EPA Office of Research and Development Human Health Toxicity Assessment Products on PFAS

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RemPlex Summit
November 12, 2021

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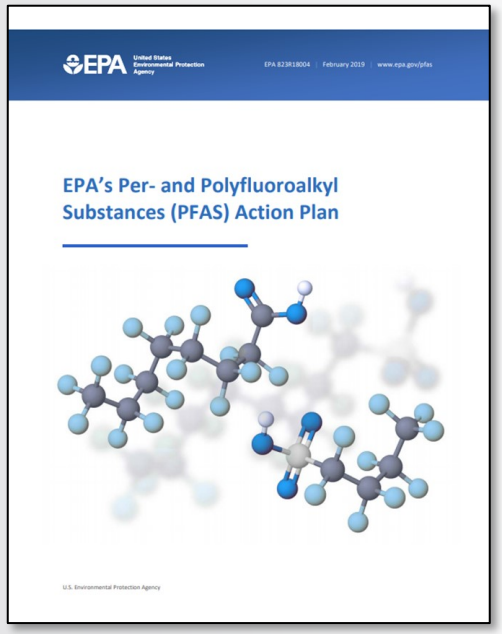
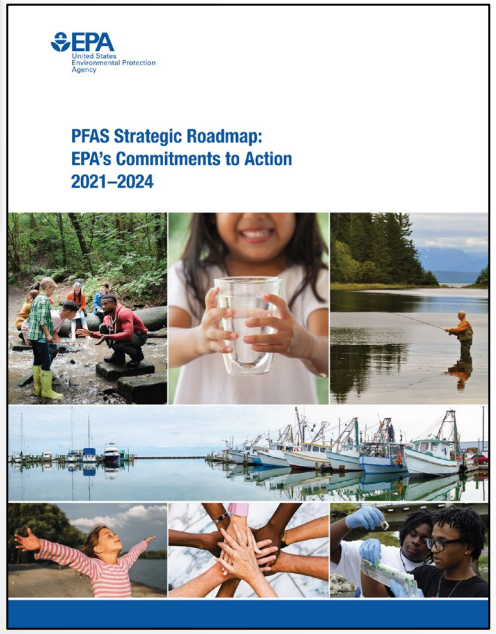
EPA PFAS Plans



As part of EPA's effort to address widespread environmental PFAS contamination and ubiquitous human exposure, EPA's Office of Research and Development (ORD) is developing various human health assessment products to characterize the evidence on the potential human health effects of these substances.

The **2019 EPA PFAS Action Plan** outlines a multimedia, multi-program, national research plan to address the challenge of PFAS (https://www.epa.gov/pfas/epas-pfas-action-plan).



The **2021 Strategic Roadmap** (announced October 2021) extends and reaffirms EPA's commitment, including finalizing ORD toxicity assessments (https://www.epa.gov/pfas/pfas-strategic-roadmap-epas-commitments-action-2021-2024)

- Amongst other actions, EPA plans to establish a national primary drinking water regulation for PFOA/PFOS and designate certain PFAS as hazardous substances to require reporting of releases, etc.

EPA Needs More PFAS Toxicity Information

- Decision-making on PFAS is hindered by a limited number of available human health toxicity assessments
- ORD is developing federal, peer-reviewed toxicity assessments for priority PFAS
  - ORD assessments are used by EPA Programs and Regions in combination with nationwide- or site-specific exposure information and other considerations to set clean-up and regulatory values
- Developing assessments on individual PFAS cannot address the timing and extent (thousands of PFAS) of the need, but grouping of PFAS is hindered by lack of data
  - ORD tiered toxicity testing aims to fill data gaps and inform decisions on grouping and prioritization (not discussed in detail today, but see: https://www.epa.gov/chemical-research/pfas-chemical-lists-and-tiered-testing-methods-descriptions)
  - ORD systematic evidence maps collect and inventory the current data on thousands of PFAS

EPA-ORD Efforts on PFAS and Human Health

Individual Toxicity Assessments (Part 1)

- For PFAS with more robust datasets
- Toxicity values support regulatory decisions and can serve as index values in read-across for data-poor PFAS in their “group”

Tiered Toxicity Testing (not discussed in detail)

- New approach methods (NAMs) to fill data gaps
- Testing structurally diverse PFAS using in vitro toxicity and toxicokinetic assays
- Aids grouping for read-across and informs prioritization decisions

Systematic Evidence Mapping (Part 2)

- Inventories available toxicity data across the broader PFAS class
- Parallels PFAS tiered toxicity testing
- Highlights data gaps and fit-for-purpose assessment opportunities for emerging PFAS of concern

ORD Toxicity Assessments

Prioritizing EPA PFAS Toxicity Assessments

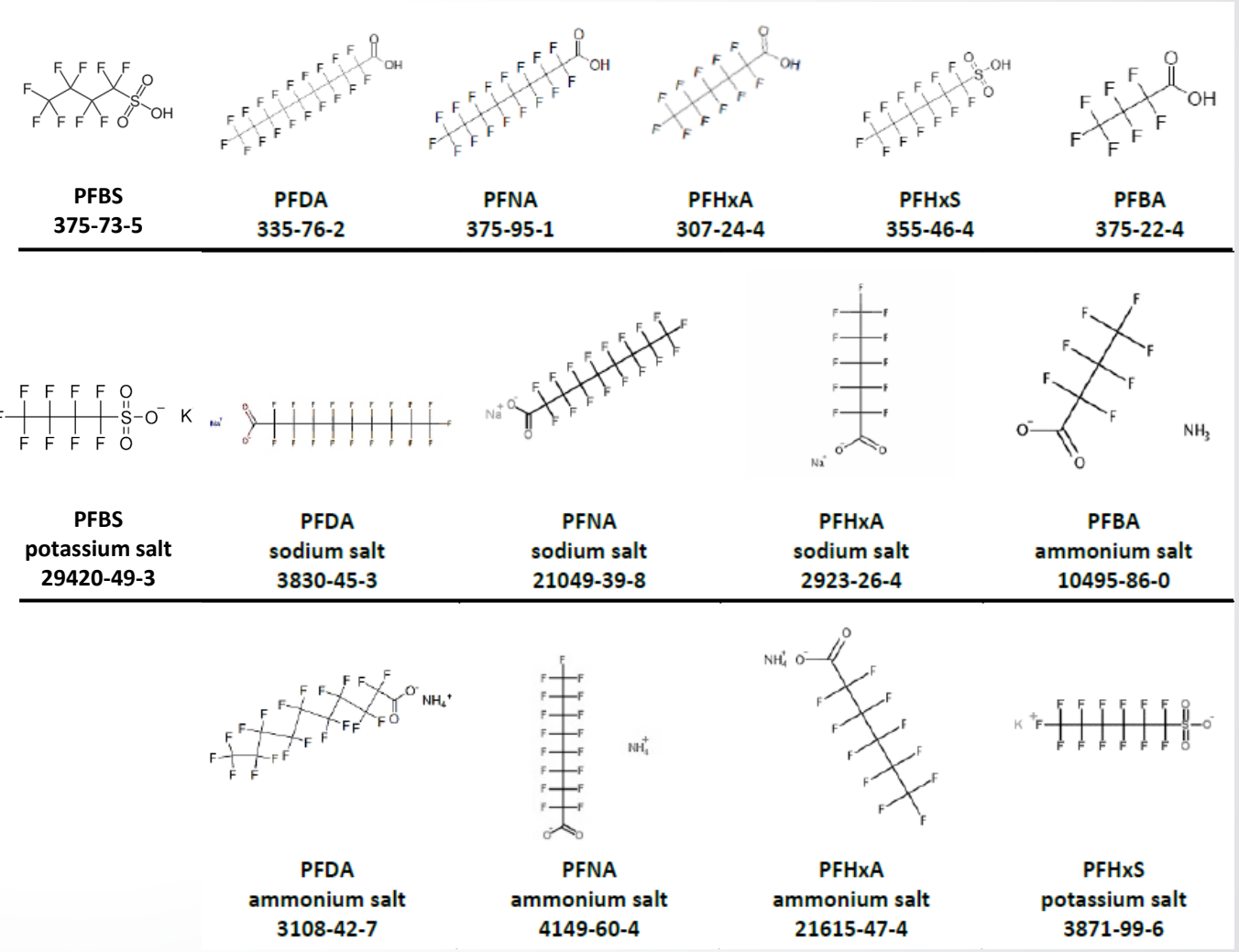
Toxicity assessments include hazard identification (judging the potential for exposure to cause various health effects) and dose-response analyses (estimating levels of exposure at which these effects are not expected to occur) based on review of the available research

Prioritized PFAS (n=7) for EPA toxicity assessments (other than PFOA and PFOS):

- PFBS, GenX chemicals (developed by Office of Water, OW), PFBA, PFHxA, PFHxS, PFNA, and PFDA
- Selected based on:
    1. Identified as a priority to inform decision-making for EPA program or regional offices, tribes, or state departments of environmental protection (all 7 PFAS had multiple interested parties)
    2. Include studies of in vivo exposure in animals that could possibly be used to derive toxicity values
    3. Quantifiable in the environment using standardized analytical methods to allow for site-specific application of toxicity values to regulatory decision-making
- Now-final PFBS (ORD) and Gen X chemicals (OW) were prioritized due to the existence of draft assessments

ORD Human Health Assessments

- PFBS & PFHxS are perfluoroalkane sulfonic acids (PFSAs); PFDA, PFNA, PFHxA, & PFBA are perfluoroalkyl carboxylic acids (PFCAs)
- PFBA, PFBS, and PFHxA are considered short-chain; the others are long-chain PFAS
- PFBS was introduced as a short-chain substitute for PFOS; PFBA and PFHxA were introduced as substitutes for PFOA
- Shorter chain PFAS generally have faster elimination from the body and thus are generally presumed to be less toxic



*not shown or discussed: Gen X chemicals (short-chain, 6-carbon)

Methods and Key Science Issues

November 2019 Systematic Review Protocol for the 5 ORD (IRIS) PFAS assessments (ORD's PFBS assessment, drafted prior to this protocol, used different, but parallel, approaches)

https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345065

Outlines the availability of human health assessment-relevant studies

- For these PFAS, data are not currently available to inform estimation of an RfC from inhalation exposure and the data are inadequate to evaluate the potential for carcinogenicity

Describes the assessment methods to be applied across the separate IRIS assessments

- Uses systematic review methods to transparently identify, evaluate, and synthesize studies

Identifies 5 key science issues the assessments will address (2 examples presented below)

- Addressing toxicokinetic differences across species and sexes
- Interpreting the human relevance of hepatic effects in animals that involve PPARα receptors

Key Issue: Toxicokinetics

Preliminary serum half-life estimates across species and sexes presented in protocol (Darker shading indicates longer half-life)

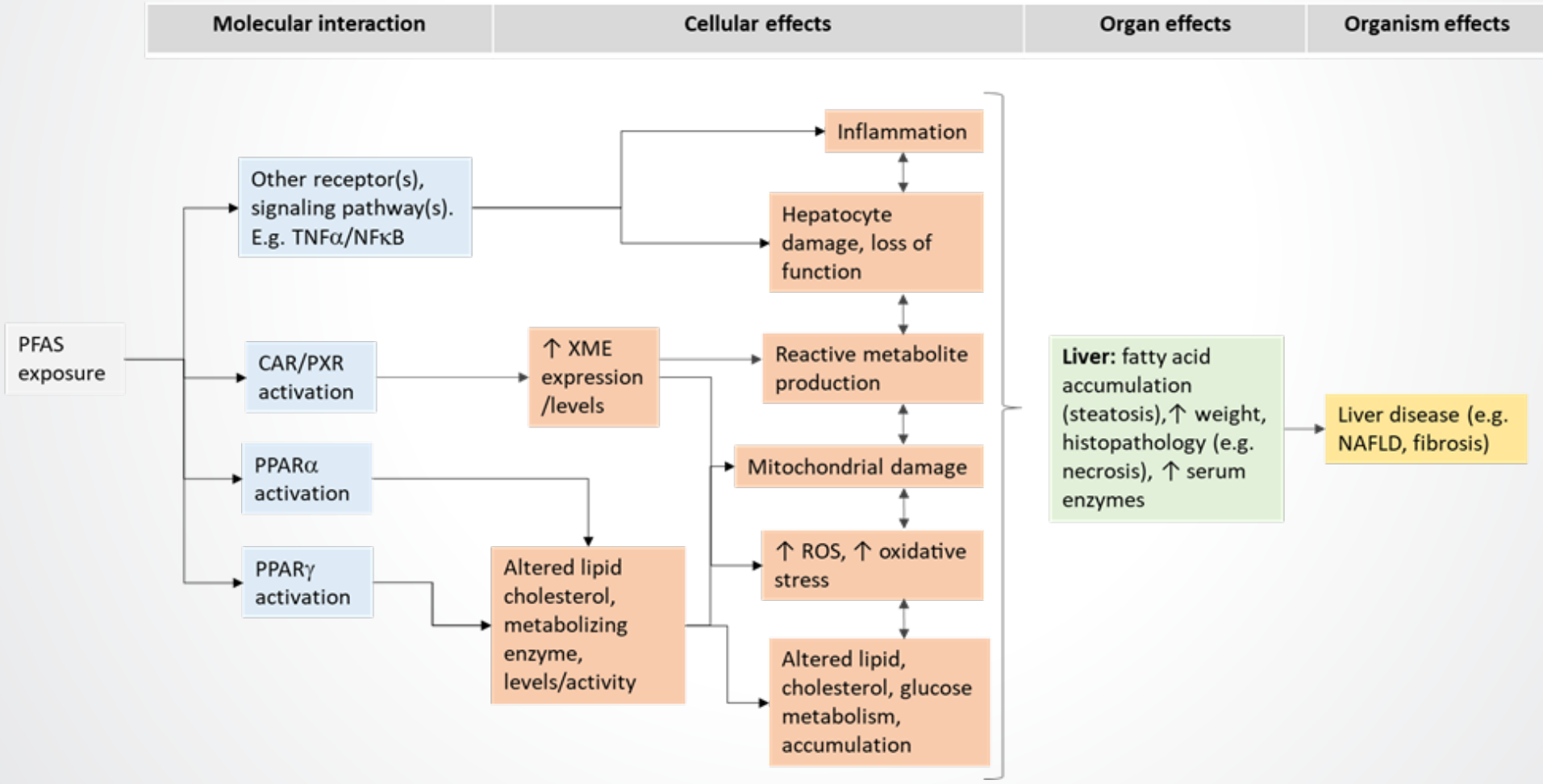
	PFBA (C4)		PFHxA (C6)		PFHxS (C6)		PFNA (C9)		PFDA (C10)	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Rat	1.0-1.8 hours	6-9 hours	0.4-0.6 hours	1.0-1.6 hours	1.8 days	6.8 days	1.4 days	30.6 days	58.6 days	39.9 days
Mouse	3 hours	12 hours	~1.2 hours	~1.6 hours	24-27 days	28-30 days	26-68 days	34-69 days	ND	
Monkey	1.7 days		2.4 hours	5.3 hours	87 days	141 days	ND		ND	
Human	3 days		32 days		8.5 years		4.3 years		12 years	

Importantly, for this and other key assessment decisions (e.g., UFs), there is a preference for data-derived adjustments and extrapolations over defaults, when such data are available and deemed reliable.

Data from Lau, C. (2015) Perfluorinated compounds: An overview. *Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances*

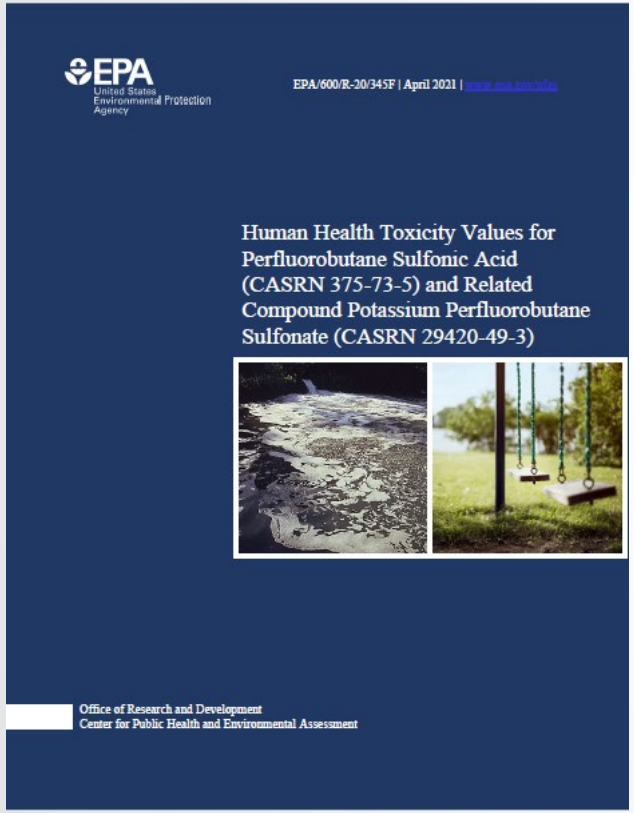
Key Issue: Influence of PPARα

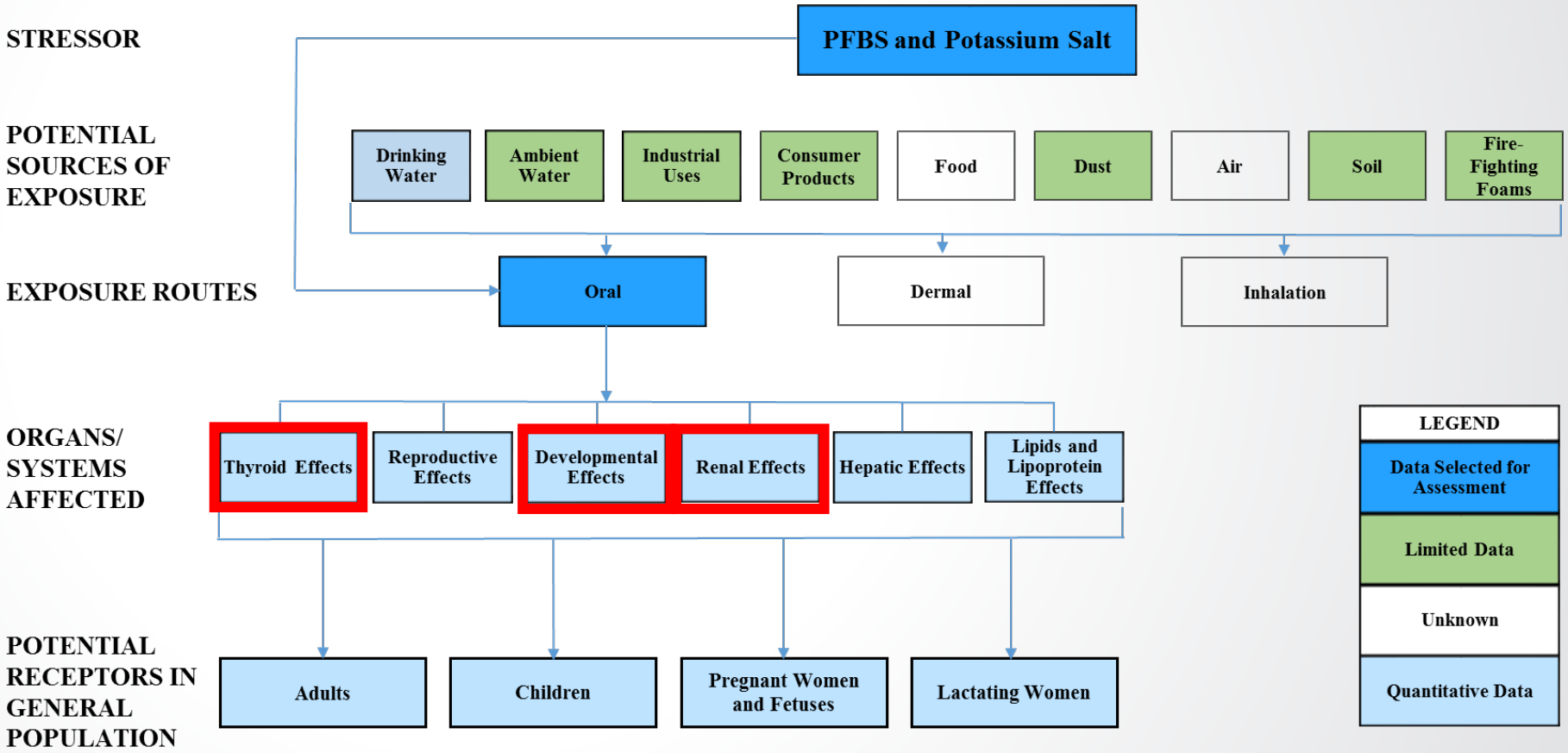
Preliminary AOP-informed Approach for Analysis of PPARα-dependence for Hepatic Effects Presented in Protocol



Final Toxicity Assessment of PFBS

Final ORD PFBS Assessment released in April 2021





https://epa.gov/pfas/learn-about-human-health-toxicity-assessment-pfbs

Final Toxicity Values for PFBS

- The thyroid (specifically, decreased thyroid hormone [total T4]) in newborn mice was identified as the critical effect from a single generation developmental study (Feng et al. 2017) for both the lifetime (chronic) RfD and the subchronic RfD
  - Decreased T4 was not associated with reflex increases in TSH; this is consistent with a human clinical condition known as "hypothyroxinemia".

Thyroid Effects		POD ($BMDL_{HED}$)	Uncertainty Factors						RfD mg/kg-d
			UF_A	UF_H	UF_L	UF_S	UF_D	**UF_C**	
Developmental decreases in TH (T4) in mice	**Subchronic RfD**	0.095	3	10	1	1	3	100	**1×10^{-3}**
	Lifetime (chronic) RfD	0.095	3	10	1	1	10	300	**3×10^{-4}**

UF_A – interspecies variability; UF_H – intraspecies variability ; UF_L – LOAEL to NOAEL uncertainty; UF_S – subchronic to chronic uncertainty; UF_D – database uncertainty

Draft Toxicity Values for PFBA

- Organ-specific RfDs (osRfDs) were estimated for thyroid, liver, and developmental hazards.
- From these osRfDs, an overall RfD of ***1 × 10^{-3} mg/kg-day*** based on increased liver hypertrophy and decreased T4 in adult rats was selected.
- From the subchronic osRfDs, an overall subchronic RfD of ***7 × 10^{-3} mg/kg-day*** based on developmental delays in mice was selected

			RfD (lifetime)			Subchronic RfD (less-than-lifetime)		
System	**Basis**	**Point of Departure**	**Composite Uncertainty Factor**	**osRfD (mg/kg-d)**	**Confidence**	**Composite Uncertainty Factor**	**osRfD (mg/kg-d)**	**Confidence**
Hepatic	Increased hepatocellular hypertrophy in adult male S-D rats	$BMDL_{HED}$ Butenhoff et al. (2012)	1,000	1×10^{-3}	*Medium*	100	1×10^{-2}	*Medium*
Thyroid	Decreased total T4 in adult male S-D rats	$NOAEL_{HED}$ Butenhoff et al. (2012)	1,000	1×10^{-3}	*Medium-low*	100	1×10^{-2}	*Medium-low*
Developmental	Developmental delays after gestational exposure in CD1 mice[a]	$BMDL_{HED}$ Das et al. (2008)	100	7×10^{-3}	*Medium-low*	100	7×10^{-3}	*Medium-low*

[a] POD based on delayed vaginal opening used to represent three developmental delays observed in the study

Preliminary Hazard Cross-view

Potential Effects	PFBA	PFHxA	PFDA	PFHxS	PFNA
*Developmental**					
Hepatic					
*Endocrine**					
Immune					
Reproductive					
Hematological					
Nervous System					
*Renal**					
Cancer					
Respiratory					
Gastrointestinal					
Inhalation					

Supporting evidence exists
(may not match hazard ID decisions in public drafts)

Some evidence suggests
(generally, would benefit from additional study)

Neutral
(studies exist but are inconclusive overall)

Poorly studied
(bioassays exist but are not robust [e.g., 1 short-term])

Lack of informative studies
(observational studies may exist but are not robust)

Note that these preliminary observations are based on DRAFT assessments and may change

*Health effects of primary concern (i.e., developmental delays; thyroid hormone disruption; and renal hyperplasia) in the final PFBS assessment (2021)

EPA Toxicity Values (OW and ORD)

PFAS	RfD (mg/kg-d)	Critical Effect (Study)
PFBS (ORD; '21; final)	0.0003	Decreased serum total T4 in PND1 (developmental) F_1 mice (Feng et al., 2017; gestational exposure study)
GenX chemicals (OW; '21; final)	0.000003	Constellation of liver lesions in F_1 female mice (DuPont, 2010; reproductive and developmental toxicity study)
PFBA (ORD draft)	0.001 (draft)	Decreased serum total T4 and liver hepatocellular hypertrophy in adult rats (Butenhoff et al., 2012; subchronic study)
PFOS (OW; '16; final)	0.00002	Decreased pup weight (developmental) in rats (Luebker et al., 2005; 2-generation reproductive toxicity study)
PFOA (OW; '16; final)	0.00002	Skeletal effects (developmental) and accelerated puberty in males (Lau et al., 2006; gestational exposure study)

Current Status on Assessments Next Steps

	Executive Review (ORD)	Agency Review	Interagency Consultation	Public Comment	External Peer Review
PFBS	Complete	Complete	Complete	Complete	Complete Q3 FY21
PFBA	Complete	Complete	Complete Q3 FY21	Public comment ended 11/8/21	Q1 FY22
PFHxA	Complete	Complete Q2 FY21	Complete Q1 FY22	Q2 FY22	-
PFDA	Complete	Q1 FY22	-	-	-
PFHxS	Ongoing	Q2 FY22	-	-	-
PFNA	Q2 FY22	-	-	-	-

See IRIS Program Outlook (updated 3x/year) for current timing on public steps: https://www.epa.gov/iris/iris-program-outlook

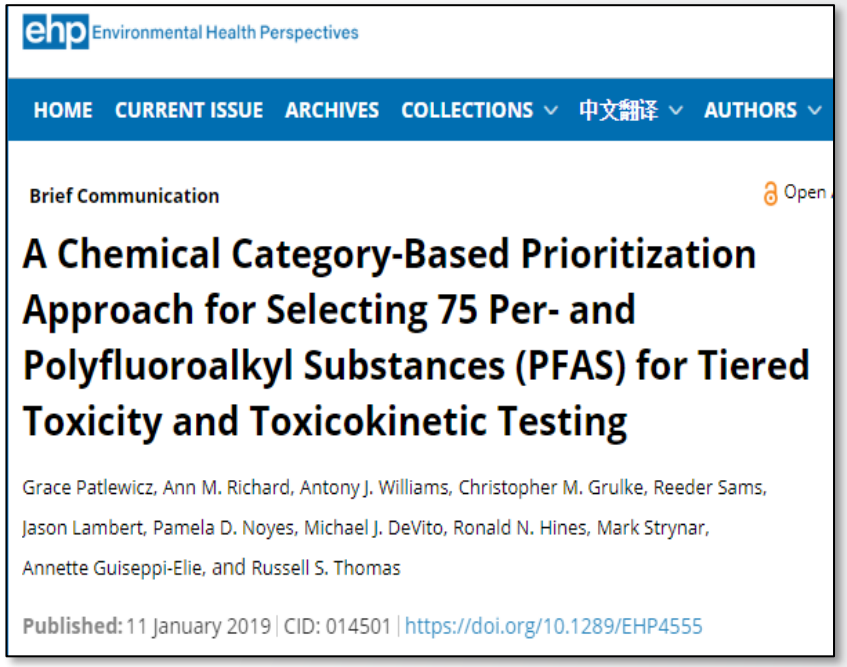
ORD PFAS Systematic Evidence Maps (SEMs)

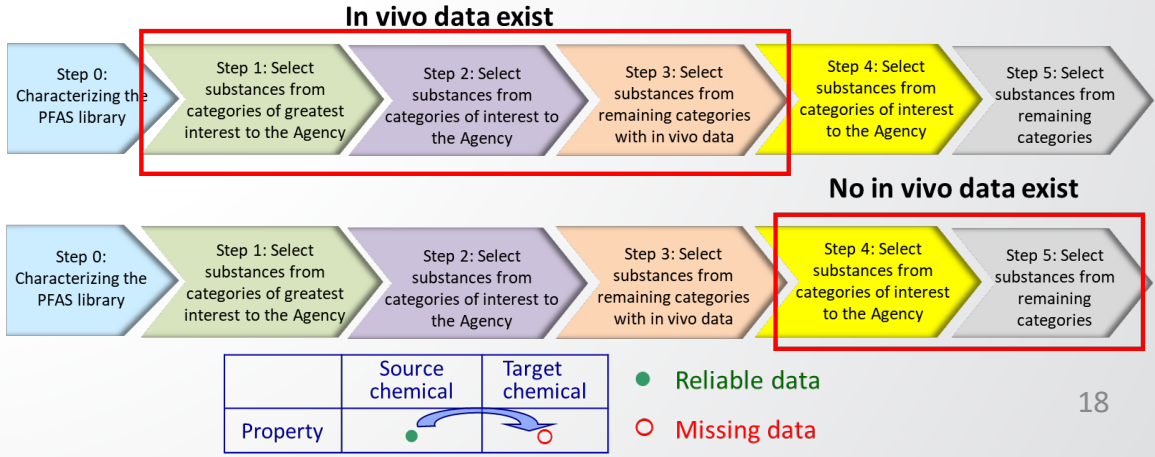
SEMs Complement ORD Tiered Testing

- Tiered toxicity testing is being conducted by ORD using a suite of in vitro and toxicokinetic assays: https://www.epa.gov/chemical-research/pfas-chemical-lists-and-tiered-testing-methods-descriptions
- "PFAS 150": 75 PFAS (and later 75 more) initially selected for testing: https://comptox.epa.gov/dashboard/chemical_lists/epapfas75s1; https://comptox.epa.gov/dashboard/chemical_lists/EPAPFAS75S2
- "PFAS 430" library of procurable, unique, DMSO-solubilized PFAS: https://comptox.epa.gov/dashboard/chemical_lists/EPAPFASINV
- More than 9000 PFAS have been identified ("PFAS 9000")

Goal 1 of Testing: develop/use toxicity data on "source" PFAS to infer (read-across) missing information for "target" PFAS

Goal 2: characterize biological activity of the PFAS landscape





Systematic Evidence Mapping

What are Systematic Evidence Maps?

- Pre-decisional analyses that use systematic review methods to compile and summarize the available evidence
- Front end compilation of evidence does not include hazard ID or toxicity values
- Highly visual and interactive data summaries that are publishable in journals
- Generally, can be quickly developed (≤ 1 year), depending on the evidence base and available resources, using standardized templates and tools

How are they used?

- *Prioritization and Scoping*: determine the extent to which the evidence supports an assessment, and of what type
- *Problem Formulation*: characterize the extent and nature of the evidence and reveal science issues/research needs
- *Updating*: rapidly characterize new evidence to update an assessment or decide whether an update is warranted

PFAS SEM Approaches

Identify and summarize animal bioassay and epidemiological evidence for ~9000 PFAS

- Searched in batches complementing tiered testing (PFAS “150”, “430”, “9000”)
- List of 9,000 substances and structures includes most PFAS in the EPA CompTox chemicals dashboard (https://comptox.epa.gov/dashboard/chemical_lists/PFASSTRUCT)

Systematic review methods used to search for, screen, and compile the literature

- Use of machine-learning and automated approaches
- Summarize in vivo study methods (including critical evaluation of key methodological features), design, and findings
- ADME studies, PBPK models, *in vitro* studies, and exposure-only human studies tracked as supplemental for future use

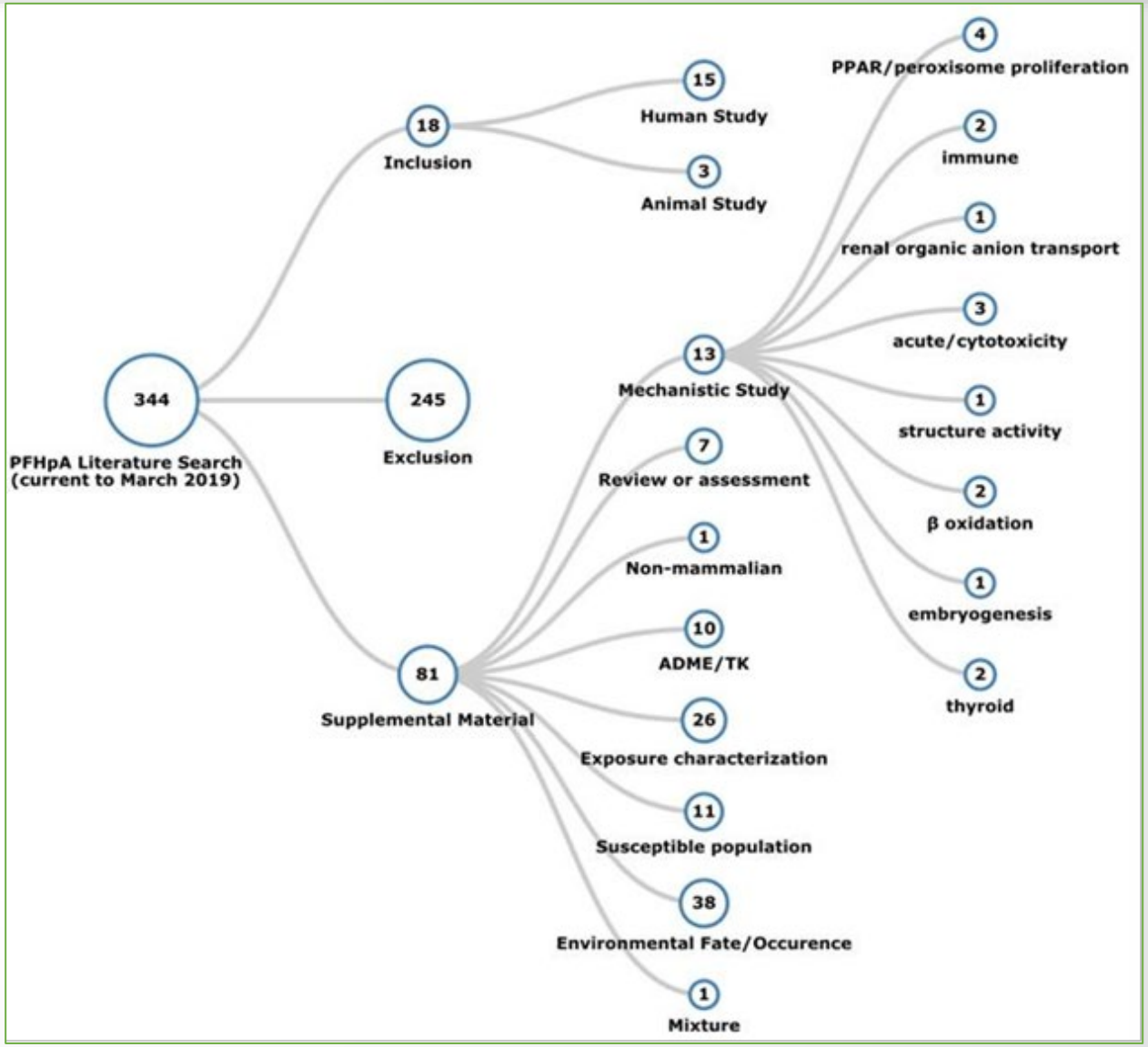
Anticipated uses

- Identify evidence to inform ORD tiered testing efforts and quickly address emerging PFAS assessment needs
- Create a repository that is easily updated, web-based, and shareable to characterize the available evidence and data gaps

When used together with the screening-level toxicity data being generated, these SEMs can help identify data gaps and sources of toxicity information to inform EPA decisions to group and prioritize the thousands of PFAS that exist

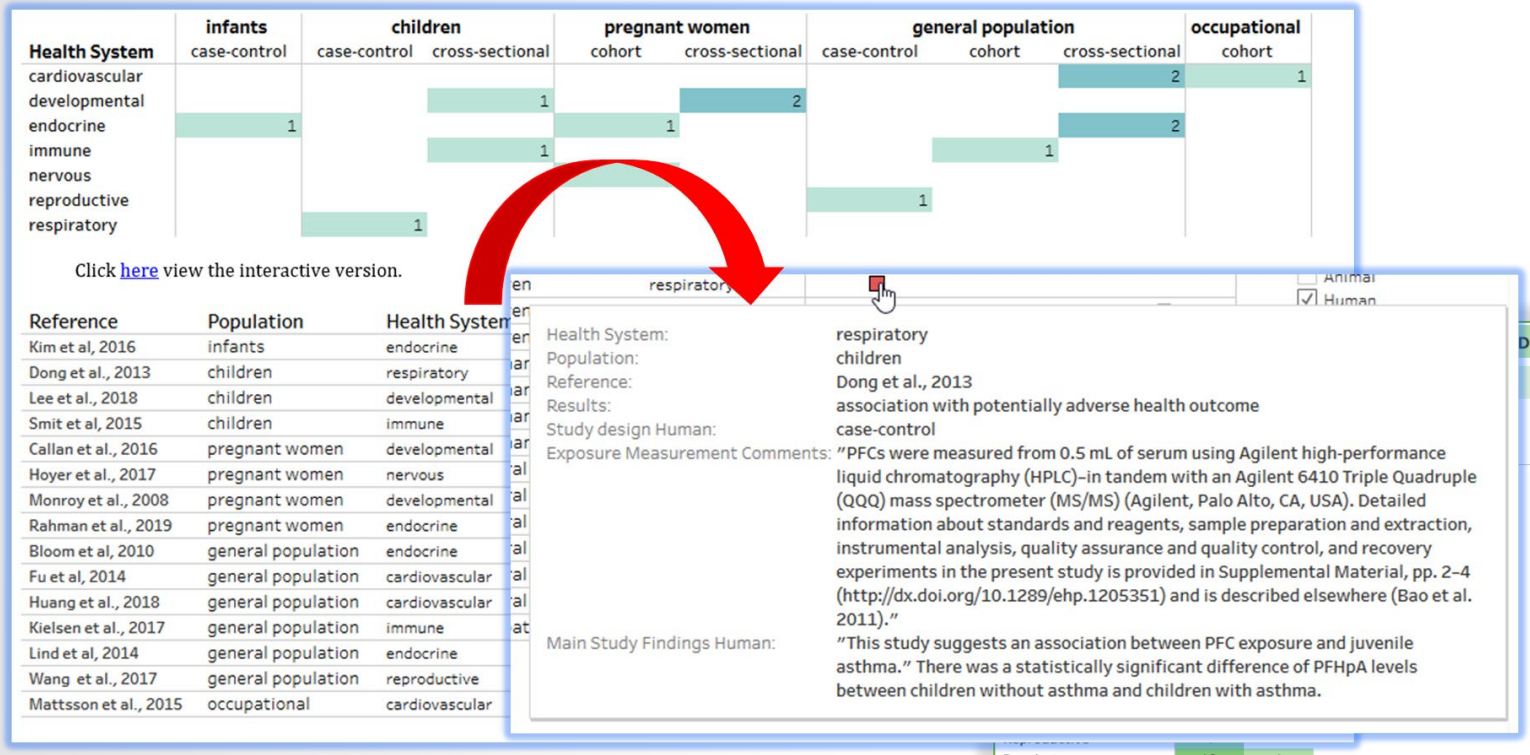
Interactive Displays: Categorize Studies

Health Assessment Workspace Collaborative [HAWC] Literature Flow Diagrams (Interactive, *click* to see more)

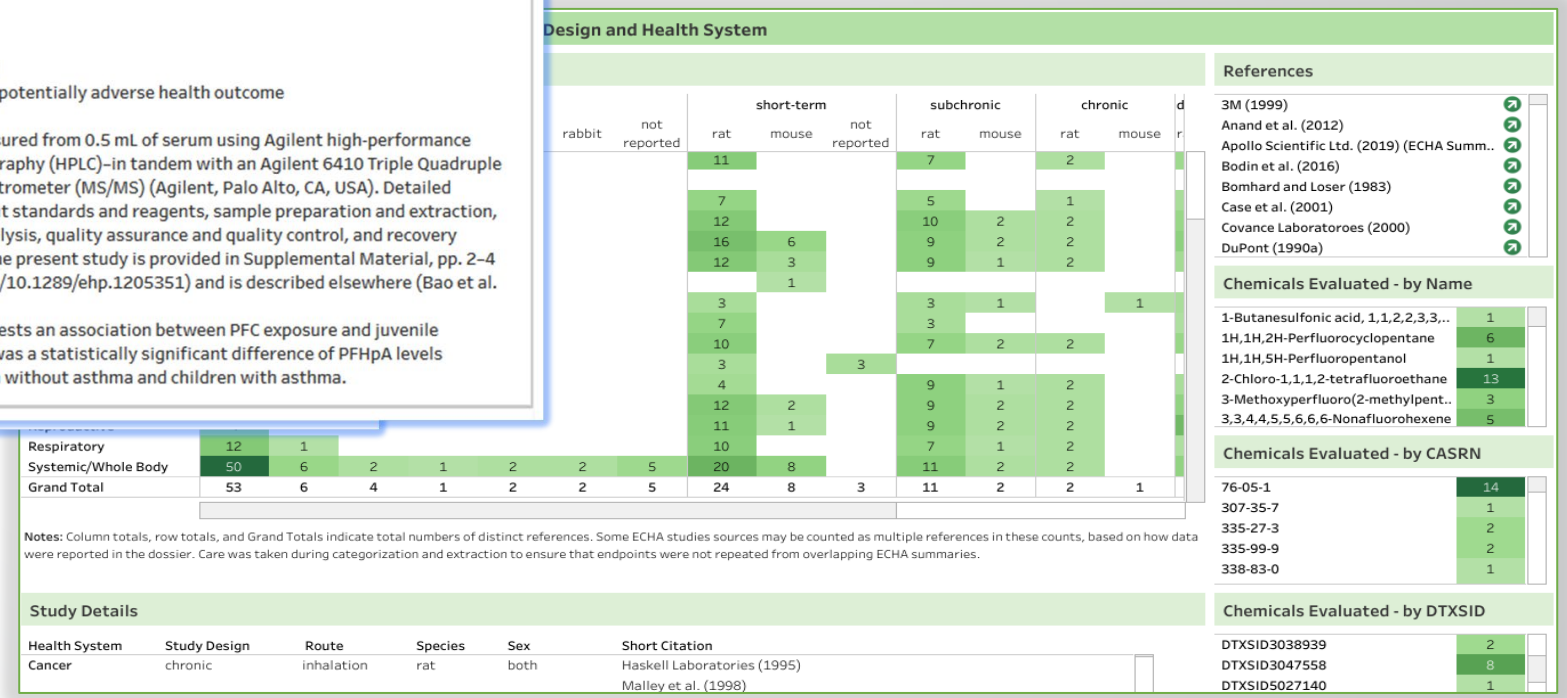


Interactive Displays: Literature Inventory

Epidemiological Studies

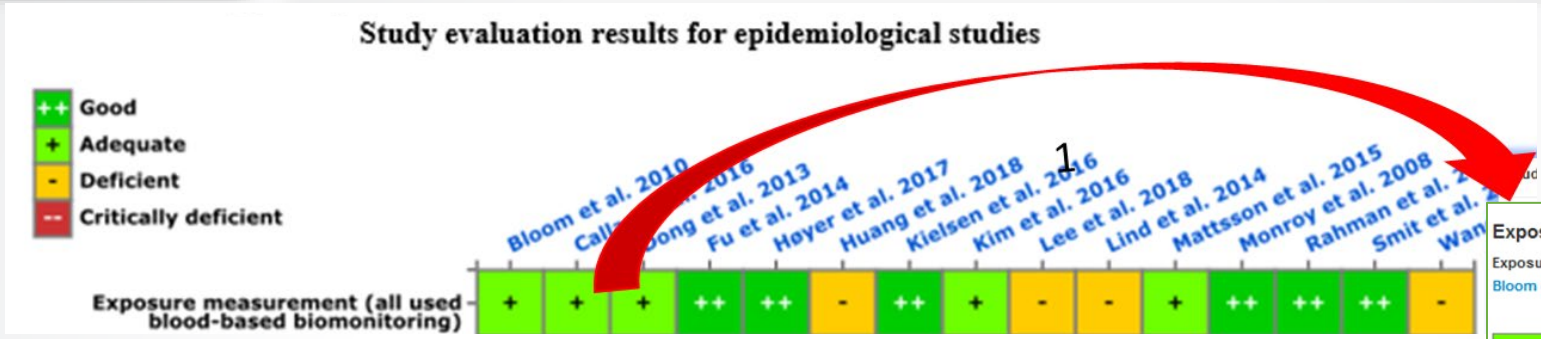


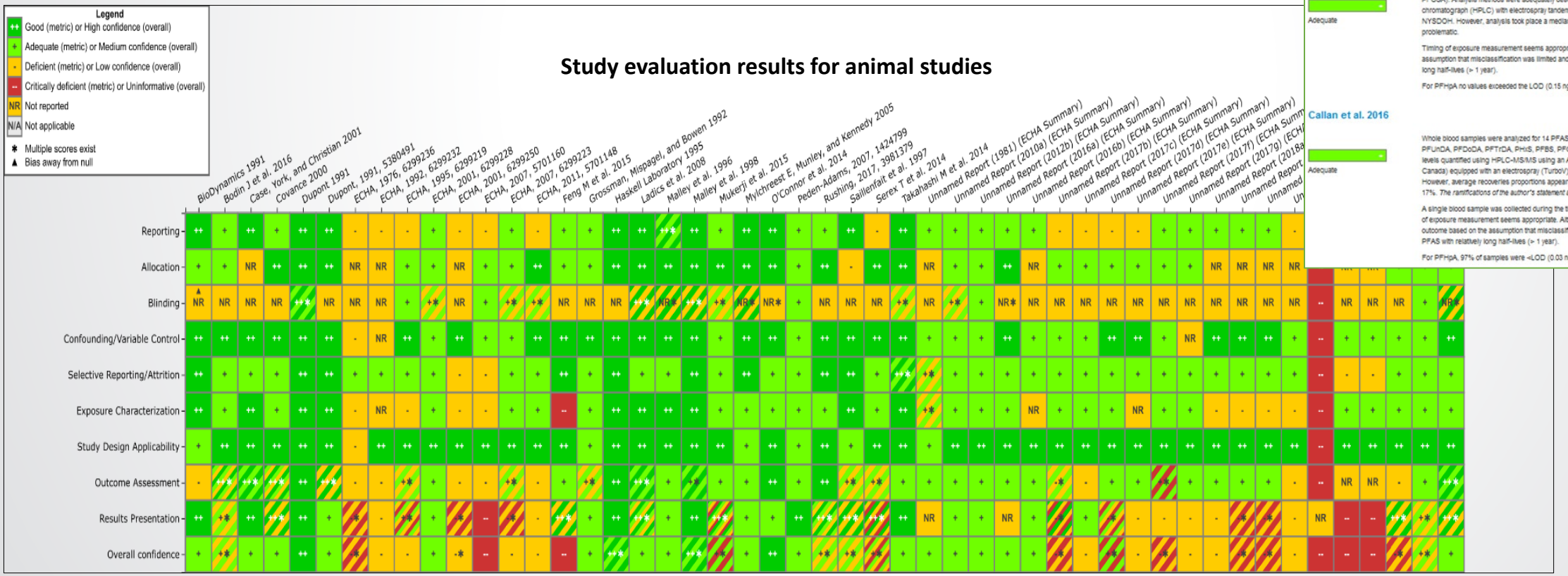
Animal Studies

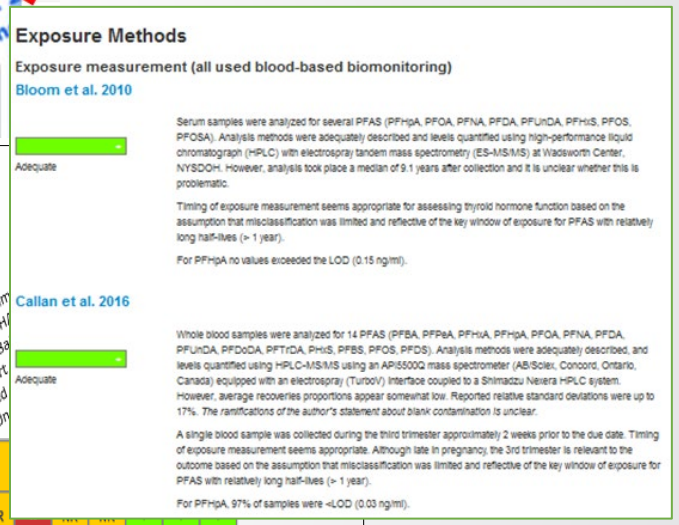


https://public.tableau.com/app/profile/literature.inventory/viz/PFAS-150EvidenceMapVisualizations/AnimalStudies

Interactive Displays: Study Evaluation



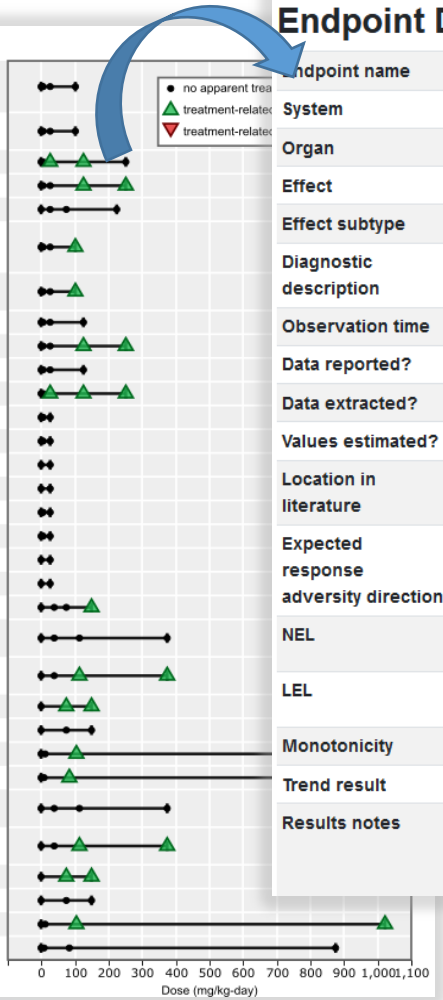




Interactive Displays: Data Extraction

Animal studies data extraction (example)

Chemical	Endpoint	Study	Animal Description	Route	Exposure Duration
6:2 Fluorotelomer alcohol	Liver Weight, Absolute	Mukerji et al. 2015	P0 Mouse, Crl:CD-1(ICR)BR (♀)	oral gavage	14d pre-mating, 14d mating, gestation, lactation
			P0 Mouse, Crl:CD-1(ICR)BR (♂)	oral gavage	109 d (premating-sacrifice)
		Serex T et al. 2014	Rat, Crl:CD(SD) (♀)	oral gavage	90 d
			Rat, Crl:CD(SD) (♂)	oral gavage	90 d
		Unnamed report (2005a) (ECHA summary)	Rat, Crl:CD(SD) (♂♀)	oral gavage	28 d
	Liver Weight, Relative	Mukerji et al. 2015	P0 Mouse, Crl:CD-1(ICR)BR (♀)	oral gavage	14d pre-mating, 14d mating, gestation, lactation
			P0 Mouse, Crl:CD-1(ICR)BR (♂)	oral gavage	109 d (premating-sacrifice)
		ECHA, 2007, 5701160	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)
		Serex T et al. 2014	Rat, Crl:CD(SD) (♀)	oral gavage	90 d
		ECHA, 2007, 5701160	Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)
		Serex T et al. 2014	Rat, Crl:CD(SD) (♂)	oral gavage	90 d
6:2 Fluorotelomer methacrylate	Liver Weight, Absolute	ECHA, 2007, 6299223	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)
			Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)
	Liver Weight, Absolute, Recovery	ECHA, 2007, 6299223	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)
			Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)
	Liver Weight, Relative	ECHA, 2007, 6299223	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)
			Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)
	Liver Weight, Relative, Recovery	ECHA, 2007, 6299223	Rat, Crl:CD(SD) (♀)	oral gavage	28d (1dose/d)
			Rat, Crl:CD(SD) (♂)	oral gavage	28d (1dose/d)
Trifluoroacetic acid	Liver Weight, Absolute	Unnamed Report (2010a) (ECHA Summary)	P0 Rat, Crl:CD(SD)IGS BR (♀)	oral gavage	GD 6-19
		Unnamed Report (2012b) (ECHA Summary)	P0 Rat, Crl:CD(SD)IGS BR (♀)	oral gavage	up to 57 d (premating-lactation)
			P0 Rat, Crl:CD(SD)IGS BR (♂)	oral gavage	38 d (premating-termination)
		Saillenfait et al. 1997	P0 Rat, Sprague-Dawley (♀)	oral gavage	GD 10-20
			F1 Rat, Sprague–Dawley (♂♀)	oral gavage	GD 10-20
		Unnamed Report (2016a) (ECHA Summary)	Rat, Wistar Rj:Wi (Iops Han) (♀)	oral diet	90 d
			Rat, Wistar Rj:Wi (Iops Han) (♂)	oral diet	90 d
	Liver Weight, Relative	Unnamed Report (2012b) (ECHA Summary)	P0 Rat, Crl:CD(SD)IGS BR (♀)	oral gavage	up to 57 d (premating-lactation)
			P0 Rat, Crl:CD(SD)IGS BR (♂)	oral gavage	38 d (premating-termination)
		Saillenfait et al. 1997	P0 Rat, Sprague-Dawley (♀)	oral gavage	GD 10-20
			F1 Rat, Sprague–Dawley (♂♀)	oral gavage	GD 10-20
		Unnamed Report (2016a) (ECHA Summary)	Rat, Wistar Rj:Wi (Iops Han) (♀)	oral diet	90 d
			Rat, Wistar Rj:Wi (Iops Han) (♂)	oral diet	90 d



Liver Weight, Absolute

Endpoint Details

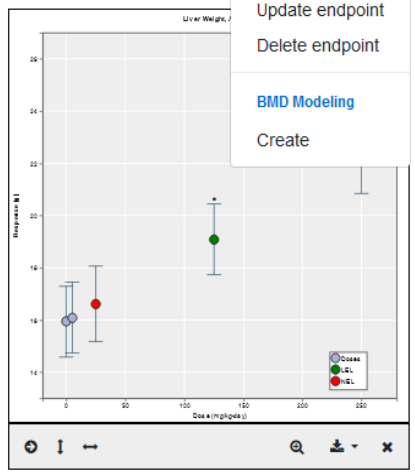
Endpoint name	Liver Weight, Absolute
System	Hepatic
Organ	Liver
Effect	Clinical Observation
Effect subtype	Organ Weight
Diagnostic description	Liver, Weight
Observation time	90 d
Data reported?	✔
Data extracted?	✔
Values estimated?	–
Location in literature	Table 5
Expected response adversity direction	---
NEL	25 mg/kg-day
LEL	125 mg/kg-day
Monotonicity	--
Trend result	not reported
Results notes	"Following 90 days of dosing, effects on organ weights were present in the testes, liver and kidney of males (Table 5) and in livers and kidneys

Actions

Endpoint Editing
Update endpoint
Delete endpoint

BMD Modeling
Create

Plot



Dataset

Dose (mg/kg-day)	Number of Animals	Response (g)	Standard Deviation
0	10	15.94	1.9
5	10	16.09	1.9
25[a]	10	16.62	2.02
125[b,c]	10	19.09	1.89
250[b]	8	22.84	2.39

[a] NEL (No effect level)
[b] Significantly different from control ($p < 0.01$)
[c] LEL (Lowest effect level)

Summary of SEM Findings to Date

Many PFAS are data poor

- PFAS 150: 136 animal studies for 35 PFAS, 166 human studies for 11 PFAS
- PFAS 430: searched 341 unique chemicals (not in PFAS 150); 142 had data
- PFAS 9000: 9,266 PFAS chemicals were searched; 416 have records

Very few inhalation toxicity studies available for any PFAS

- ORD exploring approaches for extrapolating from oral administration studies

Current Status on SEMs Next Steps

PFAS 150: Manuscript submitted September 2021

PFAS 430: Manuscript planned for late FY22

- 119 animal bioassay studies undergoing extraction and study evaluation; 48 human studies identified
- Animal bioassay results will be included in CCTE Chemicals Dashboard

PFAS 9000: Screening underway

- 26,000 records being screened at title and abstract level

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INTEGRATED RISK INFORMATION SYSTEM

ORD PFAS Assessment Product Leads		
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PFBS Chemical Managers	**Beth Owens**	**Jason Lambert**
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PFDA Chemical Managers	**Luci Lizarraga**	**Phillip Kaiser**
PFHxS Chemical Managers	**Ingrid Druwe**	**Xabier Arzuaga**
PFNA Chemical Managers	**Pam Noyes**	**Johanna Congleton**
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