Approaches to Hazard and Dose-Response Assessment of PFAS: PFBS Example

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Understanding and Applying Read-Across for Human Health Risk Assessment Workshop

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The views expressed in this presentation are those of the author and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency

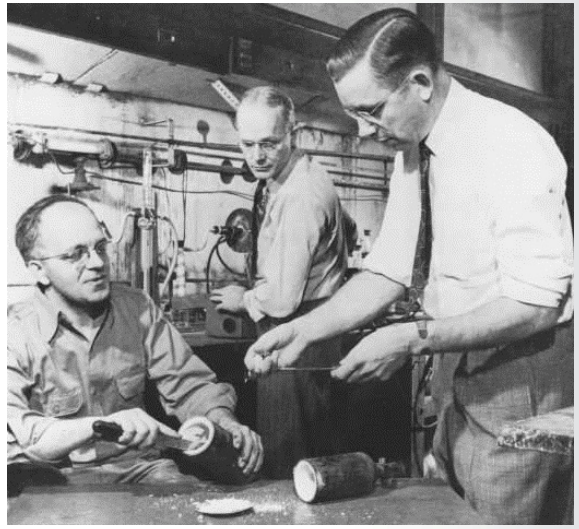
The author has no conflicts of interest to disclose

Outline of this presentation

- Background
- Scope of the Problem
- Anatomy of an example PFAS assessment-PFBS
- Human Health Risk Assessment 2.0
  - New Approach Methods to the rescue?

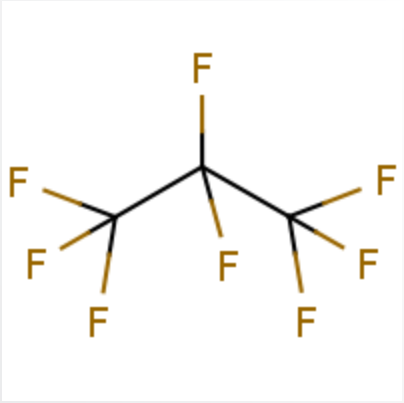
Background

- PFAS discovered accidentally April, 1938 by Roy Plunkett of DuPont
- DuPont chemists were working with chlorofluorocarbon refrigerants
- 100 lbs of tetrafluoroethylene (TFE) gas was loaded into pressurized cylinders at approximately -109°F
- The gentlemen shown in the image discovered, upon opening of the cylinders, the absence of gas; instead what remained was a white powdery polymer, Polytetrafuoroethylene (PTFE)
- PTFE was tested and found to be chemically inert, heat resistant, and to have low surface friction
- DuPont proposed a commercial application in 1945, trademarked as Teflon™
- PFAS soon gained broad application in commerce
- Annual revenue associated with PFAS applications in the billions $$

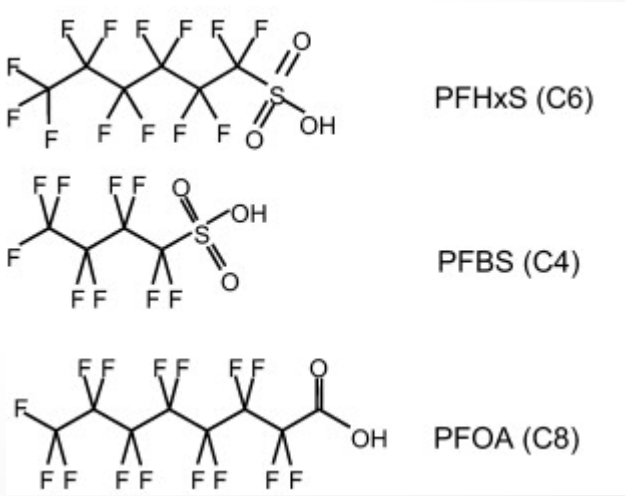


PFC versus PFAS

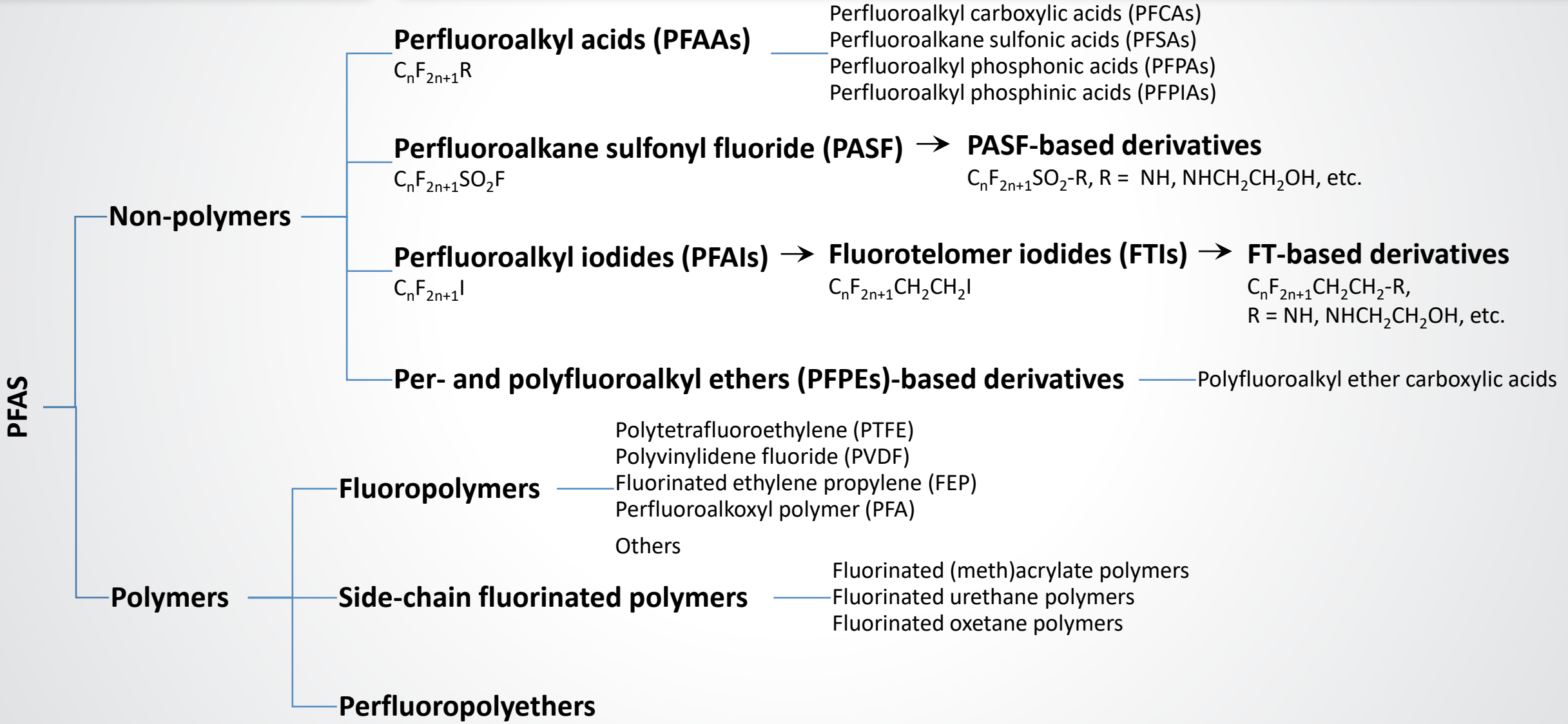
- PFCs can refer to two distinct but related sets of chemicals - perfluorinated chemicals or perfluorocarbons (contain carbon and fluorine only)
- PFAS refer to per- and polyfluoroalkylated substances, a subset of perfluorinated chemicals
- **Per**fluoroalkyl substances - *all* of the H atoms attached to C atoms have been replaced by F atoms
- **Poly**fluoroalkyl substances - *all* of the H atoms attached to *at least one* (but not all) C atoms have been replaced by F atoms



Perfluoropropane
PFC-218



Thousands of Chemicals: More Than Just PFOA and PFOS

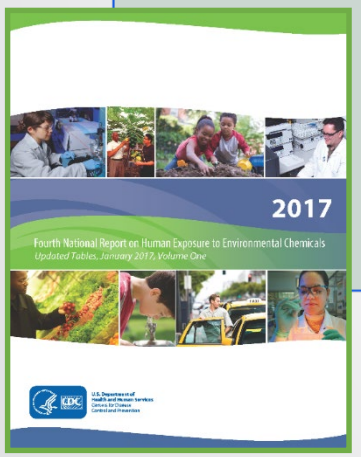


State and International Guideline Values

International Agency	PFOA (µg/ L)	PFOS (µg/ L)	Comments
US EPA	0.07	0.07	Health advisories (2016)
Delaware Health and Social Services	0.4	0.2	Drinking Water Notice Guidance Value (2013)
German Ministry of Health	0.3	0.3	Health-based level; composite precautionary guidance value for PFOA + PFOS (additive) is 0.1 µg/L (2006)
Maine Department of Environmental Protection	0.1	-	Groundwater Remedial Action Guidelines (2014)
UK Health Protection Agency	0.3	0.3	Maximum acceptable concentrations in drinking water (2007)
Michigan Department of Environmental Quality	0.42	0.011	Ambient Water Quality Standard (human health criteria for water plus organism) (2013)
Danish Ministry of the Environment	0.1	0.1	Health-based quality criteria (2015)
Minnesota Department of Health	0.3	0.3	Health Guidelines for Perfluorochemicals in Drinking Water (2009)
New Jersey Department of Environmental Protection	0.013	0.09	Composite for PFOA, PFOS and precursor PFOSA
Swedish EPA			Maximum Contaminant Level Recommendation (draft) (2017)
North Carolina Division of Water Quality	1	-	Pregnant women or women who are trying to get pregnant and infants should not drink if combination of seven PFCs (includes PFOA and PFOS) >0.9 (µg/ L)
Dutch National Institute for Public Health and the Environment			Interim Maximum Allowable Concentration for Groundwater (2012)
Vermont Agency of Natural Resources			Environmental Risk Limit (2010)
Department of Health	0.02	0.53	Drinking Water Guidance Value; based on child's exposure scenario (2016)

PFAS and NHANES

PFAS in serum		99–00	03–04 -----11–12	13–14
Short-alkyl chain	PFBS		X	X
	PFHpA	X	X	X
Long-alkyl chain	PFHxS	X	X	X
	PFOS	X	X	X[a]
	PFOA	X	X	X[a]
	PFNA	X	X	X
	PFDA	X	X	X
	PFUnDA	X	X	X
	PFDoDA	X	X	X
	FOSA	X	X	
	EtFOSAA	X	X	
	MeFOSAA	X	X	X



- PFAS are in the serum of nearly all of the U.S. population
- 12 PFAS have been measured in individuals (age 12 years and older) from 1999-2000 to 2013-2014
- **Six PFAS have generally declined in the population over the 16 year period**
  - Consistent reductions have been observed for PFOS (84%), PFOA (63%), MeFOSAA (>75%), and PFHxS (37%)
- Six PFAS have not been detected over the 16 year period
  - PFBS, PFDoA, PFHpA, PFOSA, PFUA, EtFOSAA
- Cross-federal discussions ongoing to inform future biomonitoring

- This list represents an early survey (circa April 2017) of PFAS of interest across EPA Programs and Regions
- Should not be construed as comprehensive as this list evolves over time!
- Illustrative of class diversity

Category	Draft PFAS List	Acronym
Perfluoro carboxylic acids	Perfluorododecanoic acid	PFDoA
	Perfluoroundecanoic acid	PFUnA
	Perfluorodecanoic acid	PFDA
	Perfluorononanoic acid	PFNA
	Perfluorooctanoic acid	PFOA
	Perfluoroheptanoic acid	PFHpA
	Perfluorohexanoic acid	PFHxA
	Perfluoropentanoic acid	PFPeA
	Perfluorobutyric acid	PFBA
Perfluoro sulfonates	Perfluorodecanesulfonate	PFDS
	Perfluorononanesulfonate	PFNS
	Perfluorooctanesulfonate	PFOS
	Perfluoroheptanesulfonate	PFHpS
	Perfluorohexanesulfonate	PFHxS
	Perfluoropentansulfonate	PFPeS
	Perfluorobutanesulfonate	PFBS
Perfluoro sulfonamide	Perfluorooctanesulfonamide	PFOSA
Fluorotelomer sulfonates	Fluorotelomer sulfonate 8:2	FtS 8:2
	Fluorotelomer sulfonate 6:2	FtS 6:2
Perfluoro sulfonamidoacetic acids	N-ethyl-N-((heptadecafluorooctyl)sulfonyl)glycine	NEtFOSAA
	N-(Heptadecafluorooctylsulfonyl)-N-methylglycine	NMeFOSAA
Fluorotelomer alcohols	Fluorotelomer alcohol 8:2	FtOH 8:2
	Fluorotelomer alcohol 6:2	FtOH 6:2
Perfluoro ether carboxylic acids	Perfluoro(2-methyl-3-oxahexanoic) acid	GenX
	4,8-dioxa-3H-perfluorononanoic acid	ADONA
Fluorotelomer phosphates	6:2 Fluorotelomer phosphate monoester	6:2 monoPAP
	6:2 Fluorotelomer phosphate diester	6:2 diPAP
	8:2 Fluorotelomer phosphate monoester	8:2 monoPAP
	8:2 Fluorotelomer phosphate diester	8:2 diPAP
	6:2/8:2 Fluorotelomer phosphate diester	6:2/8:2 diPAP
Fluorotelomer carboxylic acid	5:3 Polyfluorinated acid	5:3 acid

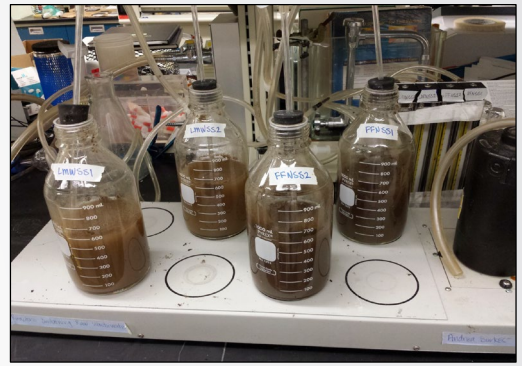
PFAS List for Consideration

This original list consisted of PFAS that were:

- included in UCMR3 monitoring and on CCL4 (OW),
- found at sites in multiple media (OLEM),
- new chemicals of interest (OPPT),
- recommended by regions (OLEM cross-regional, regional science and technology liaisons, OW drinking water programs),
- recommended by analytical methods/exposure workgroup,
- subject of ongoing NTP research, and
- representative of categories of PFAS (carboxylic acids, sulfonates, fluorotelomers, etc.)

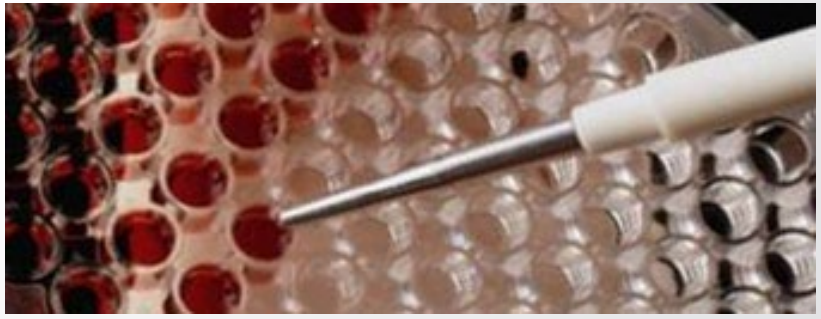
Current EPA/ORD PFAS Activities

- **Analytical Methods**
  - Establish validated methods for measuring PFAS in different environmental media



- **Human Health/Toxicity**
  - Develop standard toxicity values (RfD)
  - Apply computational toxicity for screening PFAS universe

- **Exposure**
  - Develop sampling methods to characterize sources and contaminated sites
  - Identify and estimate human exposure to PFAS from different sources

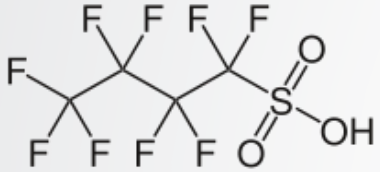


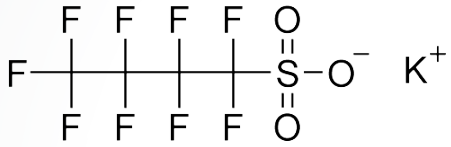
- **Treatment/Remediation**
  - Identify/evaluate methods to treat and remediate drinking water and contaminated sites

- **Technical Assistance to Regions, States, Tribes**

Anatomy of an example PFAS assessment-PFBS

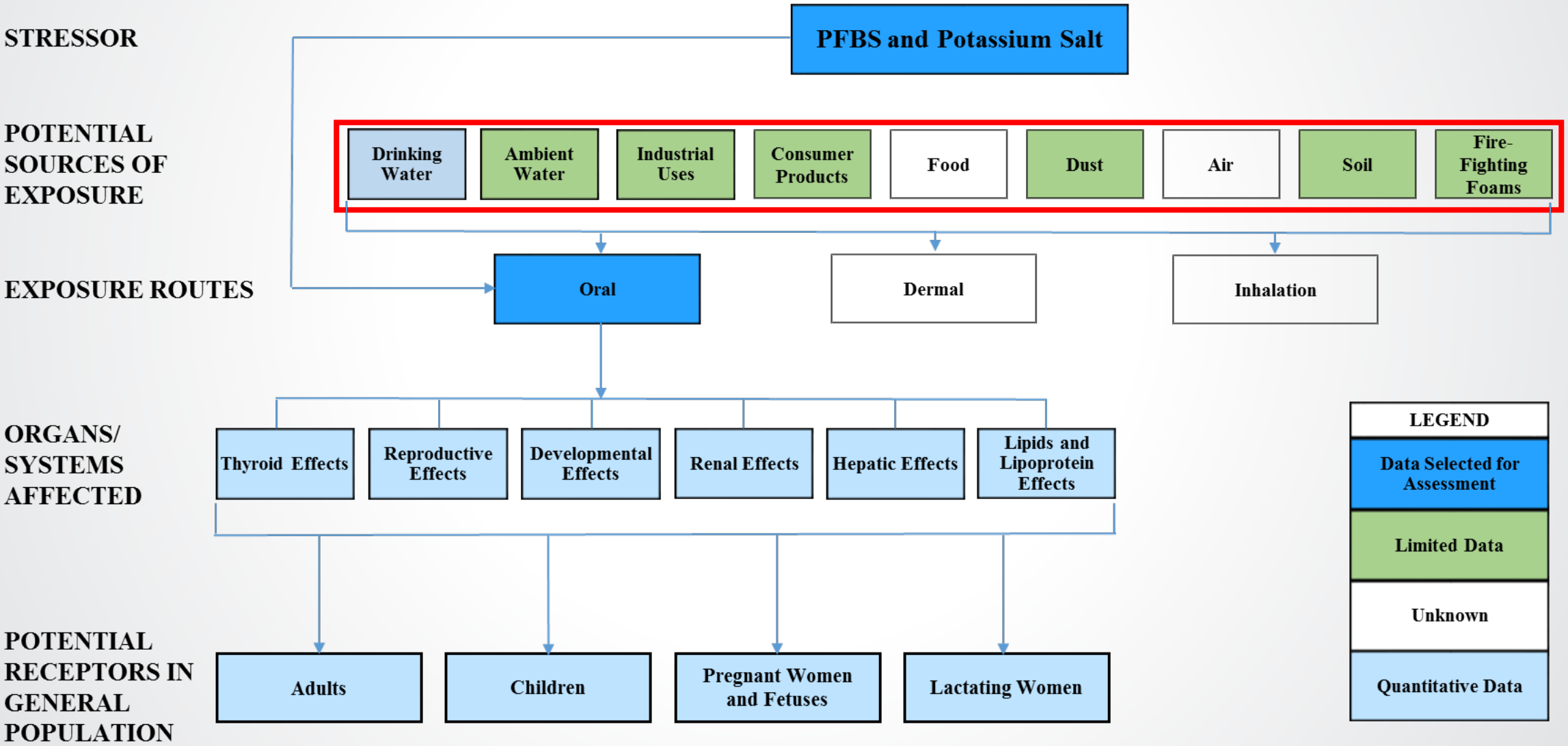
1-Perfluorobutanesulfonic Acid



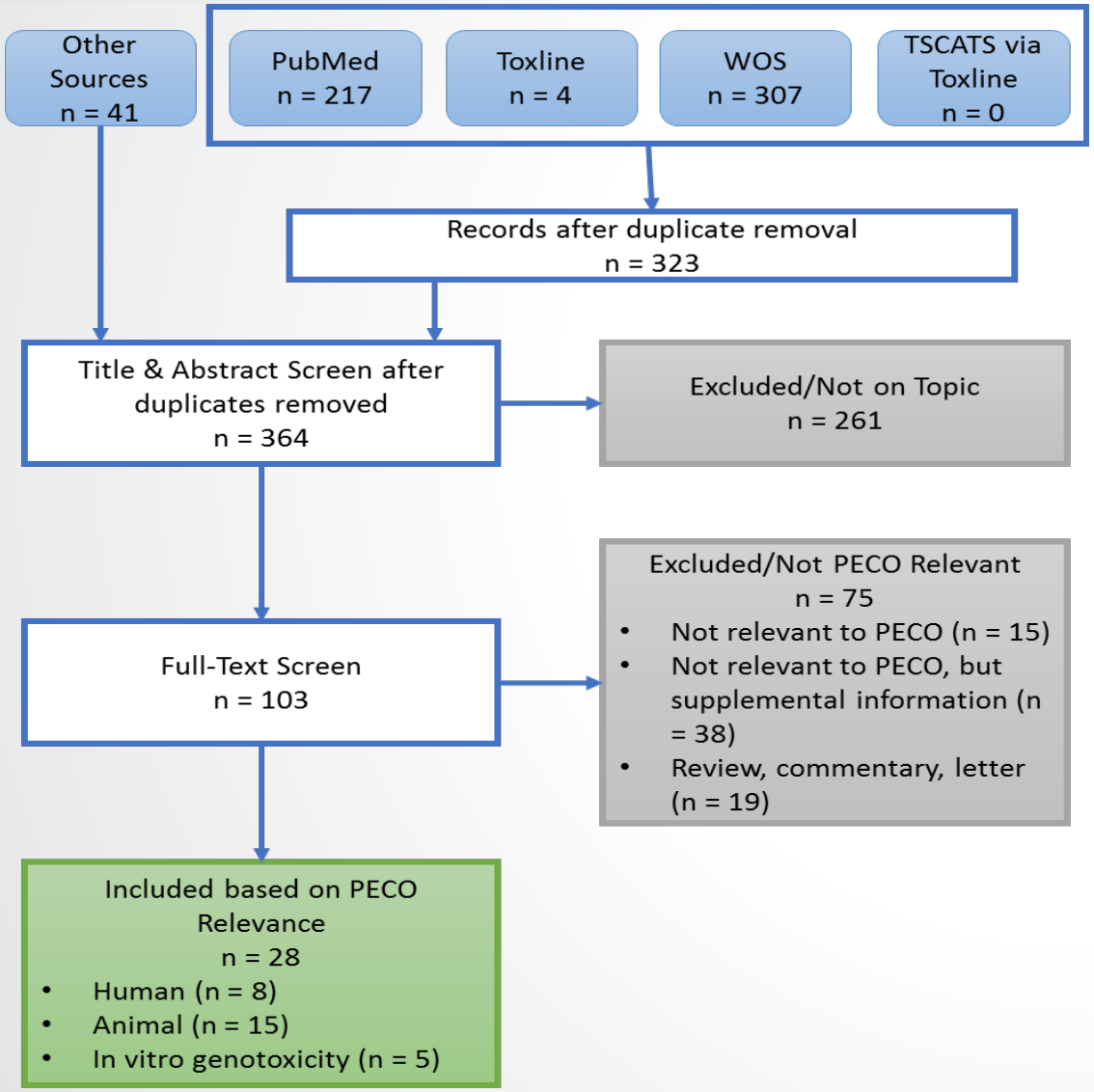


- Collection of available hazard and dose-response information
  - Also included occurrence, exposure, physicochemical properties
- Problem Formulation
- Systematic literature review and Study Quality Evaluation
- Evidence evaluation, synthesis, and integration
- Dose-response assessment and Uncertainty
  - BMD/BMRs, Dosimetric adjustment, and UF_A, oh my!

Problem Formulation-PFBS



PFBS-Systematic Literature Review

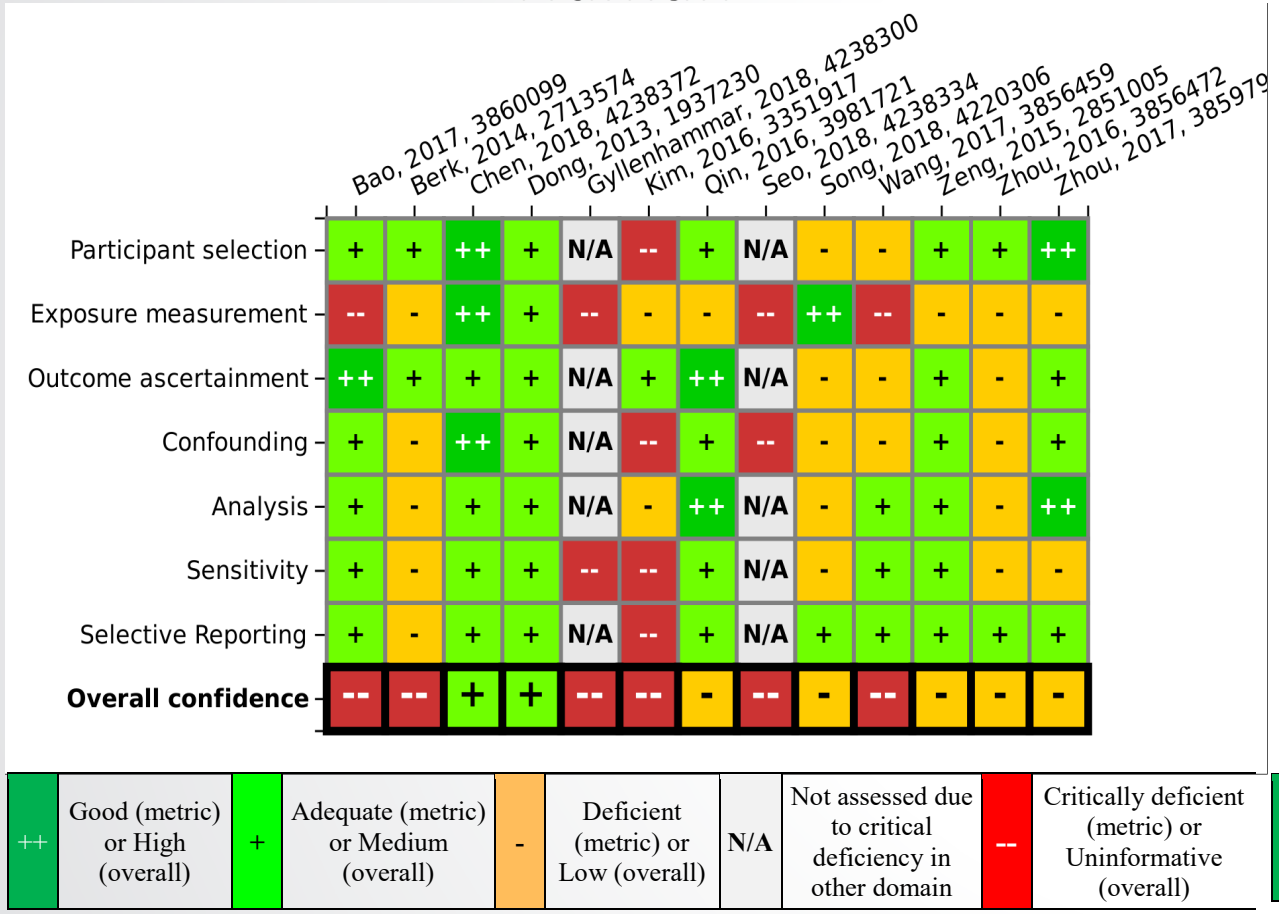


- Four online scientific databases (PubMed, Web of Science, Toxline, and TSCATS via Toxline) were searched.
- In addition, studies were identified by our colleagues in EPA/OPPT (Other Sources).
- Two screeners independently conducted a title and abstract screen.
- Studies that met the Population, Exposure, Comparator, and Outcome (PECO) criteria were then full-text reviewed and moved on to data study/data evaluation and extraction.

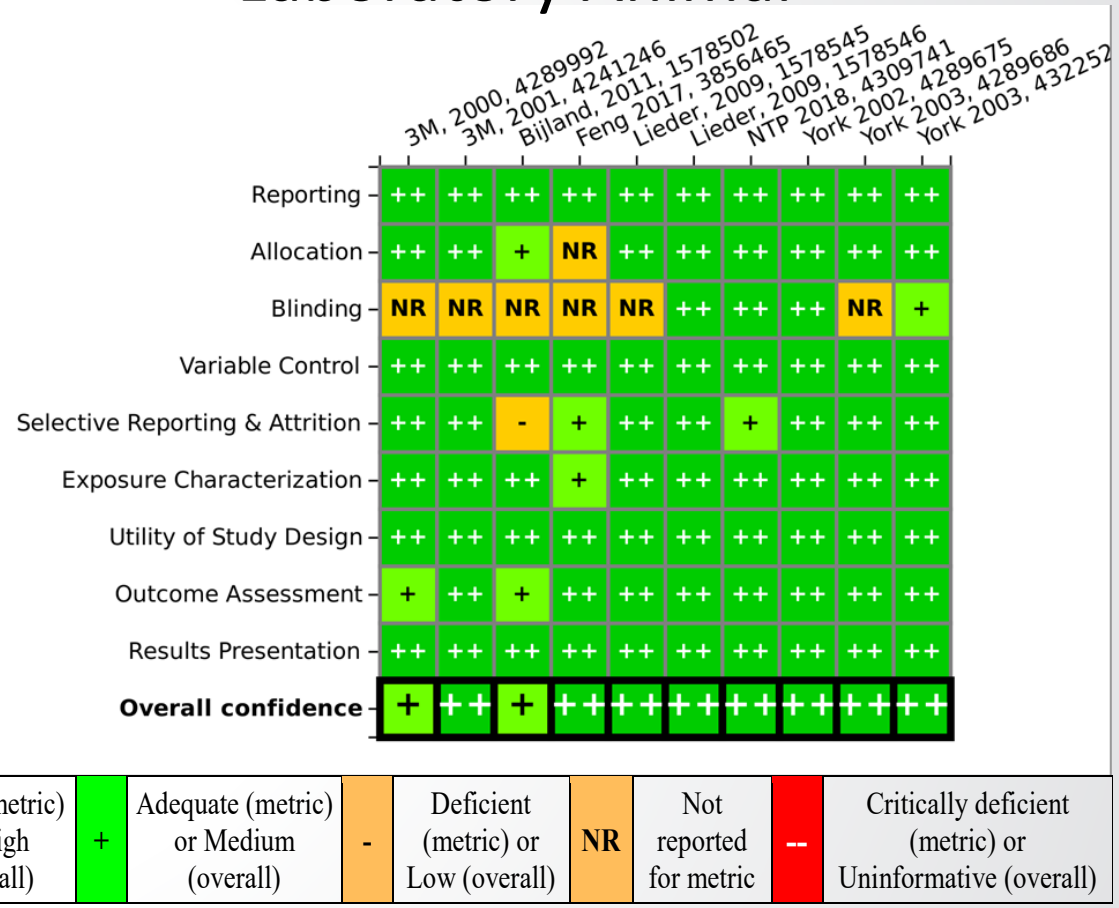
PECO element	Evidence
Population	**Human**: Any population (occupational; general population including children, pregnant women, and other sensitive populations). The following study designs will be considered most informative: controlled exposure, cohort, case-control, or cross-sectional. Note: Case reports and case series are not the primary focus of this assessment and will be tracked as supplemental material during the study screening process. **Animal**: Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, *in utero*, lactation, peripubertal, and adult stages). ***In vitro* models of genotoxicity**: The studies will be considered PECO-relevant. All other *in vitro* studies will be tagged as "not-PECO relevant, but supplemental material." **Nonmammalian model systems/*in vitro*/*in silico* NOT related to genotoxicity**: Nonmammalian model systems (e.g., fish, amphibians, birds, and *C. elegans*); studies of human or animal cells, tissues, or biochemical reactions (e.g., ligand binding assays) with *in vitro* exposure regimens; bioinformatics pathways of disease analysis; and/or high throughput screening data. These studies will be classified as non-PECO-relevant, but have supplemental information.
Exposure	**Human**: Studies providing qualitative or quantitative estimates of exposure based on administered dose or concentration, biomonitoring data (e.g., urine, blood, or other specimens), environmental or occupational-setting measures (e.g., water levels or air concentrations), residential location, job title or other relevant occupational information. Human "mixture" studies are considered PECO-relevant as long as they have the per- and polyfluoroalkyl substances (PFAS) of interest. **Animal**: Studies providing qualitative and quantitative estimates of exposure based on administered dose or concentration. Oral and inhalation studies are considered PECO-relevant. Nonoral and noninhalation studies are tagged as supplemental. Experimental mixture studies are included as PECO-relevant only if they include a perfluorobutane sulfonic acid- (PFBS-) only arm. Otherwise, mixture studies are tagged as supplemental. All studies must include exposure to PFBS, CASRN 375-73-5. Studies of precursor PFAS that identify any of the targeted PFAS as metabolites will also be included.
Comparator	**Human**: A comparison or reference population exposed to lower levels (or no exposure/exposure below detection levels) or for shorter periods of time. For D-R purposes, exposure-response quantitative results must be presented in sufficient detail such as regression coefficients presented with statistical measure of variation such as RR, HR, OR, or SMR or observed cases vs. expected cases (common in occupational studies); slope or linear regression coefficient (i.e., per unit increase in a continuous outcome); difference in the means; or report means with results of t-test, mean comparison by regression, or other mean-comparing hypothesis test. **Animal**: Quantitative exposure versus lower or no exposure with concurrent vehicle control group.
Outcome	Cancer and noncancer health outcomes. In general, endpoints related to clinical diagnostic criteria, disease outcomes, histopathological examination, genotoxicity, or other apical/phenotypic outcomes will be prioritized for evidence synthesis. Based on preliminary screening work and other assessments, the systematic review is anticipated to focus on liver (including serum lipids), developmental, reproductive, neurological, developmental neurotoxicity, thyroid disease/disruption, immunological, cardiovascular, and musculoskeletal outcomes.

Study Quality Evaluation-PFBS

Human

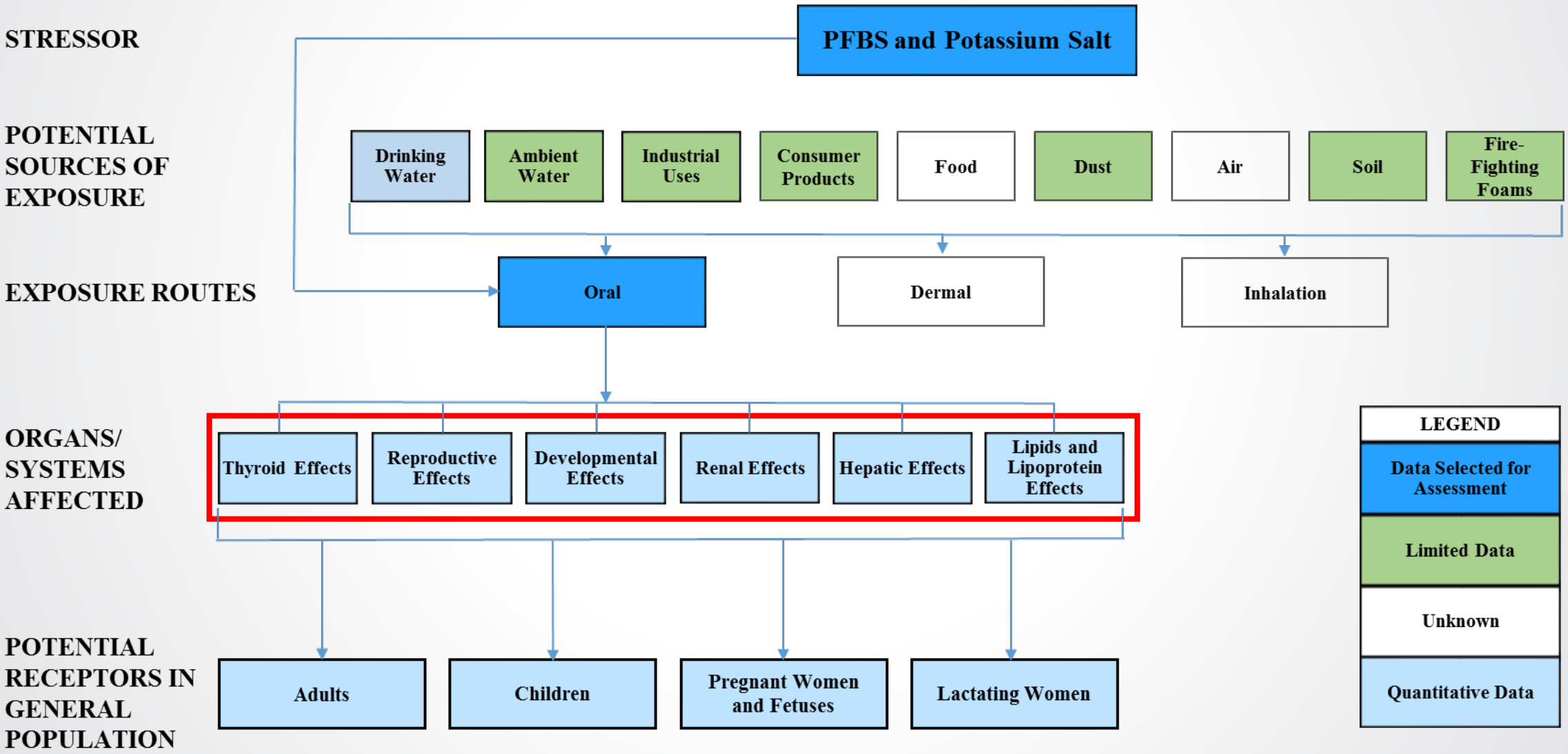


Laboratory Animal



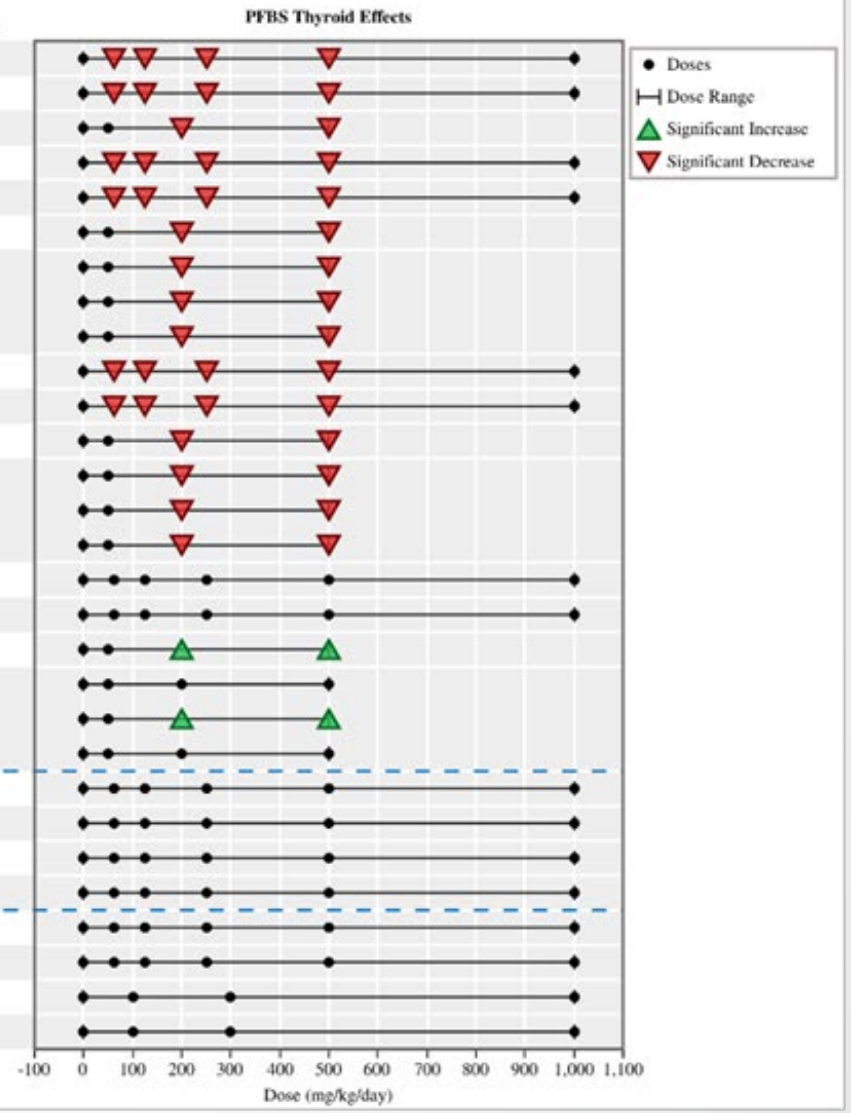
- Studies were evaluated based on predefined criteria to assess the potential for bias and insensitivity
- Overall judgments for each study were determined to define confidence in the reliability of the results

Evidence Evaluation-PFBS Effect Domains



Evidence Evaluation→Synthesis-PFBS induced Thyroid Effects

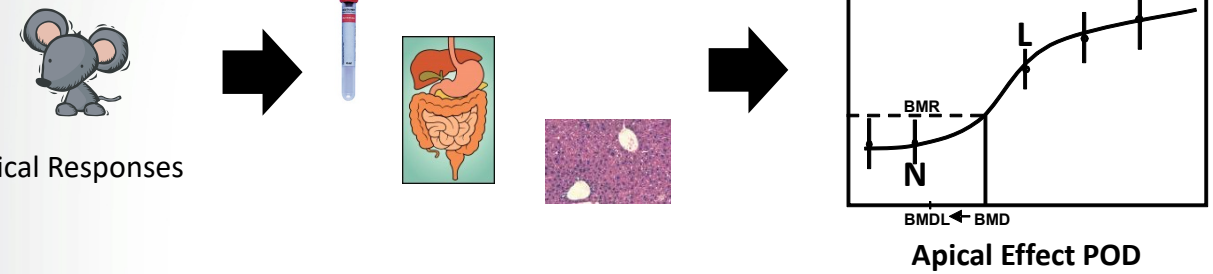
Endpoint Name	Study Name	Study Type	Animal Description	Observation Time
Tetraiodothyronine (T4), Free	NTP 2018, 4309741	short-term (28 days)	Rat, Harlan Sprague-Dawley (♂)	Day 28
			Rat, Harlan Sprague-Dawley (♀)	Day 28
	Feng 2017, 3856465	developmental (GD1 to 20)	P0 Mouse, ICR (♀)	GD20
Tetraiodothyronine (T4), Total	NTP 2018, 4309741	short-term (28 days)	Rat, Harlan Sprague-Dawley (♂)	Day 28
			Rat, Harlan Sprague-Dawley (♀)	Day 28
	Feng 2017, 3856465	developmental (GD1 to 20)	P0 Mouse, ICR (♀)	GD20
			F1 Mouse, ICR (♀)	PND1
				PND30
				PND60
Triiodothyronine (T3)	NTP 2018, 4309741	short-term (28 days)	Rat, Harlan Sprague-Dawley (♂)	Day 28
			Rat, Harlan Sprague-Dawley (♀)	Day 28
	Feng 2017, 3856465	developmental (GD1 to 20)	P0 Mouse, ICR (♀)	GD20
			F1 Mouse, ICR (♀)	PND1
				PND30
				PND60
Thyroid Stimulating Hormone (TSH)	NTP 2018, 4309741	short-term (28 days)	Rat, Harlan Sprague-Dawley (♂)	Day 28
			Rat, Harlan Sprague-Dawley (♀)	Day 28
	Feng 2017, 3856465	developmental (GD1 to 20)	P0 Mouse, ICR (♀)	GD20
			F1 Mouse, ICR (♀)	PND1
				PND30
				PND60
Thyroid Weight, Absolute	NTP 2018, 4309741	short-term (28 days)	Rat, Harlan Sprague-Dawley (♂)	Day 28
			Rat, Harlan Sprague-Dawley (♀)	Day 28
Thyroid Weight, Relative	NTP 2018, 4309741	short-term (28 days)	Rat, Harlan Sprague-Dawley (♂)	Day 28
			Rat, Harlan Sprague-Dawley (♀)	Day 28
Thyroid Histopathology	NTP 2018, 4309741	short-term (28 days)	Rat, Harlan Sprague-Dawley (♂)	Day 28
			Rat, Harlan Sprague-Dawley (♀)	Day 28
	3M, 2000, 4289992	short-term (10 days)	Rat, Crl: Cd (Sd) Ibs Br (♂)	Day 11
			Rat, Crl: Cd (Sd) Ibs Br (♀)	Day 11



Evidence Synthesis→Integration-PFBS induced Thyroid Effect

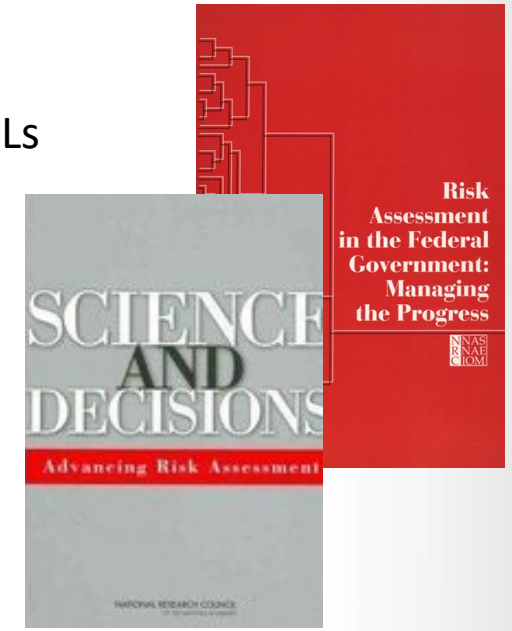
Studies and confidence	Factors that increase support for hazard	Factors that decrease support for hazard	Summary of findings	Overall evidence integration judgment and basis
Thyroid effects				
Human studies				*Supports a hazard* (animal evidence *supports a hazard*; human evidence is *equivocal*). The primary basis for this judgment is thyroid hormone decreases in mice and rats at ≥ 62.6 mg/kg-d.
No studies available to evaluate	--	--	--	
Animal studies (all oral gavage)				
Mouse Studies: • High-confidence gestational (GDs 1−20) exposure study (Feng et al., 2017) Rat Studies: • High-confidence short-term (28-d) toxicity study (NTP, 2018, 2011)	• Consistent thyroid hormone decreases (i.e., for total T3, total T4, and free T4) across two high-confidence studies of varied design. The findings were consistent across two species, sexes, life stages, and exposure durations. • Dose-response gradients were observed for those thyroid hormones. • Large magnitudes of effect (e.g., up to ~50% reductions in offspring serum hormones) were reported for those thyroid hormones.	• No factors noted.	Similar patterns of decreases in thyroid hormones (i.e., for total T3, total T4, and free T4) were observed in PFBS-exposed pregnant mice and gestationally exposed female mouse offspring at ≥ 200 mg/kg-d (Feng et al., 2017) and in adult female and male rats at ≥ 62.6 mg/kg-d (NTP, 2018, 2011). Increased TSH was reported in mouse dams and in pubertal (PND 30) offspring following gestational exposure (Feng et al., 2017), but no changes were noted in rats exposed as adults (NTP, 2011). Thyroid weight and histopathology were not changed after short-term exposure in adult male or female rats (NTP, 2018, 2011).	

Traditional Risk Assessment Practice



Apical Effect POD

POD identification
-preferably BMDLs
-If BMD fails, NOAELs or LOAELs



- Non-cancer Reference Values (RfD, RfC) = POD/UF_C
- UF_C = composite uncertainty factor
  - UF_A = animal-to-human
  - UF_H = interindividual variability
  - UF_S = subchronic-to-chronic duration
  - UF_L = LOAEL-to-NOAEL
  - UF_D = database
- Cancer Values (OSF, IUR) = increased cancer risk from a lifetime oral or inhalation exposure to a chemical. Usually expressed in units of proportion (of a population) affected per mg/kg-day (oral) or $\mu g/m^3$ (inhalation)

BMD/BMRs and Dosimetric Adjustment

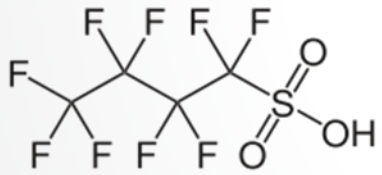
- Use of Benchmark Dose Modeling >>NOAEL>LOAEL in identifying PODs
- 1°-Biologically-based BMRs if possible; 2°-Default BMRs; show comparisons for transparency
- Dosimetric Adjustment consideration of great import; ADME transit time for PFAS is typically longer in humans

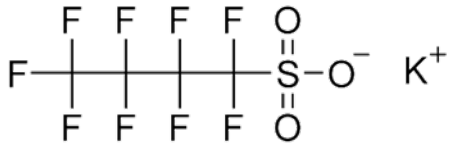
	PFBS (C4)		PFHxS (C6)		PFOS (C8)		PFBA (C4)		PFHxA (C6)		PFOA (C8)		PFNA (C9)		GEN-X	
	Female	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*
Rat	4.0 hours	4.5 hours	1.8 days	6.8 days	62-71 days	38-41 days	1.0-1.8 hours	6-9 hours	0.4-0.6 hours	1.0-1.6 hours	2-4 hours	4-6 days	1.4 days	31 days	1.3 days	3.0 days
Mouse	2.1 hours	3.3 hours	25-27 days	28-30 days	31-38 days	36-43 days	3 hours	12 hours	~1.2 hours	~1.6 hours	16 days	22 days	26-68 days	34-69 days	1.0 day	1.5 days
Monkey	3.5 days	4.0 days	87 days	141 days	110 days	132 days	1.7 days		0.1-0.8 days	0.2-1.5 days	30 days	21 days			3.3 days	2.7 days
Human	28 days		8.5 years		4.3-5.0 years		3 days		32 days		2.1-3.8 years					

For more information and details…

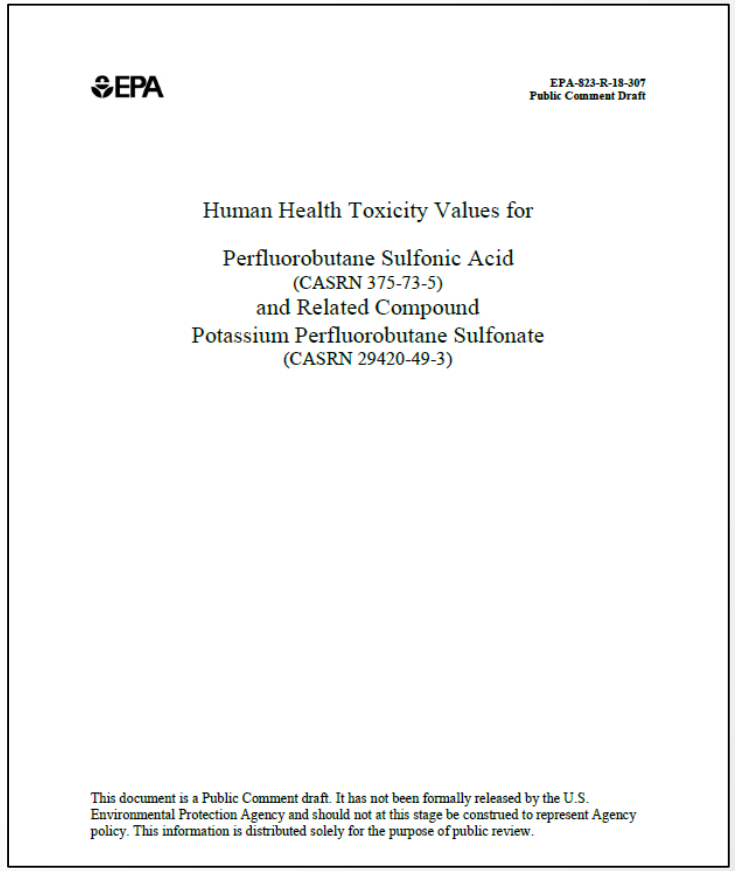
- For brevity, please see the public review draft of the PFBS assessment
  - Interactive/interoperable with Health Assessment Workspace Collaborative (HAWC)
    - Google Chrome (preferred)
    - Mozilla Firefox
    - Apple Safari

1-Perfluorobutanesulfonic Acid





https://www.epa.gov/sites/production/files/2018-11/documents/pfbs_public_comment_draft_toxicity_assessment_nov2018-508.pdf



EPA

EPA-823-R-18-307
Public Comment Draft

Human Health Toxicity Values for

Perfluorobutane Sulfonic Acid
(CASRN 375-73-5)
and Related Compound
Potassium Perfluorobutane Sulfonate
(CASRN 29420-49-3)

This document is a Public Comment draft. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency policy. This information is distributed solely for the purpose of public review.

HHRA 2.0: New Approach Methods to Accelerate Chemical Safety Evaluations

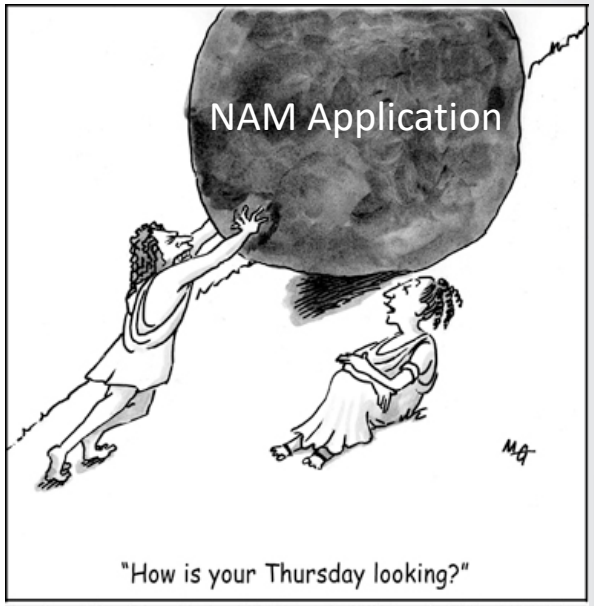
- Assessment timeline: Integrated Risk Information System (years), Provisional Peer-Reviewed Toxicity Values (months up to 2 years), ATSDR MRLs (years)
- Depending on who you talk to, there are anywhere from 20K to >80K chemicals currently in the environment/commerce; several thousand PFAS
- Collectively, across our global community of toxicology and risk assessment practice, only a small fraction of those chemicals have been assessed for toxicity; current data availability for most PFAS is limited

*For problem formulations associated with protection of human health and the natural environment, higher throughput of qualitative and quantitative information for PFAS is paramount!

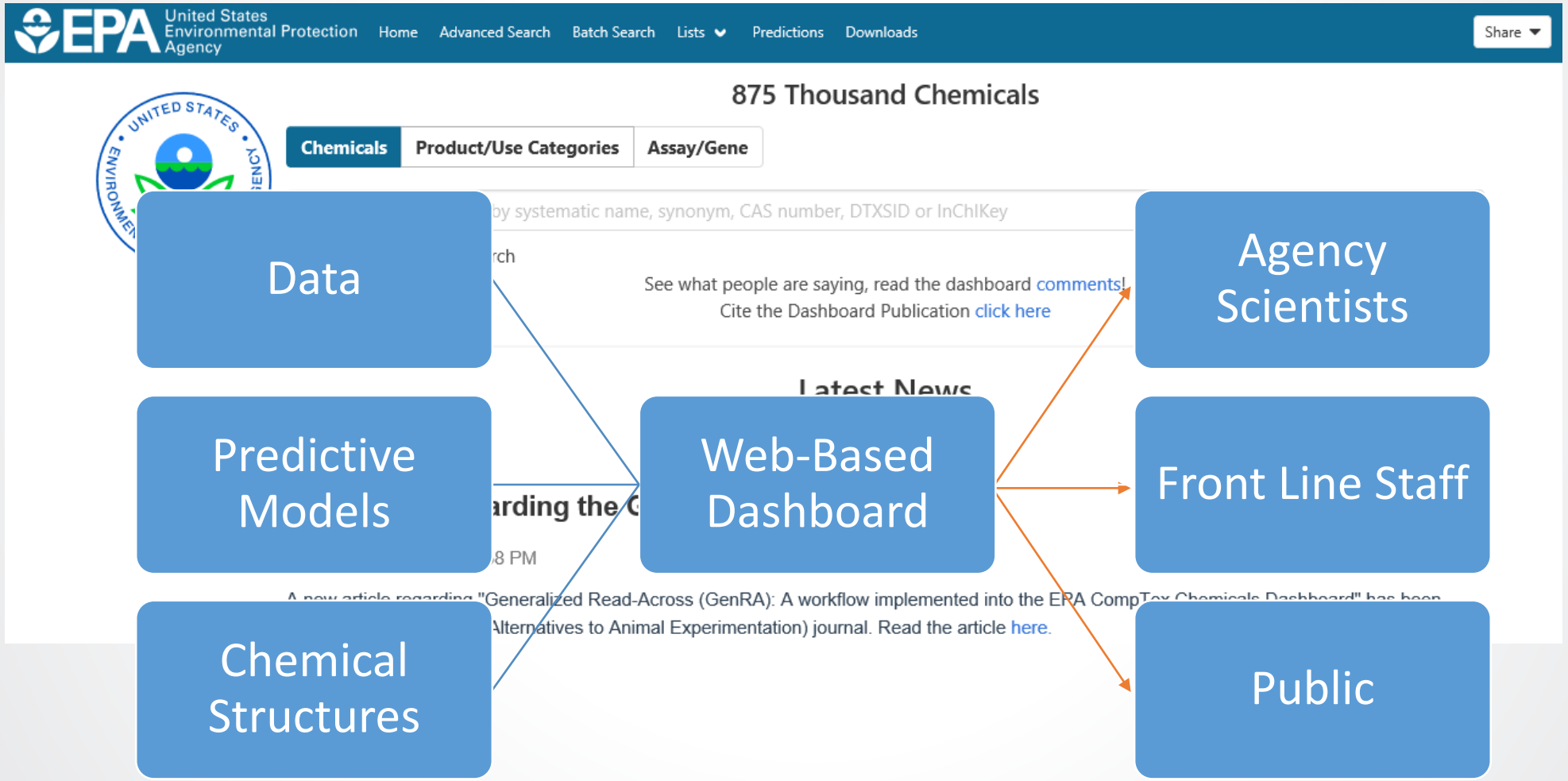
- Over the past decade, several reports, books, resource documents, etc. have been published regarding the use of New Approach Methods (NAM) across the human health risk assessment paradigm (i.e., shifting the paradigm)
- Numerous labs, centers, workgroups, and initiatives across federal, private, and academic institutions have been formed to advance NAM and Computational Toxicology platforms

NAM/CompTox Toolbox to Date

- **Data-mining**: comprehensive collection and collation of extant hazard and exposure data –(Martin et al. 2009. Environ Health Perspect 117: 392-399)
- **Chemoinformatics**: structure-activity/read-across; QSAR –(Wang et al. 2012. Regul Toxicol Pharmacol 63: 10-19; Helman et al. 2019. ALTEX Feb 4, epub ahead of print: https://www.altex.org/index.php/altex/article/view/1202)
- **High-Throughput (HT) Exposure modeling**: ExpoCast –(Egeghy et al. 2016. Environ Health Perspect. 124(6):697-702)
- **High-Throughput Toxicokinetics**: *in vitro-to-in vivo* (IVIVE) modeled dosimetry –(Wambaugh et al. 2015. Toxicol Sci 147: 55-67)
- **Bioactivity** (in vitro): cell-free and/or cell-based HT assay data –(Judson et al. 2011. Chem Res Toxicol 24: 451-462)
- **Adverse Outcome Pathway (AOP)**: expert-driven identification of signal transduction pathways along the exposure to outcome continuum. –(Edwards et al. 2015. J Pharmacol Exp Ther. epub ahead of print: http://jpet.aspetjournals.org/content/early/2015/11/04/jpet.115.228239.long)



EPA's CompTox Chemicals Dashboard



For more detailed info see: A.J. Williams et al. (2017). The CompTox Chemistry Dashboard: a community data resource for environmental chemistry. *J Cheminform* 9(1):61

CompTox Chemicals Dashboard Overview

Data Availability

- Chemical Properties
- Environmental Fate and Transport
- Hazard (*in vivo*, *in vitro*, *in silico*)
- ADME
- Exposure
- Bioactivity
- Similar Compounds
- Literature

Data Interpretability/Application

- Key components:
  - Collects known health/tox/exposure values into one place
  - Readily surface hazard/D-R information (e.g., PODs)
  - Facilitates identification of analogue(s)
  - Can inform uncertainty(ies)
  - Fill information gaps
  - Linkable data streams

Current Public Dashboard: https://comptox.epa.gov/dashboard

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