



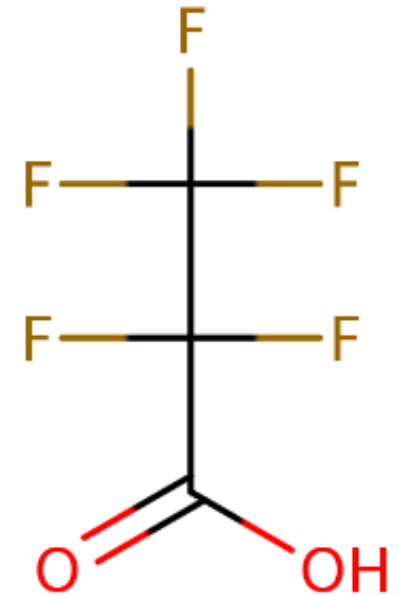
ORD Human Health Toxicity Value for Perfluoropropanoic Acid (PFPrA)

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

Background on PFPrA Request and Need

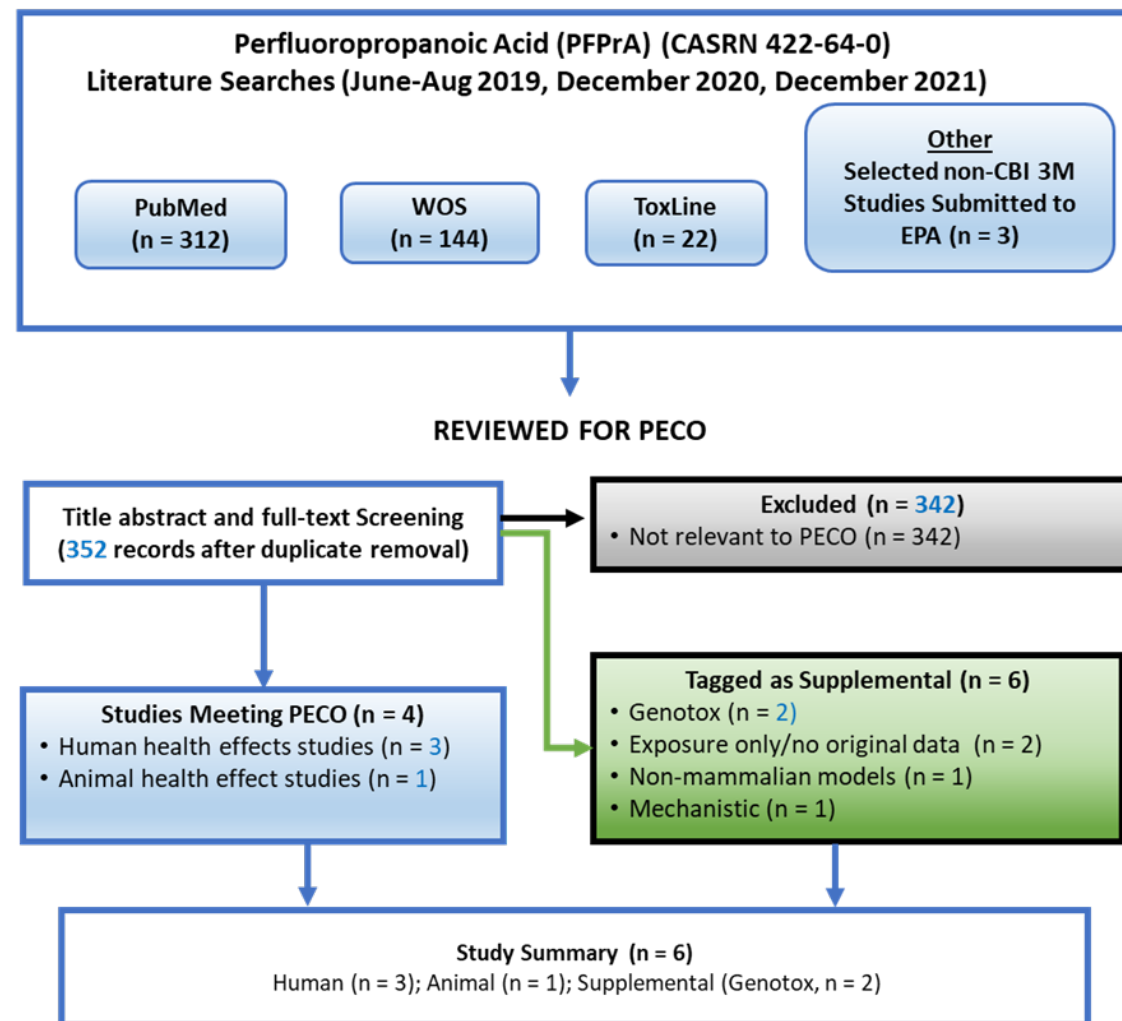
- **Wastewater sampling data around an active manufacturing plant from 2020 to 2021** revealed PFPrA was among the highest PFAS concentrations with unknown toxicological impacts
- **EPA's Office of Enforcement and Compliance Assurance (OECA)** requested technical support and nominated PFPrA for evaluation
- **ORD reviewed publicly available and industry toxicological information on PFPrA** to inform development of a toxicity assessment for site-specific evaluation of chemicals under the Safe Drinking Water Act (SDWA) in support of preliminary water screening of PFAS contamination
- ORD modeled the PFPrA assessment after the Provisional Peer Reviewed Toxicity Value (PPRTV) assessment format and process and leveraged existing literature databases to develop this **fit-for-purpose assessment product**



Literature Search and Screen for PFPrA

- Leveraged **PFAS Systematic Evidence Map**¹ for search and screen
- In addition, non-CBI industry studies were identified
- Documentation in **Health Assessment Workspace Collaborative [HAWC]**:
<https://hawcprd.epa.gov/assessment/100500281/>.
- **Human:** one *medium* confidence (Duan et al., 2020) and two *low* confidence (Song et al., 2018; Li et al., 2017) epidemiological studies
- **Animal:** one *high* confidence repeat-dose (28-day) oral gavage study in rats [conducted by the Chemicals Evaluation and Research Institute, Japan; (CERI, 2002c)].

¹See Carlson et al. (2022) and Radke et al. (2022)



Candidate PFPrA POD_{HEDs} for Chronic RfD derivation

Endpoint	BMDL mg/kg-d	POD type	POD_{HED}^a mg/kg-d	Reference
Increased relative liver weight in adult male rats	6.3	BMDL ₁₀	1.6	CERI (2002c)
Increased hepatocyte hypertrophy in adult male rats	7.9	BMDL ₁₀	2.0	CERI (2002c)
Increased serum ALP in adult male rats	20	BMDL _{1SD}	5.0	CERI (2002c)
Increased serum ALT in adult male rats	28	BMDL _{1SD}	7.0	CERI (2002c)

PFPrA Chronic RfD – Uncertainty and Confidence

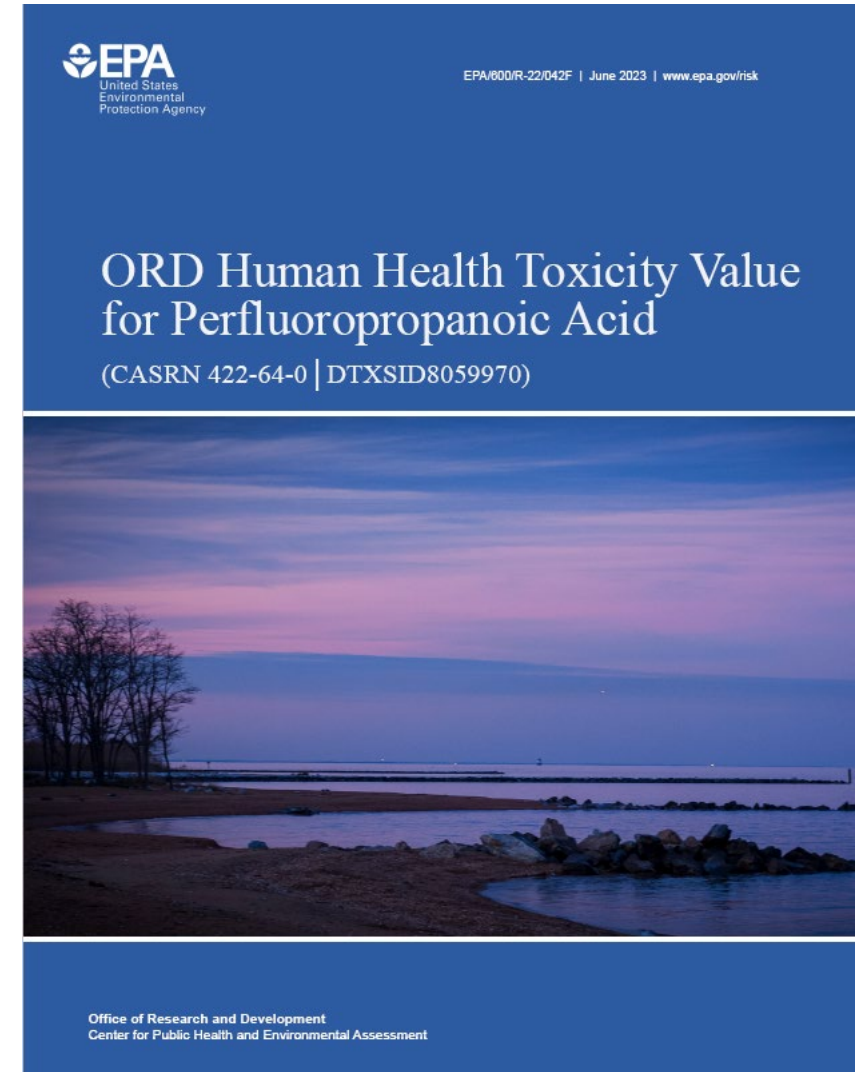
$$\begin{aligned} \text{Chronic RfD} &= \text{POD}_{\text{HED}} \div \text{UF}_C \\ &= 1.6 \text{ mg/kg-day} \div 3,000 \\ &= 0.0005 \text{ or } 5 \times 10^{-4} \text{ mg/kg-day} \end{aligned}$$

UF	Value
UF _A	3
UF _D	10
UF _H	10
UF _L	1
UF _S	10
UF _C	3,000

Confidence Categories	Designation	Discussion
Confidence in study	H	Confidence in the principal study CERI (2002c) is <i>high</i> . The study was performed by an industry/contract lab using an established OECD protocol for 28-day oral exposures in rodents and under GLP conditions. All but one of the toxicity study rating criteria were of “Good” or “High” confidence (see Figure 3 and information available on HAWC).
Confidence in database	L	Confidence in the database for PFPrA is <i>low</i> . The relevant human health assessment database consists of one <i>medium</i> and two <i>low</i> confidence human epidemiological studies, and a single 28-day repeat-dose oral rat study. No longer-duration repeat-dose studies, examining potential systemic, reproductive, developmental or immunotoxicity effects are available following exposure via any route.
Confidence in quantification of the POD _{HED}	M	Confidence in the quantification of the POD and RfD is <i>medium</i> . The POD was based on BMD modeling within the range of the observed data. Dosimetric adjustment of the POD was based on default BW ^{3/4} scaling due to the lack of chemical specific toxicokinetic data (e.g., clearance, half-life).
Confidence in the chronic RfD	L	The overall confidence in the chronic RfD is <i>low</i> and is primarily driven by <i>low</i> confidence in the available database for PFPrA.

Summary

- **ORD developed a human health toxicity assessment for PFPrA**
- **Modeled after PPRTV format and process includes:**
 - Internal peer review by EPA/ORD scientists
 - Contract-led, independent external letter peer review
 - No public comment period
- **Leveraged ORD investments in Systematic Evidence Mapping (SEM).** Literature search, screening, and study quality conducted under PFAS 150/430/Universe SEM effort
- **Example for deriving human health reference values for site-specific evaluation of chemicals under SDWA** and do not require the full Integrated Risk Information System (IRIS) review process





Thank you!

EPA Authors, Contributors, Support, Review

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PFAS SEM Activities

- **PFAS 150 SEM:** Initial effort from EPA ORD's Center for Computational Toxicology and Exposure (CCTE) identified ~150 PFAS chemicals testing a range of PFAS structures, chemistries, and with environmental relevance (Patlewicz et al. 2019, Patlewicz et al. 2022)
- **Expanded PFAS SEM:** Expanded effort that includes additional ~345 PFAS (manuscript submitted)
- **PFAS Universe:** ~15,000 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

Interactive Heat Map: Animal Studies

From: Systematic Evidence Map for Over One Hundred and Fifty Per- and Polyfluoroalkyl Substances (PFAS) Environmental Health Perspectives ([Carlson et al., 2022](#))

PFAS-150 Evidence Map Visualizations by [literature inventory](#)



ReadMe Animal Studies Human Studies

Heat Map

	acute							short-term			subchronic		ch
	mouse	rat	guinea pig	hamster	rabbit	dog	not reported	mouse	rat	not reported	mouse	rat	mouse
Developmental		4						1	12		1	9	
Reproductive									9			7	
Endocrine		1											
Exocrine		7											
Gastrointestinal									6		1	5	
Hematologic									11		1	10	
Hepatic	1	8	1			1		9	17		2	9	
Immune		4						3	10			9	
Lymphatic								1					
Metabolic									3			3	1
Musculoskeletal/Connect.									7			3	
Nervous	2	6						1	9		1	7	
Ocular	1	3							4		1	9	
Renal	1	8						3	11		1	9	
Respiratory	1	12						1	8		1	7	
Systemic/Whole Body	6	50	1	2	2	2	5	10	22		1	11	
Not reported (but NOAEL..)									3	3			
Grand Total	6	53	1	2	2	4	5	11	26	3	2	11	1

Heat Map

	rat	acute guinea pig	dog	short-term		subchronic		chronic	developmental, F1		Grand Total
				mouse	rat	mouse	rat	rat	rat	rabbit	
Cancer			1					2			2
Cardiovascular					2	1	1	2			6
Developmental									2	2	3
Reproductive					2	1	1	2	2	2	7
Endocrine					2			2			4
Gastrointestinal					1			1			2
Hematologic					2	1	1	2			5
Hepatic		1			2	1	1	2		1	7
Immune					2			2			5
Nervous					2	1	1	2			5
Ocular						1	1	2			3
Renal					2	1	1	2			5
Respiratory					2	1	1	2			5
Systemic/Whole Body	1	1		2	2	1	1	2	2	2	9
Grand Total	1	1	1	2	2	1	1	2	2	2	12

References

Bio/dynamics, 1991 (5381154)	2
Dupont Chemicals Inc, 1976 (5380449)	2
Dupont Chemicals Inc, 1990 (5380457)	2
Dupont Chemicals Inc, 1991 (5380491)	2
Dupont Chemicals Inc, 1991 (5381147)	2
Dupont Chemicals Inc, 1992 (5380493)	2
Dupont Chemicals Inc, 1992 (5380494)	2
Dupont Chemicals Inc, 1992 (5381251)	2

Chemicals Evaluated - by Name

1-Butanesulfonic acid, 1,1,2,2,3,3,...	1
1H,1H,2H-Perfluorocyclopentane	6
1H,1H,5H-Perfluoropentanol	1
2-Chloro-1,1,1,2-tetrafluoroethane	12
3-Methoxyperfluoro(2-methylpent...	3
3,3,4,4,5,5,6,6-Nonafluorohexene	5

Chemicals Evaluated - by CASRN

2837-89-0	12
Grand Total	12

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

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.

Study Details

Health Syst..	Study Design	Route	Species	Sex	Short Citation
Hepatic	short-term	inhalation	rat	both	Dupont Chemicals Inc, 1991 ECHA, 2019
				male	Dupont Chemicals Inc, 1976
				male	Iwase et al., 2006 Upham et al., 2009

Study Details

Health System	Study Design	Route	Species	Sex	Short Citation
Cancer	chronic	inhalation	rat	both	Malley et al., 1998 PAFT, 1995
				male	Dupont Chemicals Inc, 1992
Cardiovascular	acute	inhalation	dog	male	Dupont Chemicals Inc, 1992
	short-term	inhalation	rat	both	Dupont Chemicals Inc, 1991
				male	Dupont Chemicals Inc, 1976

Chemicals Evaluated - by DTXSID

DTXSID7029245	12
Grand Total	12

