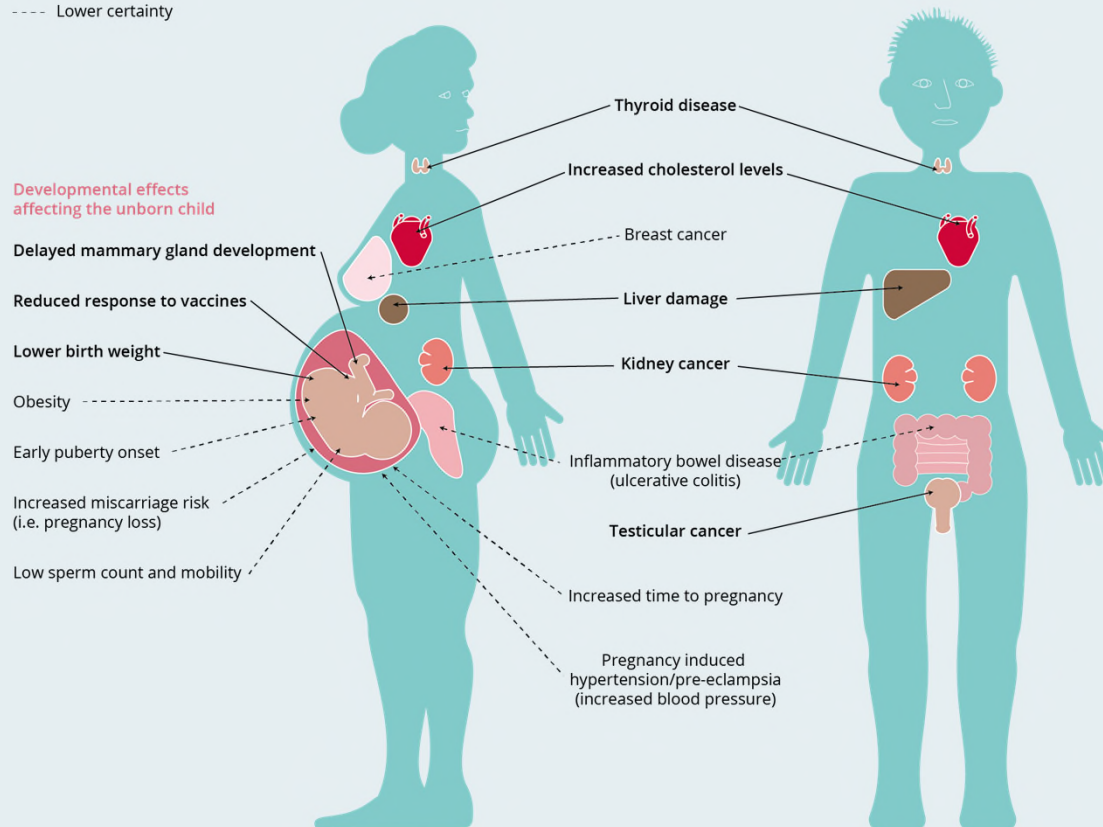


Image Source: European Environment Agency

# Data Challenging to Interpret

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- Differences in route of exposure
- Differences in exposure levels
- No control population
- Ubiquitous exposure

# Evaluating toxicity of chemicals

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- Do human and laboratory animals have similar health outcomes?
- Dose-response data in animals used to develop toxicity values



# Comparison of Animals and Humans

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- **Liver and Metabolic Toxicity**

- Mouse: enlarged and fatty liver, **decreased serum cholesterol**, triglycerides
- Humans: **increased serum cholesterol**, uric acid

- **Reproductive and Developmental Toxicity**

- Mouse: neonatal mortality, **low birth weight**, growth deficits, developmental delays
- Humans: preeclampsia, **low birth weight and small size**, delayed onset of puberty

- **Tumor Induction**

- Mouse: liver, pancreas, and **testes**
- Humans: kidney and **testes**

- **Immunotoxicity**

- Mouse: atrophy of thymus and spleen, **suppressed immune responses**
- Humans: **reduced immune responses to vaccines in children**

# Select Drinking Water Standards (in ppt)

Agency	Standard/Guidance	PFOA	PFOS	PFNA	PFHxS	PFHpA	PFDA	PFBA	PFBS	GenX
WHO	Health-Based Guideline	4000	400							
EPA +	Health Advisory	70	70							
CA	Response Level	10	40							
CT +	Action Level	70	70	70	70	70				
MA +	Proposed MCL	20	20	20	20	20	20		2000	
MI	Health-Based Values	8	16	6	51				420	370
MN	Health-Based Guidance	35	15		47			7000	3000	
NH	Proposed MCL	12	15	11	18					
NJ	Proposed MCL	14	13	13						
NY	Proposed MCL	10	10							
NC	Health Goal									140
VT+	Health Advisory	20	20	20	20	20				

+ Sum Of

# Why is there Variation in the Standards?

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- Selection of different critical effect or toxicity endpoint in animal study
- Use of different uncertainty factors
  - Large safety margins
- Use of different test species

# Critical Effects Endpoint Differences

	Toxicological Endpoint	Agency
PFOA	Hepatotoxicity	CA, NH, NJ
	Developmental	ATSDR, CT, EPA, MA, MI, MN, NY, VT
PFOS	Developmental	ATSDR, CT, EPA, MI, VT
	Immunotoxicity	CA, MA, NH, NJ, NY
PFNA	Developmental	ATSDR, MI
	Hepatotoxicity	NH, NJ
PFHxS	Thyroid	ATSDR, MI, MN
	Reproductive	NH
PFBS	Thyroid	EPA, MI
	Kidney	EPA, MA, MN
PFBA	Hepatotoxicity	MN

# Toxicity Varies Significantly

- Toxicity value = amount of chemical thought to cause minimal risk
  - Estimates included uncertainty factor



Critical Endpoint for PFOA	Species	Human Equivalent Dose (HED) (mg/kg/day)	Uncertainty Factor	Toxicity Value (RfD) (ng/kg-day)
Increased liver weight	Rat	0.0044	30	150
Decreased birth weight	Mouse	0.0109	300	40
Decreased IgM response	Mouse	0.0053	300	20
Reduced bone ossification, accelerated puberty	Mouse	0.0053	300	20
Decreased body weight, increased kidney weight	Rat	0.0064	300	20



# The relationship between various exposure factors and the MCL

Selection Variable	Chosen Value	MCL	Example
Uncertainty Factor	↑	↓	Increasing the uncertainty from 30 to 300 results in a <b>10-fold decrease</b> in the MCL, all other factors the same
Water Intake Rate	↑	↓	Using a rate for an adult vs. a lactating women results in nearly a <b>2-fold decrease</b> in the MCL, all other factors the same
Relative Source Contribution	↑	↑	Increasing the RSC from 20% to 80% results in a <b>4-fold increase</b> in the MCL, all other factors the same

# Summary

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- Ambiguous associations with adverse health effects
  - Are the effects adverse?
  - Are they transient?
- Toxicity studies are continuing, but...
  - Difficult due to the number and variety of PFAS
  - Responses differ between animals and humans
  - Lack of information on mechanism of action



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# Thank you!

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