DAY 1: May 16
10:00 AM–5:30 PM

DAY 2: May 17
12:00 PM – 3:00 PM

External Peer Review of the EPA Draft "IRIS Toxicological Review of Perfluorohexanoic Acid and Related Salts" (PFHxA)

PFHxA Peer Review Panel Meeting: Webinar Logistics

Video/Audio:

- Observers: Muted and video off by default throughout.
- Reviewers: May mute / unmute and turn video on / off.
  - During introductions and discussions: Please have video on.
  - During breaks: Mute your audio and turn video off.

If you have any issues, contact Katie (ERG):

- By email at meetings@erg.com.

Purpose of this Peer Review Meeting

- Provide a forum in which reviewers can exchange, discuss, and evolve their individual views and opinions on EPA's draft "IRIS Toxicological Review of PFHxA and Related Salts," including:
  - Their response to EPA's charge questions.
  - Any other aspect of the EPA draft PFHxA IRIS assessment they would like to discuss.
- Enable EPA and observers to listen to all reviewer discussions.
- Provide an opportunity for oral comment by members of the public who signed up to do so.

PFHxA IRIS Toxicological Review Peer Review Meeting
DAY ONE: Opening Agenda

MEETING OPENING

10:00 AM Meeting Purpose, Peer Review Process, & Reviewer Introductions

10:20 AM U.S. EPA Presentation

11:05 AM Reviewer Discussion Agenda and Process

REVIEWER DISCUSSIONS

11:10 AM Chair Opening Remarks to Panel

11:15 AM Reviewer Discussions

5:30 PM Adjourn Day One

External Independent Peer Review Meeting
Standard Process

- Pre-meeting:
  - Reviewer search and selection by ERG, including two opportunities for public comment.
  - Reviewers receive charge, review document, written public comments submitted to EPA's docket, and list of public literature identified.
  - Reviewers prepare individual written pre-meeting (i.e., preliminary) comments.
- Panel meeting:
  - Reviewers discuss their responses to EPA's charge questions and anything else they feel is relevant to the review.
  - Open to interested members of the public as observers.
  - Opportunity for oral comment.
- Post-meeting:
  - Reviewers submit final individual post-meeting comments to ERG.
  - ERG compiles them and submits them to EPA.
  - ERG provides meeting report, including high-level comment summary by charge question.

External Independent Peer Review
Key Principles

- Organized by ERG, an EPA contractor.
- No mandate to reach consensus. Agreement, where it exists, during discussion can be noted.
- Reviewers document their individual written comments.

PFHxA Peer Review Meeting
Peer Reviewer Introductions

Elaine M. Faustman, Ph.D., DABT (Panel Chair)

Panagiotis G. Georgopoulos, Ph.D.

Joseph T. Haney, Jr., M.S.

Angela M. Leung, MD, MSc.

Carla A. Ng, Ph.D.

David A. Savitz, Ph.D.

R. Thomas Zoeller, Ph.D.

U.S. Environmental Protection Agency (EPA) Presenters

Kristina Thayer, Ph.D., IRIS Program Director

Michelle Angrish, Ph.D. – PFHxA IRIS Assessment Co-chemical Manager

Laura Dishaw, Ph.D. – PFHxA IRIS Assessment Co-chemical Manager

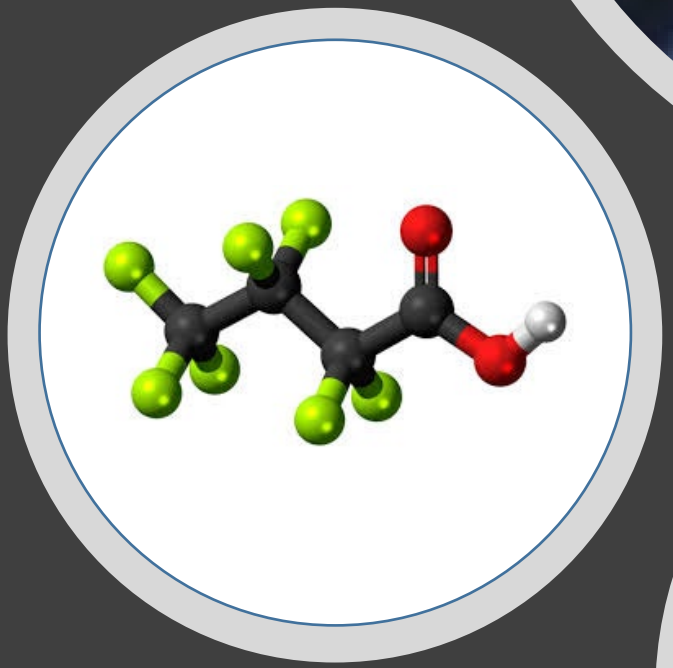
Toxicological Review of Perfluorohexanoic Acid (PFHxA) and Related Salts

Kris Thayer, PhD
U.S. EPA, Office of Research and Development, Center for Public Health and Environmental Assessment

Michelle Angrish, PhD
U.S. EPA, Office of Research and Development, Center for Public Health and Environmental Assessment

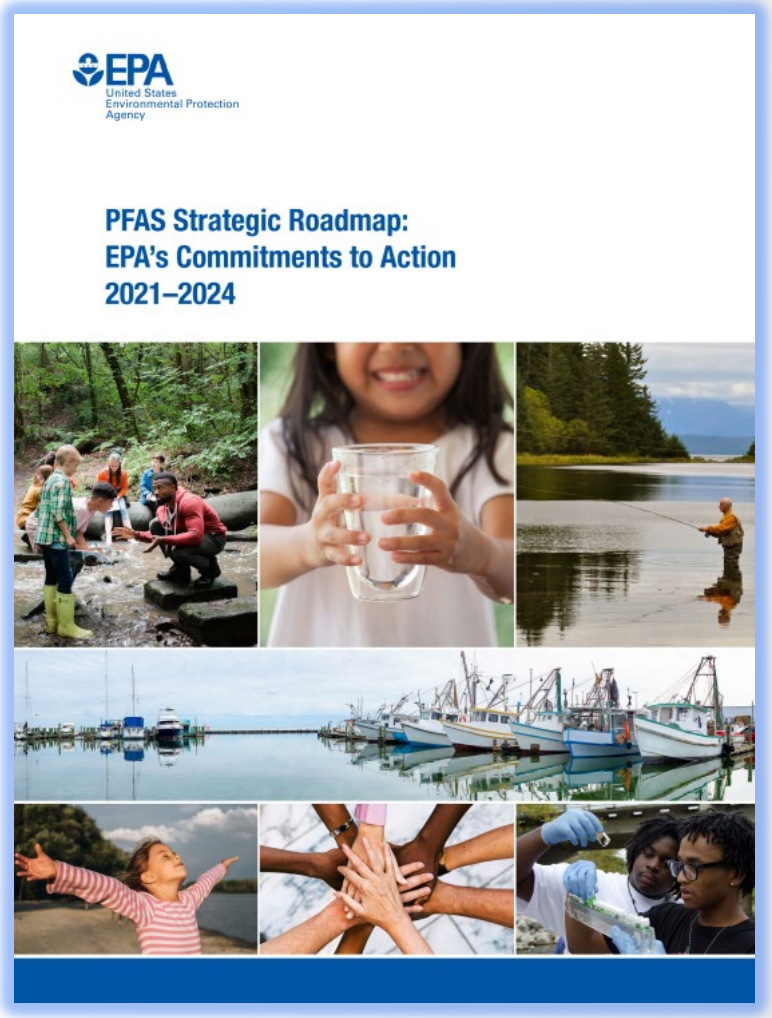
Laura Dishaw, PhD
U.S. EPA, Office of Research and Development, Center for Public Health and Environmental Assessment

May 16th, 2022



PFHxA and EPA's Broader PFAS Strategic Roadmap

- The IRIS assessment of PFHxA is being produced in parallel with separate IRIS assessments of four other PFAS, specifically PFBA, PFHxS, PFNA, and PFDA.
- The five IRIS assessments represent only one component of EPA's broader actions to address PFAS.
- For more information on the EPA's PFAS Strategic Roadmap, visit EPA's PFAS website.



https://www.epa.gov/pfas/pfas-strategic-roadmap-epas-commitments-action-2021-2024

EPA Needs More PFAS Toxicity Information

- Decision-making on PFAS is hindered by a limited number of available human health toxicity assessments
- EPA's Office of Research and Development (ORD), which includes the IRIS Program, 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
  - Tiered toxicity testing aims to fill data gaps and inform decisions on grouping and prioritization https://www.epa.gov/chemical-research/pfas-chemical-lists-and-tiered-testing-methods-descriptions
  - Systematic evidence maps collect and inventory the current data on thousands of PFAS

EPA-ORD Efforts on PFAS and Human Health

Individual Toxicity Assessments (e.g., IRIS)

- 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 (ORD-CCTE[1]-led)

- 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 (IRIS Program-led)

- 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

[1]CCTE - Center for Computational Toxicology and Exposure

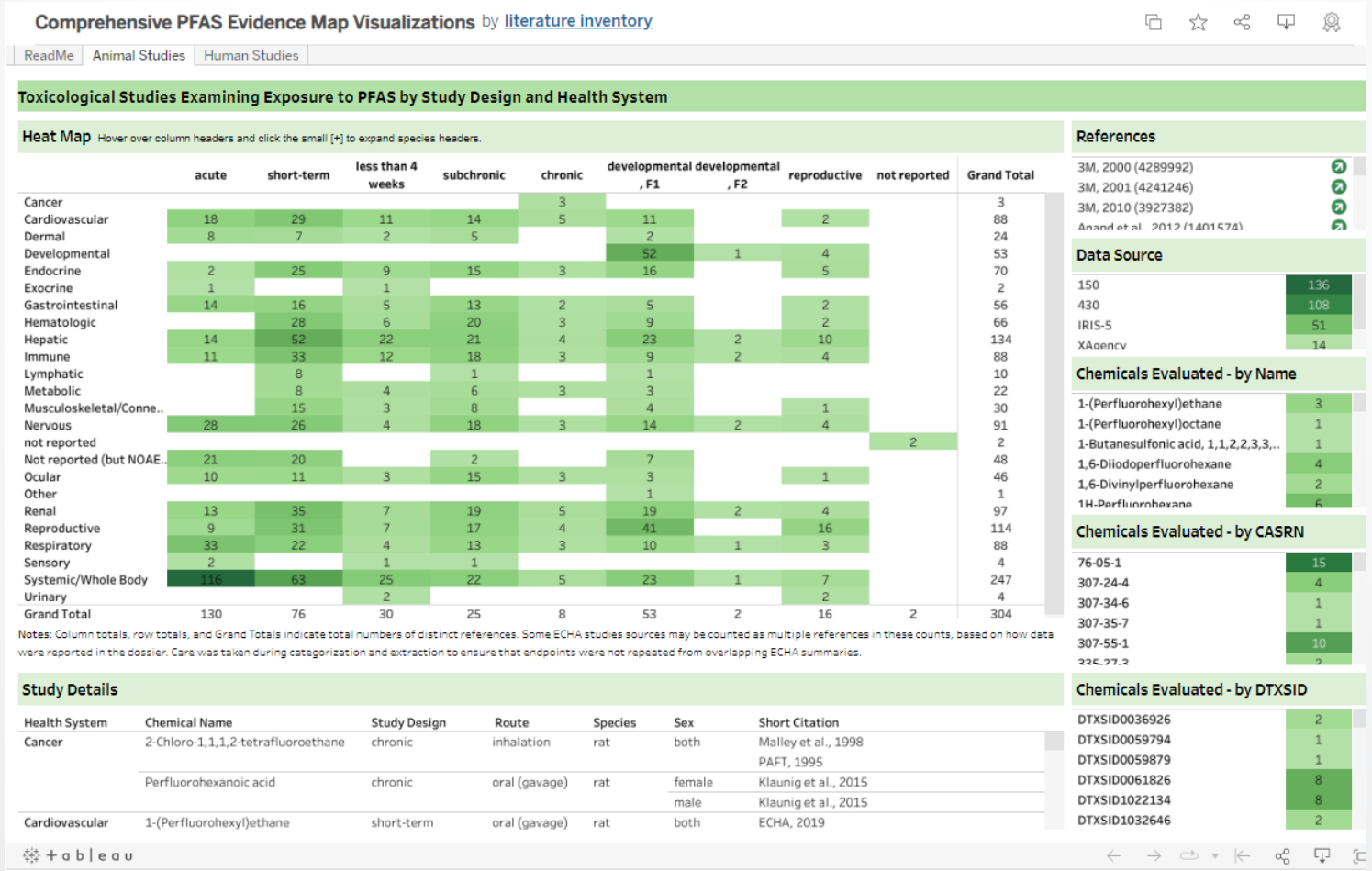
Per- and Polyfluoroalkyl Substances (PFAS) Systematic Evidence Map (SEM) Activities

- SEMs use systematic review methods to identify and summarize animal bioassay and epidemiological evidence. No hazard conclusions or toxicity values
  - **PFAS 150[1]:** Initial effort from CCTE identified ~150 PFAS chemicals testing a range of PFAS structures, chemistries, and with environmental relevance (first 75 chemicals described in publication by Patlewicz et al. 2019)
  - **PFAS 430[2]:** Expanded effort that includes additional ~430 PFAS prioritized by CCTE
  - **PFAS Universe[2]:** ~12,000 PFAS substances and structures includes most of the chemicals in the EPA CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard/chemical_lists/PFASSTRUCTv5)
- Specific goals and uses:
  - Create a repository that is easily updated, web-based, and shareable
  - Identify *in vivo* evidence to inform CCTE efforts to characterize PFAS library
  - Characterize data gaps and key research needs, including tiered toxicity testing
  - Be positioned to quickly address new PFAS assessment needs
- Key findings:
  - Many PFAS are data poor
  - Very few inhalation studies available

[1]In press at Environmental Health Perspectives (DOI 10.1289/EHP10343)
[2]In development

Combining PFAS Datasets Across EPA

- Comprehensive PFAS Dashboard in development
- Includes information from PFAS evidence maps, IRIS assessments, and other agency PFAS Assessments (GenX, PFOA, PFOS, PFBS, etc.)



Comprehensive PFAS Evidence Map Visualizations by literature inventory

ReadMe | Animal Studies | Human Studies

Toxicological Studies Examining Exposure to PFAS by Study Design and Health System

Heat Map Hover over column headers and click the small [+] to expand species headers.

	acute	short-term	less than 4 weeks	subchronic	chronic	developmental, F1	developmental, F2	reproductive	not reported	Grand Total
Cancer					3					3
Cardiovascular	18	29	11	14	5	11		2		88
Dermal	8	7	2	5		2				24
Developmental						52	1	4		53
Endocrine	2	25	9	15	3	16		5		70
Exocrine	1		1							2
Gastrointestinal	14	16	5	13	2	5		2		56
Hematologic		28	6	20	3	9		2		66
Hepatic	14	52	22	21	4	23	2	10		134
Immune	11	33	12	18	3	9	2	4		88
Lymphatic		8		1		1				10
Metabolic		8	4	6	3	3				22
Musculoskeletal/Conne..		15	3	8		4		1		30
Nervous	28	26	4	18	3	14	2	4		91
not reported									2	2
Not reported (but NOAE..	21	20		2		7				48
Ocular	10	11	3	15	3	3		1		46
Other						1				1
Renal	13	35	7	19	5	19	2	4		97
Reproductive	9	31	7	17	4	41		16		114
Respiratory	33	22	4	13	3	10	1	3		88
Sensory	2		1	1						4
Systemic/Whole Body	116	63	25	22	5	23	1	7		247
Urinary			2					2		4
Grand Total	130	76	30	25	8	53	2	16	2	304

Notes: Column totals, row totals, and Grand Totals indicate total numbers of distinct references. Some ECHA studies sources may be counted as multiple references in these counts, based on how data were reported in the dossier. Care was taken during categorization and extraction to ensure that endpoints were not repeated from overlapping ECHA summaries.

References

3M, 2000 (4289992)
3M, 2001 (4241246)
3M, 2010 (3927382)
Anand et al., 2012 (1401574)

Data Source

150	136
430	108
IRIS-5	51
XAgency	14

Chemicals Evaluated - by Name

1-(Perfluorohexyl)ethane	3
1-(Perfluorohexyl)octane	1
1-Butanesulfonic acid, 1,1,2,2,3,3,..	1
1,6-Diiodoperfluorohexane	4
1,6-Divinylperfluorohexane	2
1H-Perfluorohexane	6

Chemicals Evaluated - by CASRN

76-05-1	15
307-24-4	4
307-34-6	1
307-35-7	1
307-55-1	10
335-27-3	2

Chemicals Evaluated - by DTXSID

DTXSID0036926	2
DTXSID0059794	1
DTXSID0059879	1
DTXSID0061826	8
DTXSID1022134	8
DTXSID1032646	2

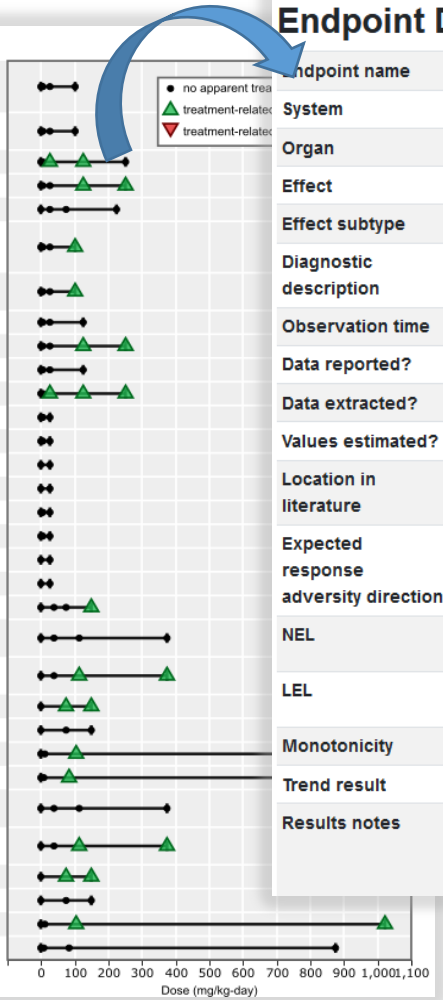
Study Details

Health System	Chemical Name	Study Design	Route	Species	Sex	Short Citation
Cancer	2-Chloro-1,1,1,2-tetrafluoroethane	chronic	inhalation	rat	both	Malley et al., 1998
						PAFT, 1995
	Perfluorohexanoic acid	chronic	oral (gavage)	rat	female	Klaunig et al., 2015
					male	Klaunig et al., 2015
Cardiovascular	1-(Perfluorohexyl)ethane	short-term	oral (gavage)	rat	both	ECHA, 2019

tableau

Interactive Displays: Data Extraction

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

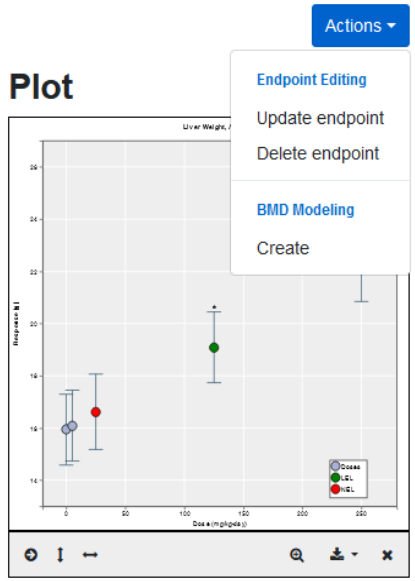


Liver Weight, Absolute

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

Plot

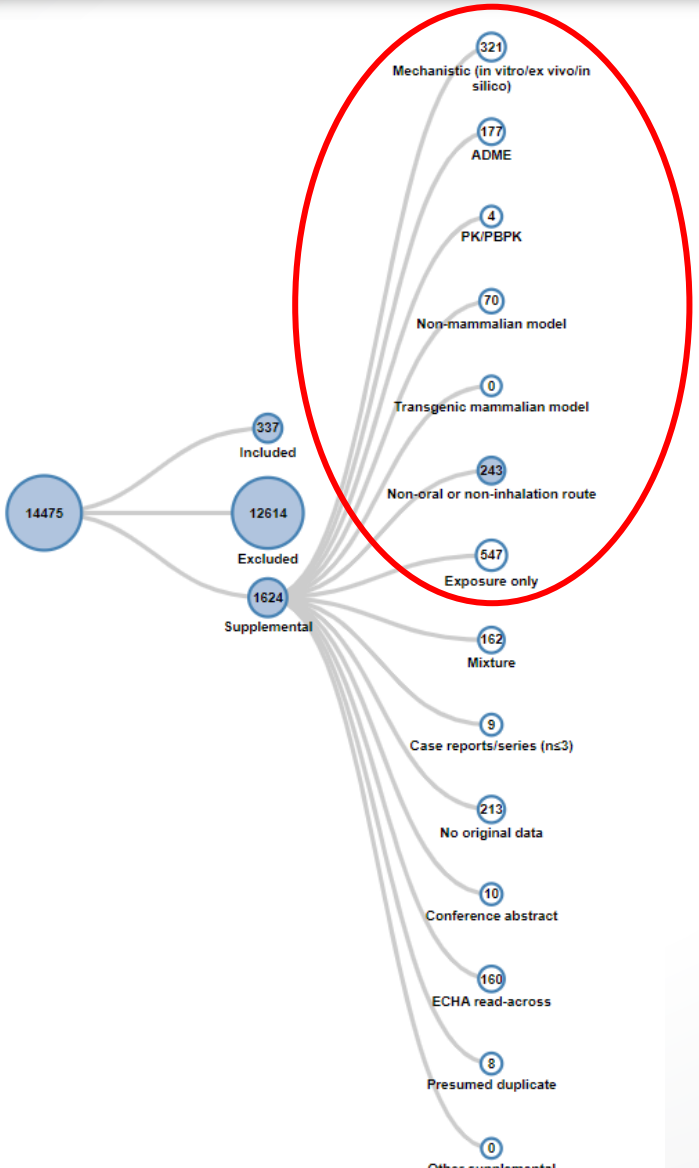


Dataset

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)

Interactive Literature Tagtree



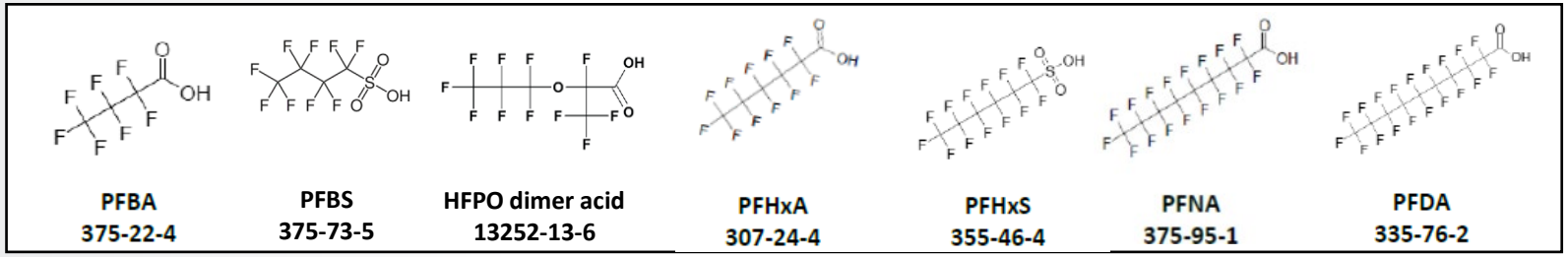
- **Created in 1985**
- **IRIS assessments contribute to decisions across EPA and other health agencies**
- **Toxicity values**
  - Noncancer: Reference Doses (RfDs) and Reference Concentrations (RfCs).
  - Cancer: Oral Slope Factors (OSFs) and Inhalation Unit Risks (IURs).
- **IRIS assessments have no direct regulatory impact until they are combined with**
  - Extent of exposure to people, cost of cleanup, available technology, etc.
  - Regulatory options.
  - Both are the purview of EPA's program offices.

Prioritizing EPA PFAS Toxicity Assessments

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

- PFBS, GenX chemicals (Office of Water-led), PFBA, PFHxA, PFHxS, PFNA, and PFDA

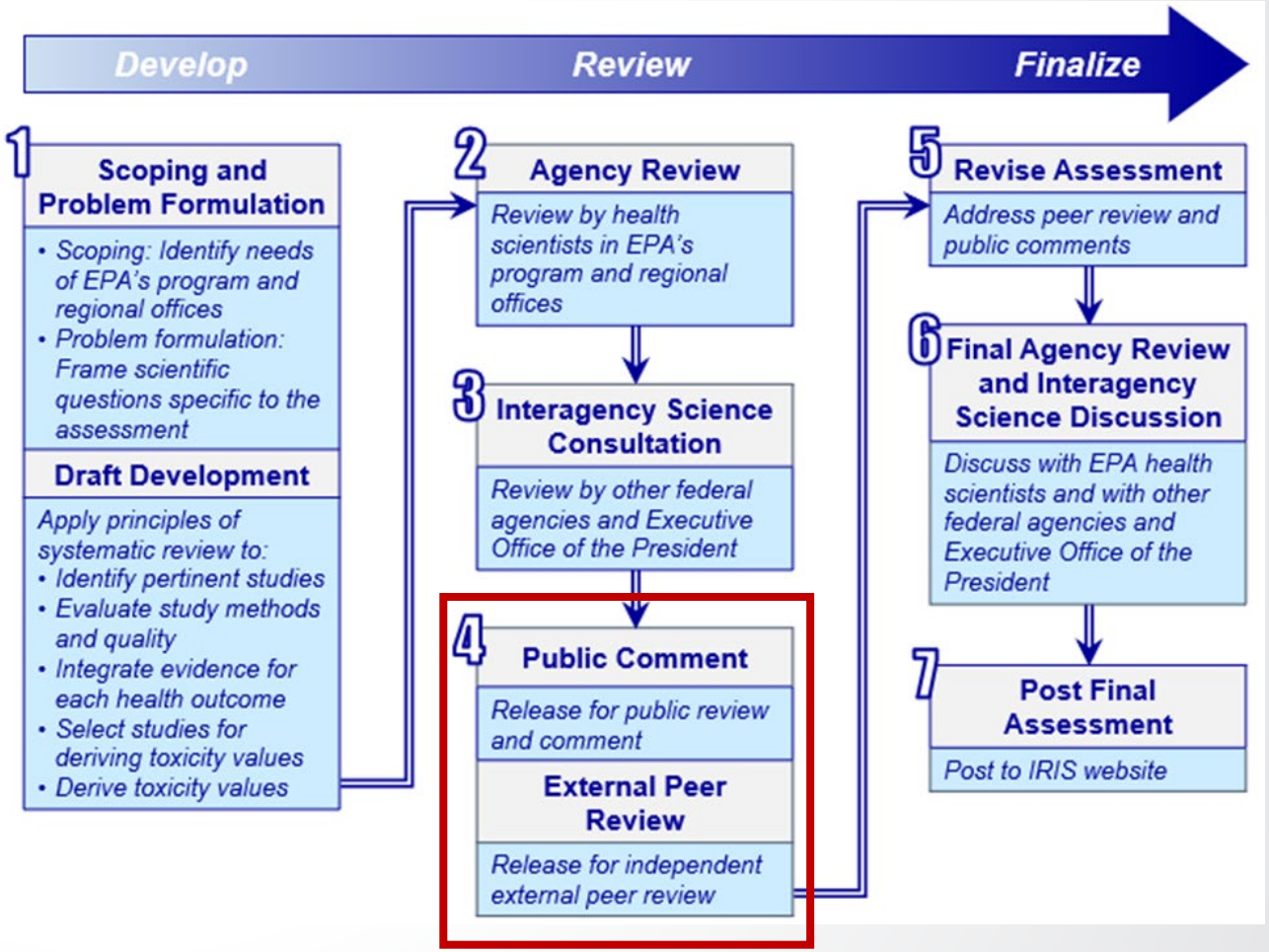
To better inform read-across, cover a range of carbon chain lengths and functional groups



- These PFAS were selected by an EPA-wide workgroup (not identified by IRIS) 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

IRIS Process: PFHxA status and remaining steps

- PFHxA released for public comment in February 2022 (comment period ended April 2022)
- EPA compiled public comments and organized by topic area
- Compilation of comments provided to Panel to consider during their review; compilation also posted to public docket



Structured Framework to Assess Evidence and Derive Toxicity Values

Evidence Synthesis

Human and animal evidence analyzed separately

Evidence Integration (Hazard Conclusions)

Certainty in Evidence Factors

- Study Evaluation
- Consistency
- Dose-Response
- Magnitude & Precision
- Coherence
- Mechanistic evidence on biological plausibility

Minimal study confidence concerns, presence of factors that increase certainty, no or few factors that decrease certainty

Study confidence concerns, no or few factors that increase certainty presence of factors that decrease certainty

- Robust
- Moderate
- Slight
- Indeterminate
- Compelling evidence of no effect

Strongest evidence, little or some uncertainty

Inconsistent or little confidence in evidence, little or some uncertainty

- Evidence demonstrates
- Evidence indicates (likely)
- Evidence suggests
- Evidence inadequate
- Strong evidence of no effect

Selecting Health Outcomes & Studies for Dose-Response

Attributes of Studies that Support Toxicity Value Derivation

Study confidence

Test species

- Humans– no interspecies extrapolation uncertainties
- Animals that respond most like humans

Human relevance of study exposures

- **Route** – Typical human environmental exposure routes (e.g., oral, inhalation)
- **Duration** – Chronic or subchronic studies (exceptions exist)
- **Exposure Levels** –
  - Near typical human environmental exposures
  - A broad range and multiple levels, for better extrapolation support

Susceptibility

- Studies that characterize the most susceptible groups
- Studies with design features that address sources of potential critical confounding for the human health effect

Study Evaluation

Individual evaluation domains

Epidemiology
Participant Selection
Exposure Measurement
Outcome Ascertainment
Confounding
Analysis
Selective Reporting
Sensitivity

Domain judgements

Judgment	Interpretation
Good	Appropriate study conduct relating to the domain and minor deficiencies not expected to influence results.
Adequate	A study that may have some limitations relating to the domain, but they are not likely to be severe or to have a notable impact on results.
Deficient	Identified biases or deficiencies interpreted as likely to have had a notable impact on the results or prevent reliable interpretation of study findings.
Critically Deficient	A serious flaw identified that makes the observed effect(s) uninterpretable. Studies with a critical deficiency will almost always be considered "uninformative" overall.

Overall study confidence for an outcome

Rating	Interpretation
High	No notable deficiencies or concerns identified; potential for bias unlikely or minimal; sensitive methodology.
Medium	Possible deficiencies or concerns noted but resulting bias or lack of sensitivity is unlikely to be of a notable degree.
Low	Deficiencies or concerns were noted, and the potential for substantive bias or inadequate sensitivity could have a significant impact on the study results or their interpretation.
Uninformative	Serious flaw(s) makes study results unusable for dose response. Uninformative studies are given the least weight during evidence synthesis and integration.

PFHxA Hazard Judgments (based on current evidence)

Organ/System	Evidence integration judgment	Summary
Hepatic, Hematopoietic, and Developmental effects	*Evidence indicates (likely)*	• See summaries on following slides • Toxicity values were derived
Endocrine (thyroid) effects	*Evidence suggests*	• See summary on following slides • No toxicity value was derived
Renal, Male/Female Reproductive, Immune, and Nervous System effects	*Evidence is inadequate*	• Some human/animal evidence available • Data are limited and/or largely null
Cancer	*Inadequate Information*	• No studies in humans • One animal study without dose-related effects • Genotoxicity evidence largely null

Hepatic Effects

- Human Evidence: ***indeterminate*** based on one *medium confidence* study with null findings
- Animal Evidence: ***robust*** based primarily on four *high confidence* studies in SD rats
  - The evidence was assessed for adaptive versus adverse effects: Coherent increases in liver weight, hepatocellular hypertrophy, ALT, AST, and ALP (increased >1.5-3.5-fold), necrosis, and congestion supported adversity based on expert panel criteria described in the PFAS protocol.
  - The evidence was assessed for human relevance (given the involvement of PPARα, which is generally more responsive in rodents than in humans): Supplemental evidence provided biologically plausible support for PPARα-dependent and independent pathways contributing to hepatic effects.
  - Data gaps: Small evidence base investigating PPARα activation by PFHxA exposure.
- **Overall: *Evidence indicates (likely)***

Hematopoietic Effects

- Human Evidence: ***indeterminate*** based on one *uninformative* study
- Animal Evidence: ***moderate*** based primarily on four *high confidence* studies in SD rats
  - Consistent and coherent findings across 4 studies (ranging from short term to chronic exposure durations, in both sexes, generally at ≥200 mg/kg-day)
    - Decreased red blood cells, hematocrit, hemoglobin, and mean corpuscular hemoglobin (MCH)
    - Increased mean corpuscular volume (MCV)
    - Increased reticulocytes (large magnitude of effect, as high as 356%)
      - Judged to potentially reflect a compensatory response to red blood cell loss, which was supported by coherent compensatory erythrogenic responses in spleen and bone (indicated by splenic extramedullary hematopoiesis and bone marrow erythroid hyperplasia)
    - Evidence considered moderate based on uncertainty around determining a minimally biological significant response for the observed outcomes.
- **Overall: *Evidence indicates (likely)***

Developmental Effects

- Human Evidence: ***indeterminate*** based on no available studies
- Animal Evidence: ***moderate*** based primarily on 3 *high confidence* studies in mice and rats
  - Increased perinatal mortality in mice (at ≥175 mg/kg-d)
  - Decreases in fetal and offspring body weights in rats and mice (at ≥100 mg/kg-d)
  - Delayed eye opening in mice (at ≥350 mg/kg-d)

  - Based on EPA guidelines, the potential influence of maternal toxicity was evaluated and judged not to be a driver for the observed developmental effects
    - 5% decrease in terminal dam BW (minus uterine wt.) in one rat study, only in 500 mg/kg-d group
    - Decreased dam BW gain in a second rat study, limited to early gestation (GD 0-7)

- **Overall: *Evidence indicates (likely)***

Endocrine Effects

- Human Evidence: ***indeterminate*** based on one *low confidence* study
  - Thyroid hormone effects reported (↓T3 and TSH), but lacks coherence across related measures

- Animal Evidence: ***slight*** based primarily on two *high confidence* studies in rats
  - 28 d study: Decrease thyroid hormone (T4 and T3) levels in males only (at ≥62.5 mg/kg-d)
    - Large effect magnitude (up to 73% decrease in T4) with strong dose response gradient
  - 90 d study: Increased thyroid epithelial cell hypertrophy (at ≥100 mg/kg-day)
    - Observed in both males and females, but higher incidence in females
  - No thyroid histopathology effects in 3 other *medium or high confidence* studies

- **Overall: *Evidence suggests, but is not sufficient to infer;*** toxicity value not derived

Data-Derived Extrapolation Factor (DDEF)

Sex	Species	Animal clearance (L/hr-kg)	Human clearance (L/hr-kg)	DDEF (CL_H:$CL_{A[s]}$)
Male	Rat	0.163	Mean (90% CI): $1.84\ (1.00–3.49) \times 10^{-3}$ **Preferred approach**	1.1×10^{-2}
	Mouse	0.0894		2.1×10^{-2}
Female	Rat	0.383		4.8×10^{-3}
	Mouse	0.206		8.9×10^{-3}
Male	Rat	0.163	0.137 **Alternative approach**	0.84
	Mouse	0.0894		1.5
Female	Rat	0.383		0.36
	Mouse	0.206		0.67

- Clearance values for humans are not available but DDEF can be calculated based on:
  - **Preferred approach**: uses $t_{1/2}$ obtained by Bayesian PK analysis of human data & average volume of distribution for male and female monkeys (most similar species with full PK data available)
  - **Alternative approach:** allometric scaling of clearance (CL), extrapolated from animal CL values
- Uncertainty exists with both approaches, but a data-driven approach is preferred (i.e., using the available ADME data for PFHxA)

Interspecies Uncertainty Factor (UF_A)

- Evidence bases for developmental and hematopoietic effects lacked data to inform UF_A
- Selection of UF_A for hepatic effects thoroughly considered the potential impact of PPARα
  - Insufficient evidence to support PPARα as the primary mode of action, or to support that humans would not be expected to exhibit more sensitive responses than rodents
  - Two in vitro studies from the same lab suggest PFHxA can induce human PPARα at similar or lower concentrations than mouse PPARα
  - In vivo mechanistic evidence for increased hepatic expression of both PPARα and CAR target genes by PFHxA, consistent with involvement of both pathways for other PFAS
  - Indirect evidence from structurally similar PFAS, including in PPARα knockout and humanized mouse models, indicate PPARα-independent pathways contribute to hepatic injury

- **UF_A = 3 applied to account for residual uncertainty in characterizing the pharmacokinetic and pharmacodynamic differences across species**

Database Uncertainty Factor (UF_D)

- Evidence base includes the following *high or medium confidence* studies:
  - One chronic study in rats
  - Two subchronic studies in rats
  - Two developmental studies in rats and mice
  - One one-generation reproductive study in rats
- Evidence base lacks:
  - A multigenerational study
  - Studies on outcomes of interest given findings for other PFAS (e.g., immune; neurodevelopmental)
  - Certainty in the protectiveness of maternal doses as applied to effects in offspring

- **UF_D = 3 applied to address potential data gaps**

Toxicity Values

Organ/System *Integration judgement*	Toxicity Value	Value (mg/kg-d)		Confidence	UF_C	Basis
		PFHxA	PFHxA-Na			
Hepatic *Evidence indicates (likely)*	osRfD	4×10^{-4}	4×10^{-4}	*Medium*	300	Increased hepatocellular hypertrophy in adult rats (Loveless et al., 2009)
	Subchronic osRfD	1×10^{-3}	1×10^{-3}	*Medium*	100	
Hematopoietic *Evidence indicates (likely)*	osRfD	5×10^{-3}	6×10^{-3}	*High*	100	Decreased red blood cells in adult rats (Klaunig et al., 2015)
	Subchronic osRfD	8×10^{-4}	8×10^{-4}	*High*	100	
Developmental *Evidence indicates (likely)*	osRfD	5×10^{-4}	5×10^{-4}	*Medium*	100	Decreased F1 body weight at PND 0 (Loveless et al., 2009)
	Subchronic osRfD	5×10^{-4}	5×10^{-4}	*Medium*	100	
Overall RfD and Subchronic RfD		5×10^{-4}	5×10^{-4}	Medium	100	Developmental effects

RfC not derived – no inhalation studies available

Newly Identified Studies

- Studies not included in the PFHxA public comment draft were submitted by public commenters.
- All submitted references were identified by the literature update strategies (see below)
- The PFHxA literature search was updated in April 2022 as part of routine yearly updates (last in May 2021)
- Based on the PFBA peer review, in this update (for all 5 IRIS PFAS) and future updates, in addition to the standard search approaches outlined in the protocol, published systematic evidence maps (SEMs) were searched
  - PFAS database by Pelch et al. (https://pfastoxdatabase.org/) and evolving EPA database[1]
  - Note: Dozens of studies were not identified by database searches (e.g., had no PFHxA keyword), only in SEMs
- All newly identified literature was screened using the PFHxA assessment PECO criteria
- Studies that met PECO or supplemental criteria were provided in a handout to the panel and posted to the docket
- These were characterized by EPA as to whether and why they would impact conclusions in the public comment draft
- EPA has charged the panel to comment on EPA's inclusion of the newly identified studies (i.e., before finalization), as well as the panel's interpretation of each newly included study's expected impact on the public draft's conclusions

[1]In press at Environmental Health Perspectives (DOI 10.1289/EHP10343)

Newly Identified Studies: April 2022 Update

122 new studies were identified: 7 human studies and 1 genotoxicity study met the PECO criteria. The remaining studies were tagged as "supplemental"; 15 supplemental studies, informing to hepatic, endocrine, and nervous system effects, were characterized by EPA as important to incorporate prior to assessment finalization because they address key science issues or major data gaps in the PFHxA evidence base (see separate handout in docket). Studies meeting PECO are shown below:

HERO ID	Reference	Health Outcome	Preliminary Results Summary	EPA Characterization
9956482	Verlarde et al. (2022)	Cancer	Positive association with breast cancer (adjusted OR = 2.66 in Q4 vs Q1, 95% CI: 0.95–7.66), but association is not monotonic across quartiles.	Will not change draft conclusions given the lack of exposure-response relationship and bias concerns (selection bias, timing of exposure measurement) noted in preliminary review. However, given the notable data gap (cancer), important to incorporate prior to finalization.
10273407	Liu et al. (2022)	Hepatic	Positive correlation with albumin and direct bilirubin	Will not change draft conclusions due to few studies and limited nature of findings. However, viewed as important to incorporate prior to finalization because evaluation of the human relevance of hepatic effects is a key science issue (see protocol), and metabolic effects represent an important data gap.
5080586	Tian et al. (2019)	Metabolic	Significant positive association for BMI (β = 0.07 (0.00, 0.13)	
6315698	Zeeshan et al. (2020)	Ocular	Significant association ($p < 0.05$) between serum PFHxA and vitreous disorder (OR = 1.39), corneal pannus (OR = 0.72), and combined eye disease (OR =1.06).	Not important to incorporate prior to finalization. Will not change draft conclusions due to single study per outcome and weak or null findings, and do not address notable data gaps or key assessment uncertainties.
9962001	Pierozan et al. (2021)	Cancer (genotoxicity)	PFHxA did not induce genotoxicity in vitro	
6505874	Li et al. (2020)	Developmental	Weak inverse correlation (-0.13; $p>0.05$) with infant weight gain, weak positive correlation with length	
6316202	Jin et al. (2020)	Developmental	No association with mRNA expression of transporters, statistically significant difference between preterm and full-term transplacental transfer efficiency	
5918630	Zeng et al. (2019)	Renal	Small positive association ($p<0.05$) with uric acid	

Overview of Public Comments

ORGANIZED BY TOPIC AREA:

- Systematic Review Methods and Documentation **(15)**
- Noncancer Hazard ID (General) **(1)**
- Hepatic Effects **(4)**
- Hematopoietic effects **(4)**
- Developmental Effects **(6)**
- Endocrine Effects **(2)**
- Other Noncancer Health Effects **(6)**
- Carcinogenicity **(1)**
- Susceptible Populations and Lifestages **(1)**
- Noncancer Toxicity Value Data Selection **(10)**
- Noncancer Toxicity Value Derivation **(20)**
- Formatting, Editorial, and Text Clarifications **(46)**
- IRIS Handbook and Process **(2)**
- PFAS Cumulative Risk Assessment Decisions **(2)**

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PFHxA IRIS Toxicological Review Peer Review Meeting
DAY ONE: Opening Agenda

MEETING OPENING

10:00 AM Meeting Purpose, Peer Review Process, & Reviewer Introductions

10:20 AM U.S. EPA Presentation

11:05 AM Reviewer Discussion Agenda and Process

REVIEWER DISCUSSIONS

11:10 AM Chair Opening Remarks to Panel

11:15 AM Reviewer Discussions

5:30 PM Adjourn Day One

Peer Review Meeting
Key Things to Know

- Agenda:
  - We will start on time each day and go no later than end time on the agenda.
  - Discussion and break times may be adjusted by reviewers.
  - Observers may come and go as you please (same Zoom link for both days).
- Discussions:
  - EPA's charge questions are the framework for discussions.
  - Discussions are among reviewers only.
  - Reviewers may ask for clarifications.
  - EPA may offer clarification.
  - Discussion will occur only via webinar and will conclude at the end of the meeting.
  - Final documentation will be reviewer post-meeting comments.

EPA Requested Categorization of Reviewer Recommendations

- **Tier 1: *Necessary Revisions*** – Use this category for any revisions you believe are necessary to adequately support and substantiate the analyses or scientific basis for the assessment conclusions, or to improve the clarity of the presentation in the PFHxA Toxicological Review.
- **Tier 2: *Suggested Revisions*** – Use this category for any revisions you encourage EPA to implement to strengthen the analyses or scientific basis for the assessment conclusions, or to improve the clarity of the presentation in the PFHxA Toxicological Review.
- **Tier 3: *Future Considerations*** – Use this category for any advice you have for scientific exploration that might inform future work. While these recommendations are generally outside the immediate scope or needs of the PFHxA Toxicological Review, they could inform future reviews or research efforts.

PFHxA Peer Review Meeting
DAY 1: Reviewer Discussion

11:15 AM	***Systematic Review Methods and Documentation***
	- Charge Question 1 (~45 minutes)
12:00 PM	BREAK (15 minutes)
12:15 PM	**- Charge Question 2** (~30 minutes)
	Non-Cancer Hazard Identification—Hepatic Effects
	- Charge Question 3(a) (~15 of 35 minutes)
	Carcinogenicity
	- Charge Questions 9 and 10 (~25 minutes)
	Non-Cancer Hazard Identification—Hematopoietic Effects
	- Charge Question 3(c) (~15 minutes)
1:40 PM	BREAK (20 minutes)

PFHxA Peer Review Meeting
DAY 1: Reviewer Discussion (cont.)

2:00 PM	***Non-Cancer Hazard Identification (cont.)—Hepatic (cont.), Developmental, Endocrine, and All Other Effects***
	- Charge Question 3 (cont.) (~65 minutes)
3:05 PM	***Noncancer Toxicity Value Data Selection***
	- Charge Question 4 (~45 minutes)
3:50 PM	BREAK (20 minutes)
4:10 PM	***Noncancer Toxicity Value Data Selection***
	- Charge Question 5 (~35 minutes)
4:45 PM	***Noncancer Toxicity Value Derivation***
	- Charge Questions 6 and 7 (~50 minutes)
5:30 PM	ADJOURN

ERG

PFHxA Peer Review Meeting Charge Questions

Charge Question 1

The Toxicological Review for PFHxA describes and applies a systematic review protocol for identifying and screening pertinent studies. The protocol is described in brief detail in Section 1.2.1 (Literature Searching and Screening) and in full detail in Appendix A (Systematic Review Protocol for the PFAS IRIS Assessments). Please comment on whether the search strategy and screening criteria for PFHxA literature are clearly described. If applicable, please identify additional peer-reviewed studies of PFHxA that the assessment should incorporate [*see also footnote*].

Charge Question 1 Footnote

Newly identified studies (i.e., studies identified by EPA or the public that meet PECO criteria but were not addressed in the external review draft, for example due to recent publication) will be characterized by EPA and presented to the peer review panel. This characterization will focus on EPA's judgment of whether the studies would have a material impact on the conclusions (i.e., identified hazards or toxicity values) in the external review draft. The peer review panel is asked to review EPA's characterization and provide tiered recommendations to EPA regarding which studies, if any, to incorporate into the assessment before finalizing.

Charge Question 2

The Toxicological Review provides an overview of individual study evaluations and the results of those evaluations are made available in the Health Assessment Workplace Collaborative linked here HAWC. Note that a "HAWC FAQ for assessment readers" document, linked here (scroll to the bottom of the page, and the document is available for download under "attachments"), is intended to help the reviewer navigate this on-line resource. Data from studies considered informative to the assessment are synthesized in the relevant health effect-specific sections, and study data are available in HAWC.

Charge Question 2 (cont.)

a) Please comment on whether the study confidence conclusions for the PFHxA studies are scientifically justified and clearly described, considering the important methodological features of the assessed outcomes. Please indicate any study confidence conclusions that are not justified and explain any alternative study evaluation decisions.

b) Results from individual PFHxA studies are presented and synthesized in the health system-specific sections. Please comment on whether the presentation and analysis of study results are clear, appropriate, and effective to allow for scientifically supported syntheses of the findings across sets of studies.

Charge Question 3

For each health effect considered in the assessment and outlined below, please comment on whether the available data have been clearly and appropriately synthesized to describe the strengths and limitations. For each, please also comment on whether the weight-of-evidence decisions for hazard identification are scientifically justified and clearly described.

Charge Question 3 (cont.)

a) For hepatic effects, the Toxicological Review concludes the available ***evidence indicates*** PFHxA likely causes hepatic effects in humans under relevant exposure circumstances. This conclusion is based on studies of rats showing increased liver weight, hepatocellular hypertrophy, increased serum enzymes, and decreased serum globulins. The hepatic findings for PFHxA were similar for other PFAS and determined to be adverse and relevant to humans.

Charge Question 3(a) (cont.)

i. Additional considerations influenced the hepatic effects hazard identification decisions. Appendix A (Systematic Review Protocol for the PFAS IRIS Assessments) outlines the human relevance of hepatic effects in animals that involve PPARα receptors as a key science issue. To the extent supported by the PFHxA literature (and to a lesser extent, literature for other PFAS), the Toxicological Review evaluates the evidence relevant to the potential involvement of PPARα and non-PPARα pathways with respect to the reported hepatic effects. The Toxicological Review ultimately concludes evidence from in vivo (including genetic mouse models) and in vitro studies support a potential role for multiple pathways operant in the induction of hepatic effects from PFHxA exposure but those pathways cannot be specifically determined. Please comment on whether the conclusions regarding the available animal and mechanistic studies are scientifically justified and clearly described. The hepatic findings for PFHxA were similar for other PFAS and determined to be adverse and relevant to humans.

Charge Question 9

The Toxicological Review concludes that there is *inadequate information to assess carcinogenic potential* for PFHxA and that this descriptor applies to oral and inhalation routes of human exposure. Please comment on whether the available animal and mechanistic studies and the analysis presented in the Toxicological Review are scientifically justified and clearly described.

Charge Question 10

Given the conclusion there *was inadequate information to assess carcinogenic potential* for PFHxA (Charge Question 5), the Toxicological Review does not derive quantitative estimates for cancer effects for either oral or inhalation exposures. Is this decision scientifically justified and clearly described?

Charge Question 3

For each health effect considered in the assessment and outlined below, please comment on whether the available data have been clearly and appropriately synthesized to describe the strengths and limitations. For each, please also comment on whether the weight-of-evidence decisions for hazard identification are scientifically justified and clearly described.

Charge Question 3 (cont.)

c) For hematopoietic effects, the Toxicological Review concludes the available ***evidence indicates*** PFHxA likely causes hematopoietic effects in humans under relevant exposure circumstances. This judgment is based on consistent findings, including decreased red blood cells [RBCs], hematocrit, and hemoglobin, across study designs that, when interpreted together, signifies PFHxA-related hematological effects such as anemia. These findings were determined to be adverse and relevant to humans.

Charge Question 3

For each health effect considered in the assessment and outlined below, please comment on whether the available data have been clearly and appropriately synthesized to describe the strengths and limitations. For each, please also comment on whether the weight-of-evidence decisions for hazard identification are scientifically justified and clearly described.

Charge Question 3(a)

a) For hepatic effects, the Toxicological Review concludes the available ***evidence indicates*** PFHxA likely causes hepatic effects in humans under relevant exposure circumstances. This conclusion is based on studies of rats showing increased liver weight, hepatocellular hypertrophy, increased serum enzymes, and decreased serum globulins. The hepatic findings for PFHxA were similar for other PFAS and determined to be adverse and relevant to humans.

Charge Question 3(a) (cont.)

i. Additional considerations influenced the hepatic effects hazard identification decisions. Appendix A (Systematic Review Protocol for the PFAS IRIS Assessments) outlines the human relevance of hepatic effects in animals that involve PPARα receptors as a key science issue. To the extent supported by the PFHxA literature (and to a lesser extent, literature for other PFAS), the Toxicological Review evaluates the evidence relevant to the potential involvement of PPARα and non-PPARα pathways with respect to the reported hepatic effects. The Toxicological Review ultimately concludes evidence from in vivo (including genetic mouse models) and in vitro studies support a potential role for multiple pathways operant in the induction of hepatic effects from PFHxA exposure but those pathways cannot be specifically determined. Please comment on whether the conclusions regarding the available animal and mechanistic studies are scientifically justified and clearly described. The hepatic findings for PFHxA were similar for other PFAS and determined to be adverse and relevant to humans.

Charge Question 3 (cont.)

b) For developmental effects, the Toxicological Review concludes the available ***evidence indicates*** PFHxA likely causes developmental effects in humans under relevant exposure circumstances. This judgment is based primarily on gestational exposure experiments in mice, with supportive findings in rats exposed throughout gestation and lactation, showing increased perinatal mortality, decreased offspring body weight, and delayed eye opening. These effects are similar to those observed for other PFAS following developmental exposure and were determined to be adverse and relevant to humans.

Charge Question 3 (cont.)

d) For endocrine effects, the Toxicological Review concludes the available evidence suggests, but is not sufficient to infer, that PFHxA may cause endocrine effects in humans under relevant exposure circumstances. This conclusion is based on some evidence of thyroid effects based on hormone and histopathological changes in two rat studies; however, the data is limited, lacking consistency across studies, and histopathological changes may be explained by non-thyroid related effects.

e) For all other potential health effects (i.e., renal, male and female reproductive, immune, and nervous system), the Toxicological Review concluded the available evidence is inadequate to assess whether PFHxA may cause effects in humans under relevant exposure circumstances. In general, these conclusions were driven by sparse evidence bases or data that were largely null.

Charge Question 4

For PFHxA, no RfC was derived. The study chosen for use in deriving the RfD is the Loveless et al. (2009) one-generation reproductive toxicity study based on decreased offspring body weight in rats exposed continuously throughout gestation and lactation to PFHxA sodium salt via the dam. Is the selection of this study and these effects for use in deriving the RfD for PFHxA scientifically justified and clearly described?

a) If yes, please provide an explanation.

b) If no, please provide an alternative study(ies) or effect(s) that should be used to support the derivation of the RfD and detail the rationale for use of such an alternative.

Charge Question 4 (cont.)

c) As part of the responses in "a" or "b" above, please comment on whether the effects selected are appropriate for use in deriving the RfD, including considerations regarding adversity (or appropriateness in representing an adverse change) and the scientific support for their selection.

d) Given the lack of studies on inhalation exposure to PFHxA, no reference concentration (RfC) is derived. Please comment on this decision.

Charge Question 5

In addition, for PFHxA, an RfD for less-than-lifetime ("subchronic") exposures is derived. No "subchronic" RfC was derived. The same study and outcome were chosen for use in deriving the RfD. Is the selection of this study and these effects for the derivation of the subchronic RfD for PFHxA scientifically justified and clearly described?

a) If yes, please provide an explanation.

b) If no, please provide an alternative study(ies) and/or effect(s) that should be used to support the derivation of the subchronic RfD and detail the rationale for use of such an alternative.

Charge Question 5 (cont.)

c) As part of the responses in "a" or "b" above, please comment on whether the effects selected are appropriate for use in deriving the RfD, including considerations regarding adversity (or appropriateness in representing an adverse change) and the scientific support for their selection.

d) Given the lack of studies on inhalation exposure to PFHxA, no "subchronic" RfC is derived. Please comment on this decision.

Charge Question 6

EPA used benchmark dose modeling (USEPA, 2012) to identify points-of-departure (PODs) for oral exposure to PFHxA. Are the modeling approaches used, selection and justification of benchmark response levels, and the selected models used to identify each POD for toxicity value derivation scientifically justified and clearly described?

Charge Question 7

Appendix A identifies the potential for pharmacokinetic differences across species and sexes as a key science issue and lays out a hierarchy for using relevant pharmacokinetic data in extrapolating oral doses between laboratory animals and humans. Section 5.2.1 describes the various approaches considered and the rationale for the selected approach. Given what is known and not known about the potential interspecies differences in PFHxA pharmacokinetics, EPA used the ratio of human-to-animal serum clearance values assuming the volume of distribution (Vd) in humans is equivalent to that in monkeys to adjust the POD to estimate a human equivalent dose (HED) in the derivation of the respective RfDs.

Charge Question 7 (cont.)

a) Is applying the ratio of human-to-animal serum clearance values for PFHxA scientifically justified and clearly described? If not, please provide an explanation and detail the preferred alternative approach.

b) Does the Toxicological Review clearly describe the uncertainties in evaluating the pharmacokinetic differences between the experimental animal data and humans?

DAY 1: May 16
10:00 AM–5:30 PM

DAY 2: May 17
12:00 PM – 3:00 PM

External Peer Review of the EPA Draft "IRIS Toxicological Review of Perfluorohexanoic Acid and Related Salts" (PFHxA)

PFHxA Peer Review Panel Meeting: Observer Webinar Logistics

Video/Audio:

- Observers: Muted and video off by default throughout.

If you have any issues, contact Katie (ERG):

- By email at meetings@erg.com.

PFHxA Peer Review Meeting
DAY 2: Reviewer Discussion

12:00 PM	Facilitator Remarks
12:05 PM	Reviewer Discussion (cont.)
	Noncancer Toxicity Values Derivation
	- Charge Question 8 (40 minutes)
12:45 PM	Reviewer Integrative Comments and Discussion
1:15 PM	BREAK (15 minutes)
1:30 PM	Individual Reviewer Recommendations
2:50 PM	Closing Remarks
3:00 PM	ADJOURN

EPA Requested Categorization of Reviewer Recommendations

- **Tier 1: *Necessary Revisions*** – Use this category for any revisions you believe are necessary to adequately support and substantiate the analyses or scientific basis for the assessment conclusions, or to improve the clarity of the presentation in the PFHxA Toxicological Review.
- **Tier 2: *Suggested Revisions*** – Use this category for any revisions you encourage EPA to implement to strengthen the analyses or scientific basis for the assessment conclusions, or to improve the clarity of the presentation in the PFHxA Toxicological Review.
- **Tier 3: *Future Considerations*** – Use this category for any advice you have for scientific exploration that might inform future work. While these recommendations are generally outside the immediate scope or needs of the PFHxA Toxicological Review, they could inform future reviews or research efforts.

PFHxA Peer Review Meeting
Peer Reviewer Introductions

Elaine M. Faustman, Ph.D., DABT (Panel Chair)

Panagiotis G. Georgopoulos, Ph.D.

Joseph T. Haney, Jr., M.S.

Angela M. Leung, MD, MSc.

Carla A. Ng, Ph.D.

David A. Savitz, Ph.D.

R. Thomas Zoeller, Ph.D.

Charge Question 8

EPA has evaluated and applied uncertainty factors to account for intraspecies variability (UFH), interspecies differences (UFA), database limitations (UFD), exposure duration (UFS), and LOAEL-to-NOAEL extrapolation (UFL) for PFHxA.

a) Is uncertainty in the derivation of the toxicity values scientifically justified and clearly described? Please describe and provide comments, if needed.

Charge Question 8 (cont.)

b) For uncertainty in interspecies differences (UFA), a value of 3 is applied to account for remaining uncertainty in characterizing the pharmacokinetic and pharmacodynamic differences between laboratory animals and humans after calculation of the HED. For developmental and hematopoietic outcomes, the evidence base lacked chemical-and species-specific information that would have been useful for informing the UFA; for hepatic outcomes, however, available mechanistic and supplemental information was useful for further evaluating the interspecies uncertainty factor. Some data indicate a PPARα-dependent pathway that might support a UFA of 1. Evidence for non-PPARα modes of action, however, is available in the PFHxA (and larger PFAS) database. *(continued on next slide)*

Charge Question 8(b) (cont.)

b) *(continued from prior slide)* Thus, uncertainty remains regarding the potential differences in sensitivity across species due to the involvement of both PPARα-dependent and-independent pathways. Further, data are lacking to determine with confidence the relative contribution of each of these pathways. As such, the Toxicological Review concludes the available data are not adequate to determine if humans are likely to be equally or less sensitive than laboratory animals with respect to the observed hepatic effects and that a value of UFA=3 is warranted to account for the residual uncertainty in pharmacodynamic differences across species. Please comment on whether the available animal and mechanistic studies support this conclusion and whether the analysis presented in the Toxicological Review is scientifically justified and clearly described.

Charge Question 8 (cont.)

c) To inform uncertainty in intraspecies variability (UFH), the assessment evaluates and considers the available evidence on potential susceptibility to PFHxA within different populations or lifestages, including any potential human health impacts from early life exposure. Are the available information and data appropriately considered and the resultant UFH values scientifically justified and clearly described?

d) Are the provided rationales for the remaining uncertainty factors (UFL, UFD, UFS) scientifically justified and clearly described? If not, please explain.