DAY 1: Feb 22
10:30 AM–3:30 PM

DAY 2: Feb 23
10:30 AM – 2:45 PM

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

PFBA Peer Review Panel Meeting: Webinar Logistics

Video/Audio:

- Observers: Muted and video off by default throughout.
- Oral commenters:
  - Will be unmuted by ERG.
  - May use video if you would like.
- Reviewers: May mute / unmute and turn video on / off.
  - During introductions, oral comment, 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 where:

- Reviewers can exchange, discuss, and evolve their individual views and opinions on EPA's draft "IRIS Toxicological Review of PFBA and Related Salts," including:
  - Their response to EPA's charge questions.
  - Any other aspect of the EPA draft PFBA IRIS assessment they would like to discuss.
- Interested members of the public can make an oral comment prior to reviewer discussions.
- EPA and observers can listen to all reviewer discussions.

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

MEETING OPENING

10:30 AM	**Meeting Purpose, Agenda, & Reviewer Introductions**
10:45 AM	**U.S. EPA Presentation**
11:15 AM	**Public Comments**
11:25 AM	**Reviewer Discussion Agenda and Process**

REVIEWER DISCUSSIONS

11:30 AM	**Chair Opening Remarks to Panel**
11:40 AM	**Reviewer Discussions**
3:30 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 high-level meeting summary by charge question.

External Independent Peer Review
Key Principles

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

PFBA Peer Review Meeting
Peer Reviewer Introductions

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

Jeffrey W. Fisher, Ph.D.

Panagiotis G. Georgopoulos, Ph.D.

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

Alan M. Hoberman, Ph.D., DABT

David A. Savitz, Ph.D.

R. Thomas Zoeller, Ph.D.

U.S. Environmental Protection Agency (EPA) Presenters

Kristina Thayer, Ph.D., IRIS Program Director

J. Allen Davis, M.S.P.H., PFBA Co-chemical Manager

Michele M. Taylor, Ph.D., PFBA Co-chemical Manager

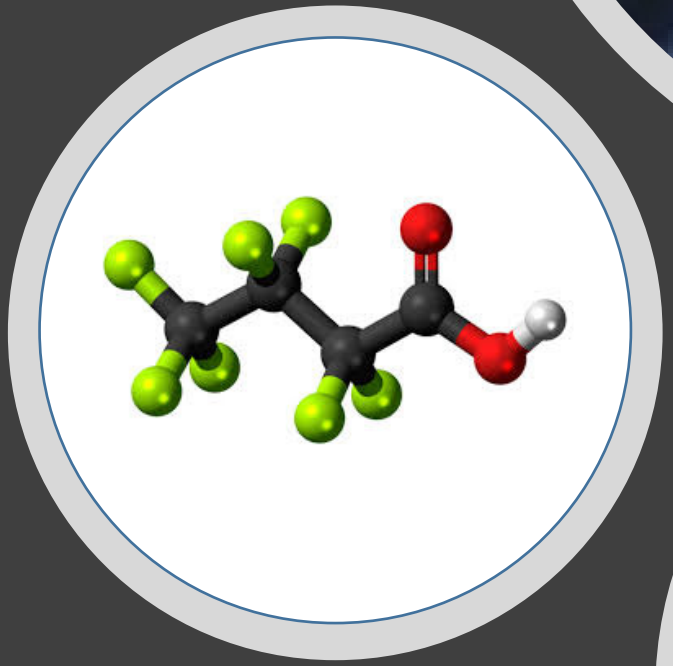
Toxicological Review of Perfluorobutanoic Acid (CASRN 375-22-4) and Related Salts

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

J. Allen Davis, MSPH
U.S. EPA, Office of Research and Development, Center for Public Health and Environmental Assessment

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

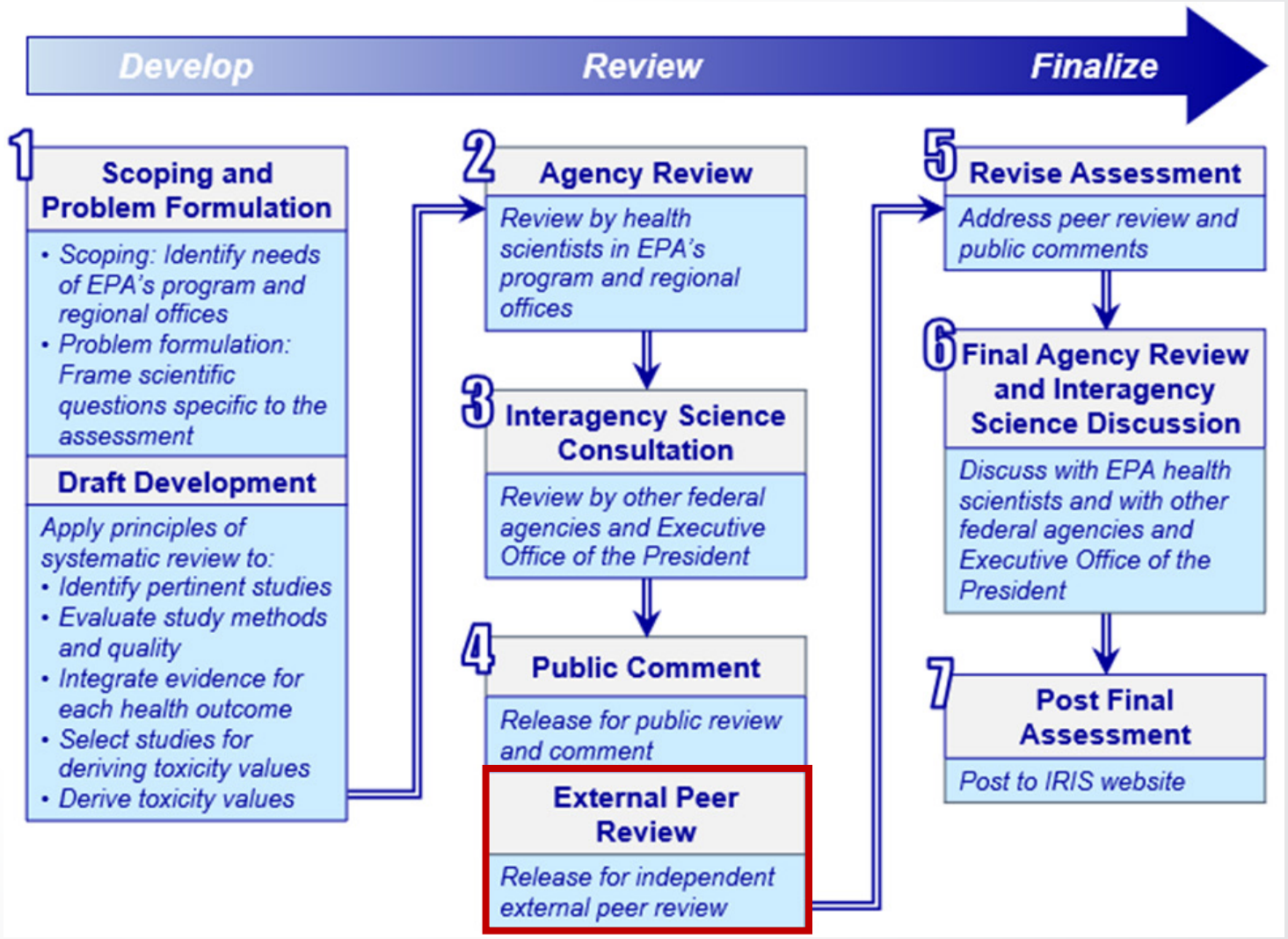
February 22, 2022



- **Created in 1985 to foster consistency in the evaluation of chemical toxicity across the Agency.**
- **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 of these are the purview of EPA's program offices.

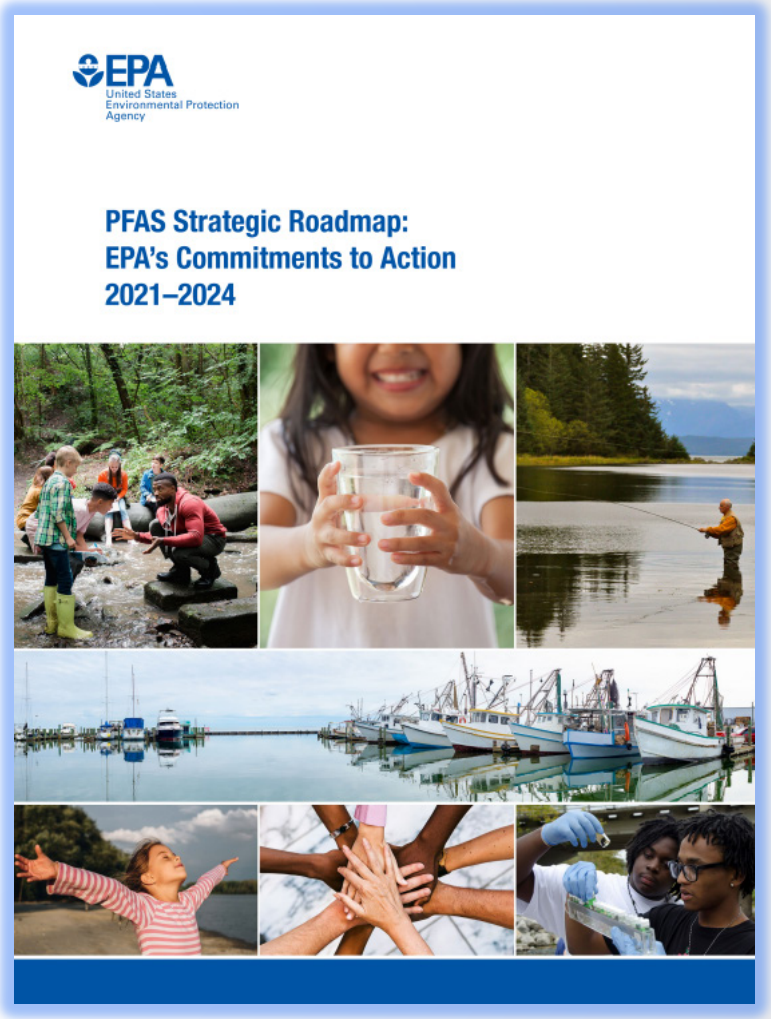
IRIS Process

- PFBA currently in Step 4
- PFBA released for Public Comment in August 2021 (comment period ended November 2021)
- Received multiple sets of public comments
- EPA compiled comments and organized by topic area
- Compilation of comments provided to Panel to consider during their review; compilation also posted to public docket



PFBA and EPA's Broader PFAS Strategic Roadmap

- The IRIS assessment of PFBA is being produced in parallel with separate IRIS assessments of four other PFAS, specifically PFHxA, 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

Structured Framework to Assess Evidence and Derive Toxicity Values

Evidence Integration

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

Consistent among studies with minimal bias & sensitivity analyses, additional support

Less consistent or low confidence evidence, no additional support

- 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

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

Animal*	Epidemiological*
Reporting Quality	Exposure measurement
Selection or Performance Bias	Outcome ascertainment
Confounding/Variable Control	Population Selection
Reporting or Attrition Bias	Confounding
Exposure Methods Sensitivity	Analysis
Outcome Measures and Results Display	Sensitivity
	Selective reporting

Domain judgements

Judgment	Interpretation
Good (++)	Appropriate study conduct relating to the domain & 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 is interpreted to be the primary driver of any observed effect or makes the study uninterpretable.

Overall study confidence for an outcome

Confidence	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 are 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 studyresults or their interpretation.
Uninformative	Serious flaw(s) makes study results unreliable for hazard identification. Study is not used without exceptional justification (e.g., to highlight data gaps).

PFBA Assessment Hazard Conclusions

- Sufficient evidence in the PFBA database to draw hazard conclusions for:
  - Thyroid – evidence indicates (likely)
  - Hepatic – evidence indicates (likely)
  - Developmental – evidence indicates (likely)
- Evidence was insufficient to draw hazard conclusion for reproductive effects or other non-cancer health effects
  - Hypertension
  - Renal function
  - Hematological effects
  - Ocular effects
- No PFBA-related effects on body weight observed in any study
- No human or animal studies available to inform the potential for PFBA-induced carcinogenicity

Thyroid Hazard

- Decreases in total and free T_4, increased thyroid weight, and increased thyroid follicular hypertrophy/hyperplasia observed in adult male rats
- Decreased T_4 was not associated with compensatory increases in TSH, consistent with a human clinical condition known as “hypothyroxinemia”
- PFBA-induced thyroid effects consistent with other PFAS (e.g., PFBS)
- Evidence integration summary discusses the human relevance of thyroid effects
  - Rodents are considered a representative model for evaluating the potential for thyroid effects in humans
  - Decreases in total or free T_4 in the absence of increases in TSH are considered biologically relevant to humans
- The ***evidence indicates*** PFBA exposure is likely to cause thyroid toxicity in humans based primarily on *consistent* and *coherent* pattern of thyroid effects from two high confidence studies in rats

Hepatic Hazard

- Increases in liver weights and increased liver lesions (hypertrophy, necrosis, and vacuolation) in adult male rats and mice and in pregnant mice and their offspring
- Mechanistic evidence specific to PFBA and other structurally related PFAS provides support for both PPARα-dependent and -independent pathway contributions to hepatic toxicity
- The ***evidence indicates*** PFBA exposure is likely to cause hepatic toxicity in humans based primarily on *consistent and coherent* pattern of liver effects (between liver weights and histopathology) across multiple high and medium confidence studies, multiple species, sexes, exposure durations, and study designs

Hepatic Hazard and Adversity

- The PFBA assessment uses panel recommendations from Hall et al. (2012) and other considerations to judge whether hepatic effects are adverse or adaptive in nature
  - Coincident histological evidence of liver injury (e.g., necrosis) supports the conclusion that liver weight changes and/or histological changes are “adverse”
  - Steatotic vacuolar degeneration, specifically microvesicular vacuolation, identified by Hall et al. (2012) as sufficient supporting evidence
  - Vacuolation observed in humanized PPARα mice is consistent with microvesicular vacuolation, and accumulation of lipids in the liver is an apical key event leading to hepatic steatosis

Developmental Hazard

- Coherent pattern of developmental effects (delayed eye opening, vaginal opening, and preputial separation, full-litter resorption, and decreased survival) observed in mice exposed in utero
- Consistent patterns of delayed pubertal milestones have been observed following exposure to other PFAS
- The ***evidence indicates*** PFBA exposure is likely to cause adverse developmental effects in humans based primarily on coherent developmental effects in a high confidence study of gestationally exposed mice

Data-informed dosimetric adjustment (DAF)

- The ratio of serum clearance was used to calculate the DAF and the human equivalent dose (HED) using measured serum clearance in rodents and estimated human serum clearance
- Alternative DAFs based on $BW^{0.75}$ provided for comparison
- Use of chemical-specific information to inform dosimetric adjustments in lieu of default $BW^{0.75}$ approach is consistent with EPA guidelines

Sex	Species	Animal *CL* (mL/kg-h)	Human *CL* (mL/kg-h)	DAF (CL_H:CL_A)	DAF ($BW^{0.75}$)
Male	Rat	21.61[a]	4.95[c]	0.229	0.236
	Mouse	10.10[b]		0.490	0.139
Female	Rat	96.62[a]		0.051	0.236
	Mouse	27.93[b]		0.177	0.139

[a] Average of 30 mg/kg oral and i.v. exposures
[b] Average of 10 mg/kg and 30 mg/kg oral exposures
[c] Calculated using the equation $CL_{human}\ (\text{mL/kg-h}) = \ln(2) \times \frac{1}{t_{1/2,\text{human}}(\text{h})} \times V_{\text{d,monkey}}\ (\text{mL/kg})$

Oral Reference Dose

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

System	Basis	Point of Departure	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*
Thyroid	Decreased total T4 in adult male S-D rats	$NOAEL_{HED}$ Butenhoff et al. (2012)	1,000	1×10^{-3}	*Medium-low*
Developmental	Developmental delays after gestational exposure in CD1 mice[a]	$BMDL_{HED}$ Das et al. (2008)	100	7×10^{-3}	*Medium-low*

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

Subchronic Oral Reference Dose

- Similar to the RfD, several subchronic osRfDs were estimated (below)
- From these subchronic osRfDs, an overall subchronic RfD of ***7×10^{-3} mg/kg-day*** based on developmental delays was selected. Confidence in the subchronic RfD is medium-low.

System	Basis	Point of Departure	Composite Uncertainty Factor	osRfD (mg/kg-d)	Confidence
Hepatic	Increased hepatocellular hypertrophy in adult male S-D rats	$BMDL_{HED}$ Butenhoff et al. (2012)	100	1×10^{-2}	*Medium*
Thyroid	Decreased total T4 in adult male S-D rats	$NOAEL_{HED}$ Butenhoff et al. (2012)	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*

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

Newly Identified Studies

- Studies not included in the PFBA public comment draft were identified during routine literature search updates as well as by public commenters, specifically the Natural Resources Defense Council
- These studies were screened using the PFBA assessment PECO criteria. Studies that met PECO or were identified as supplemental material were documented in a handout to the external peer reviewers and posted to the PFBA docket
- The studies characterized by EPA as to whether and why they would change assessment conclusions in the public comment draft
- In the charge to external peer reviewers, EPA has asked the panel to comment on the inclusion the newly identified studies prior to finalizing the assessment, as well as their expected impact.

Newly Identified Studies

- Seven studies failed to meet the PFBA PECO criteria but were tagged as "supplemental". None were interpreted by EPA as impactful to the assessment conclusions or data gaps.
- Eight studies meeting PECO criteria were similarly interpreted as not impactful to draft conclusions. However, two of these studies assessed an important data gap (immune).

Reference	Met PECO Criteria?	Health Outcome	Results Summary	EPA characterization
Grandjean et al. (2020)	Yes [1,2]	Immune (COVID-19 Severity)	Elevated OR (1.57) for increased COVID-19 severity in >LOD vs <LOD	Will not change assessment conclusions due to few studies and limited nature of findings. However, viewed as important to incorporate prior to assessment finalization because immune effects represent an important data gap for PFBA in light of data on other PFAS (PFOA; PFOS).
Zeng et al. (2020)	Yes [2]	Immune (Hepatitis B Surface Antibody)	Lower antibody levels with higher exposure ($p<0.05$)	
Duan et al. (2020)	Yes [2]	Cardiometabolic (Insulin Resistance)	No association with fasting glucose or HbA1c levels	Will not change assessment conclusions due to single study per outcome and weak or null findings, and do not address notable data gaps. Not viewed as important to incorporate prior to assessment finalization.
Tian et al. (2019)	Yes [2]	Cardiometabolic (Body Weight)	No association with BMI or waist circumference, higher odds of overweight/obesity in women only	
Banjabi et al. (2020)	Yes [1,2]	Osteoporosis	OR=0 in 2nd-4th quartiles	
Zeng et al. (2019)	Yes [1,2]	Urinary (Uric Acid)	Small positive association ($p<0.05$) with uric acid	
Zeeshan et al. (2020)	Yes [1,2]	Ocular Conditions	No association with eye disease	
Jin et al. (2020)	Yes [2]	Developmental (Postnatal Growth)	Weak inverse correlation (-0.13; $p>0.05$) with infant weight gain, weak positive correlation with length	

[1] Identified in literature search updates conducted after the PFBA public comment draft was released.
[2] Identified by public commenters (the full set of comments as submitted are available here: https://www.regulations.gov/docket/EPA-HQ-ORD-2020-0675)

New Immunotoxicity Studies

- Two studies met PECO and were considered by EPA as important to incorporate prior to finalization as they inform an important data gap (immune effects)
- Grandjean et al. (2020): OR = 1.57 for increased COVID severity (>LOD vs <LOD)
  - Disease severity not direct measure of immune suppression
  - >LOD vs <LOD exposure characterization can not be used quantitatively
- Zeng et al. (2020): lower Hepatitis B antibody levels with higher exposure (p = 0.05)
  - Concerns over exposure and outcome misclassification (cross-sectional timing of exposure measurement inappropriate for outcome)
  - No consideration of Hepatitis B vaccination or exposure

New Immunotoxicity Studies

- Currently, the PFBA assessment discusses immunotoxicity as “an area of concern across several constituents of the larger PFAS family” but that there are no PFBA-specific studies available
- Given the few studies and limited nature of the evidence, the Grandjean et al. (2020) and Zeng et al. (2020) studies are not interpreted by EPA to change the draft hazard conclusions and cannot be used in quantitative derivations
- While inclusion of these studies in the assessment would provide additional context to database uncertainty factor selection, they are not interpreted by EPA as sufficient to reduce the uncertainty associated with current data gaps to understanding the potential for PFBA exposure to cause sensitive human health effects, such as (potentially) immunotoxicity

Assessment-Specific Comments

ORGANIZED BY TOPIC AREA:

- Pharmacokinetics and Dosimetric Adjustments **(5)**
- Consideration of (read-across) evidence from other PFAS in PFBA-specific decisions **(2)**
- Literature Search and Screening **(6)**
- Thyroid Hazard **(2)**
- Hepatic Hazard **(3)**
- Developmental Hazard **(3)**
- Susceptible Populations and Lifestages **(3)**
- Uncertainty Factors and RfD **(6)**
- Formatting, Editorial, and Text Clarifications **(57)**
- Timing and Selection of PFAS for Assessment by EPA, Regulatory Action, or Risk Communication by EPA on PFAS **(5)**
- Future Use of PFBA Conclusions by EPA in PFAS Cumulative Risk Assessment Decisions **(2)**

PFBA Assessment Contacts

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

10:30 AM	**Meeting Purpose, Agenda, Process & Reviewer Introductions**
10:45 AM	**U.S. EPA Presentation**
11:15 AM	**Public Comments**
11:25 AM	**Reviewer Discussion Agenda and Process**
11:30 AM	**Chair Opening Remarks to Panel**
11:40 AM	**Reviewer Discussions**

PFBA Peer Review Meeting
Public Oral Comments

Katie Pelch, Natural Resources Defense Council

PFBA IRIS Toxicological Review Peer Review Meeting
DAY ONE: Agenda

MEETING OPENING

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11:25 AM	**Reviewer Discussion Agenda and Process**

REVIEWER DISCUSSIONS

11:30 AM	**Chair Opening Remarks to Panel**
11:40 AM	**Reviewer Discussions Commence**
3:30 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.
  - At the beginning of each day and after each break, I will state where we are in the agenda.
  - Observers may come and go as you please (same Zoom link for all meetings).
- 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.

PFBA Peer Review Meeting
Agenda

DAY ONE (Tuesday, February 22)

10:30 AM – 11:30 AM	Meeting Opening
11:30 AM – 3:30 PM	Reviewer Discussions

DAY TWO (Wednesday, February 23)

10:30 AM – 2:45 PM	Reviewer Discussions

PFBA Peer Review Meeting
DAY 1: Reviewer Discussion

11:40 AM	***Systematic Review Documentation***
	- Charge Question 1 (25 minutes)
12:05 PM	BREAK (20 minutes)
12:25 PM	**- Charge Question 2** (30 minutes)
	Hazard Identification—Hepatic Effects
	- Charge Questions 3(b) and 4 (35 minutes)
1:30 PM	BREAK (15 minutes)
1:45 PM	***Hazard Identification—Other Effects***
	- Charge Question 3(a)(c)(d) (55 minutes)
	Noncancer Toxicity Values Data Selection
	- Charge Question 6 (45 minutes)
3:25 PM	Day One Wrap Up
3:30 PM	ADJOURN

ERG

PFBA Peer Review Meeting
Charge Questions

Charge Question 1

The Toxicological Review describes and applies a systematic review process for identifying and screening pertinent studies that is described in detail in Section 1.2.1 (Literature Search and Screening) and Appendix A (Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA IRIS Assessments). Please comment on whether the search strategy and screening criteria for PFBA are appropriate and clearly described. Please identify additional peer-reviewed studies of PFBA 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.

PFBA Peer Review Meeting

BREAK

The meeting will resume at 12:30 PM EST

Charge Question 2

The Toxicological Review describes the results of the evaluations of individual studies in Section 2.2 (Study Evaluation Results) and presents and analyzes the findings from those studies deemed informative in the relevant health effect-specific synthesis sections.

a) Please comment on whether the study confidence conclusions for the PFBA studies are scientifically justified, giving appropriate consideration to important methodological features of the assessed outcomes. Please specify any study confidence conclusions that are not justified and explain any alternative study evaluation decisions.

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

Charge Question 3(b)

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 have been clearly described and scientifically justified.

b) For **hepatic effects**, the Toxicological Review concludes that the available evidence indicates PFBA exposure is likely to cause hepatic effects in humans given relevant exposure circumstances, on the basis of a series of short-term, subchronic, and developmental studies in rats and mice demonstrating consistent and coherent effects with a clear biological gradient. Although the available mechanistic information indicates the effects in rodents are relevant to humans, some uncertainty remains regarding potential differences in sensitivity across species due to evidence for the involvement of both PPARα-dependent and PPARα-independent pathways in these effects (see Charge Question 4 requesting input specific to this latter uncertainty?

Charge Question 4

Appendix A (Systematic Review Protocol for the PFBA PFHxA, PFHxS, PFNA, and PFDA IRIS Assessments) identifies the human relevance of hepatic effects in animals that involve peroxisome proliferator-activated receptor alpha (PPARα) receptors as a key science issue [*see also footnote*]. To the extent supported by the PFBA 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 and in vitro studies support that multiple modes of action (MOA) are operant in the induction of hepatic effects by PFBA exposure and the relative contribution of these different MOAs cannot be concluded with confidence from the available data. Please comment on whether the available animal and mechanistic studies support this conclusion and whether the analysis presented in the Toxicological Review is clearly documented.

Charge Question 4 Footnote

The PFAS Systematic Review Protocol identifies five key science questions: (1) possible toxicokinetic differences across species and sexes, (2) the human relevance of effects in animals that involve PPARα activation, (3) potential confounding by other PFAS exposures in epidemiology studies, (4) the toxicological relevance of changes in certain urinary and hepatic endpoints in rodents, and (5) characterizing uncertainty due to missing chemical-specific data). Three of the questions are most pertinent to the Toxicological Review of PFBA. Key science question 1 is addressed in Charge Questions 9.a and 9.b, Key science question 2 is addressed in Charge Questions 3.b and 4, and Key science question 4 is addressed in Charge Question 6.c.

PFBA Peer Review Meeting

BREAK

The meeting will resume at 1:50 PM EST

Charge Question 3 (cont.)

For each health effect considered in the assessment, 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 have been clearly described and scientifically justified.

a) For **thyroid effects**, the Toxicological Review concludes that the available evidence indicates PFBA exposure is likely to cause thyroid toxicity in humans given relevant exposure circumstances, primarily on the basis of short-term and subchronic studies in male rats reporting a consistent and coherent pattern of thyroid effects following PFBA exposure, but also drawing from the consistency of effects when considering evidence from structurally related PFAS. The Toxicological Review concludes the thyroid effects are considered relevant to humans in the absence of evidence to suggest otherwise?

Charge Question 3 (cont.)

For each health effect considered in the assessment, 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 have been clearly described and scientifically justified.

c) For **developmental effects**, the Toxicological Review concludes that the available evidence indicates PFBA exposure is likely to cause developmental effects in humans given relevant exposure circumstances, on the basis of a coherent pattern of delays in acquisition of three different developmental milestones in a single study in mice, with the findings presumed relevant to humans in the absence of evidence to suggest otherwise. The assessment discusses similar effects observed for structurally related PFAS.

d) For **reproductive effects and other noncancer effects** (i.e., cardiometabolic effects, renal effects, ocular effects, body weight), the Toxicological Review concludes there is inadequate evidence to determine whether PFBA exposure has the potential to cause these effects in humans on the basis of the sparsity of available evidence.

Charge Question 6

For PFBA, no reference concentration (RfC) was derived. The Butenhoff et al. (2012) 90-day rat study was the study chosen for use in deriving the RfD on the basis of an increased incidence of hepatocellular hyperplasia and decreased total T4 in male rats. Is the selection of this study and these effects for use in deriving the RfD for PFBA scientifically justified?

a) If so, please provide an explanation.

b) If not, 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 6 (cont.)

For PFBA, no reference concentration (RfC) was derived. The Butenhoff et al. (2012) 90-day rat study was the study chosen for use in deriving the RfD on the basis of an increased incidence of hepatocellular hyperplasia and decreased total T4 in male rats. Is the selection of this study and these effects for use in deriving the RfD for PFBA scientifically justified?

c) As part of the recommendations 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. More specifically, Appendix A identifies interpreting the adversity of certain outcomes observed in rodents, including some hepatic effects, as a key science issue. Please consider in your recommendation the narrative in the Toxicological Review related to the decision that the observed hepatocellular hypertrophy, when considered within the broader constellation of effects, is representative of an adverse change in the organ.

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

DAY 1: Feb 22
10:30 AM–3:30 PM

DAY 2: Feb 23
10:30 AM – 2:45 PM

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

PFBA Peer Review Panel Meeting: Webinar Logistics

Observers

- Audio is muted and video off throughout by default.
- You are free to join or leave the meeting at any time.
- Email meetings@erg.com if you have any issues.

Reviewers

- Will have audio and video:
  - On during discussions.
  - Off during breaks.

PFBA Peer Review Meeting
DAY 2: Reviewer Discussion

10:30 AM **Facilitator Remarks**

10:35 AM **Reviewer Discussion**

Noncancer Toxicity Values Data Selection (cont.)

- **Charge Question 7** (20 minutes)

Noncancer Toxicity Values Derivation

- **Charge Question 8** (15 minutes)
- **Charge Question 9** (15 minutes)
- **Charge Question 10** (40 minutes)

Cancer Hazard and Toxicity Value(s)

- **Charge Question 5** (10 minutes)
- **Charge Question 11** (10 minutes)

12:25 PM BREAK (30 minutes)

PFBA Peer Review Meeting
DAY 2: Reviewer Discussion (cont.)

12:55 PM	Reviewer Integrative Comments and Discussion
1:35 PM	Individual Reviewer Recommendations
2:35 PM	Closing Remarks
2:45 PM	ADJOURN

Charge Question 7

In addition, for PFBA, an RfD for less-than-lifetime ("subchronic") exposures is derived. No "subchronic" RfC was derived. The study chosen for use in deriving the subchronic RfD is the gestational exposure mouse study by Das et al. (2008) with the RfD based on delayed acquisition of developmental milestones, as indicated by delayed time to vaginal opening, eye opening, and preputial separation in exposed male and female offspring. Is the selection of this study and these effects for the derivation of the subchronic RfD for PFBA scientifically justified?

a) If so, please provide an explanation.
b) If not, please provide an alternative study(ies) 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 7 (cont.)

In addition, for PFBA, an RfD for less-than-lifetime ("subchronic") exposures is derived. No "subchronic" RfC was derived. The study chosen for use in deriving the subchronic RfD is the gestational exposure mouse study by Das et al. (2008) with the RfD based on delayed acquisition of developmental milestones, as indicated by delayed time to vaginal opening, eye opening, and preputial separation in exposed male and female offspring. Is the selection of this study and these effects for the derivation of the subchronic RfD for PFBA scientifically justified?

c) As part of the recommendations 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 PFBA, no "subchronic" RfC is derived. Please comment on this decision.

Charge Question 8

EPA used benchmark dose modeling (USEPA, 2012) to identify points-of-departure (PODs) for oral exposure to PFBA. 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?

Charge Question 9

Appendix A identifies the potential for toxicokinetic differences across species and sexes as a key science issue and lays out a hierarchy for using relevant toxicokinetic data in extrapolating doses between laboratory animals and humans. Given what is known and not known about the potential interspecies differences in toxicokinetics of PFBA, EPA used the ratio of human-to-animal serum clearance values to adjust the POD to estimate a human equivalent dose in the derivation of the respective RfDs.

a) Is applying the ratio of human-to-animal serum clearance values for PFBA scientifically justified? If not, please provide an explanation and detail on a more appropriate approach.

b) Do the methods used to derive toxicity values for PFBA appropriately account for uncertainties in evaluating the toxicokinetic differences between the experimental animal data and humans?

Charge Question 10

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

a) Has uncertainty been adequately accounted for in the derivation of the toxicity values? Please describe and provide suggestions, if needed.

Charge Question 10 (cont.)

b) For uncertainty in interspecies differences (UFA), a value of 3 is applied to extrapolate between effects in laboratory animals and in humans. Although PPARα dependence might support a value of UFA = 1 if that were the sole mode of action, evidence for non-PPARα MOAs is available in the PFBA (and larger PFAS) database. Thus, uncertainty remains regarding the potential differences in sensitivity across species due to the involvement of both PPARα-dependent and PPARα-independent mechanisms. Further, data are lacking to determine with confidence the relative contribution of these competing MOAs. 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 toxicodynamic 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 clearly documented.

Charge Question 10 (cont.)

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

c) For uncertainty in extrapolating from subchronic to chronic exposure scenarios (UFS), a default value of 10 is applied. The assessment concludes there is conflicting evidence on whether effects manifest at lower exposure levels or are more severe at equivalent exposure levels when comparing findings across short-term and subchronic exposure durations. Thus, to account for the potential for some effects to worsen with longer durations of exposure (subchronic vs. short-term) and the lack of data on whether effects from subchronic exposures might worsen in a chronic exposure scenario, a UFS = 10 is applied in the Toxicological Review. Does the provided scientific rationale support this decision? Please explain.

Charge Question 10 (cont.)

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

d) To inform uncertainty in intraspecies variability (UFH), the assessment evaluates and considers the available evidence on potential susceptibility to PFBA 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?

e) Does the provided scientific rationale support the application of the remaining uncertainty factors (UFL, UFH, UFD)? Please explain.

Charge Question 5

The draft assessment concludes there is inadequate evidence to assess carcinogenic potential for PFBA 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, support this conclusion.

Charge Question 11

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

PFBA Peer Review Meeting

BREAK

The meeting will resume at 1:41 PM EST

PFBA Peer Review Meeting
DAY 2: Reviewer Discussion (cont.)

12:55 PM	Reviewer Integrative Comments and Discussion
1:35 PM	Individual Reviewer Recommendations
2:35 PM	Closing Remarks
2:45 PM	ADJOURN