# CRD Human Health Toxicity Value for Perfluoropropanoic Acid (PFPrA)

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### 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-forpurpose assessment product



### Literature Search and Screen for PFPrA

- Leveraged PFAS Systematic Evidence Map<sup>1</sup> for search and screen
- In addition, non-CBI industry studies were identified
- Documentation in Health Assessment Workspace Collaborative [HAWC]: <u>https://hawcprd.epa.gov/assessment/100500281/</u>).
- **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)].

<sup>1</sup>See Carlson et al. (2022) and Radke et al. (2022)



### Candidate PFPrA POD<sub>HEDs</sub> for Chronic RfD derivation

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

### PFPrA Chronic RfD – Uncertainty and Confidence

Chronic RfD =  $POD_{HED} \div UF_{C}$ = 1.6 mg/kg-day  $\div$  3,000 = 0.0005 or 5  $\times$  10<sup>-4</sup> mg/kg-day

UF	Value
UF <sub>A</sub>	3
UF <sub>D</sub>	10
UF <sub>H</sub>	10
UF <sub>L</sub>	1
UF <sub>s</sub>	10
UF <sub>C</sub>	3,000

Confidence Categories	Designation	Discussion
Confidence in study	Н	Confidence in the principal study <u>CERI (2002c)</u> 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 <sub>HED</sub>	М	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 <sup>3/4</sup> 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



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Office of Research and Development Center for Public Health and Environmental Assessment

## **₽EPA**

### 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 (<u>https://comptox.epa.gov/dashboard/chemical-lists/PFASSTRUCTV5</u>)
- 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 (<u>Carlson et al., 2022</u>)



Notes: Column totals, row totals, and Grand Totals indicate total numbers of distinct references. Some ECHA studies sources may be counted as multiple referei

were reported in the dossier. Care was taken during categorization and extraction to ensure that endpoints were not repeated from overlapping ECHA summari 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 Dotails												
Study Details			Study Details	;	Chemicals Evaluated - by DTXSID							
Health Syst Study Design	Route	Species	Sex	Short Citation	_				_			
Hepatic short-term	inhalation	rat	both	Dupont Chemicals Inc, 1991	Health System	Study Design	Route	Species	Sex	Short Citation	DTXSID7029245	12
				ECHA, 2019	Cancer	chronic	inhalation	rat	both	Malley et al., 1998	Grand Total	12
			male	Dupont Chemicals Inc, 1976						PAFT, 1995		
	oral (diet)	rat	male	Iwase et al., 2006	Cardiovascular	acute	inhalation	dog	male	Dupont Chemicals Inc, 1992		
				Upham et al., 2009		short-term	inhalation	rat	both	Dupont Chemicals Inc, 1991		
									male	Dupont Chemicals Inc, 1976		

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### Interactive Heat Map: Epi Studies

From: Epidemiology evidence for health effects of 150 per- and polyfluoroalkyl substances: A systematic evidence map Environmental Health Perspectives (<u>Radke et al., 2022</u>)

Epidemiological Studies Examining Exposure to PFAS																			
Overview of Epidemiological Evidence Base							CAS	S-RN	Outc	ome									
Overview of Epidemiological Evidence Base Expand Health Effect Category to Outcome by clicking the small [+] icon				CAS-RN Outcome			Jtcome			Outcome Selection and Exposure Methods/R Performance Methods Presentativ			ts Confounding	Analysis	Sensitivity	Selective Reporting	Overall Study Confidence		
Health Effect Category Cancer	Outcome Bladder cancer Breast cancer Cancer Liver cancer Prostate cancer rr Adiposity Atherosclerosis	Adults Adu Adults chi 7 1 1 2	Adults and chil.     Children (18 yrs)     Pregnant (18 yrs)     Grand Total     Chemical     References       7     1     1     1     PFDDA     1     Averina et al. (20 C. Donat-Vargas       7     1     1     1     PFHpA     2       7     1     1     3     PFDSA     1       1     1     1     1     Det pol     1       1     1     1     3     Det pol     1       2     1     1     1     5     Det pol				rences a et al. (202: at-Vargas et ensen et al. ( ensen et al. ( y <b>Design</b> control t	1)-741 3 ral. (20 3 (2016) 3 (2019) 3 8 3 3	3N Air Air Ait Ba Ba Ba Ba Ba Ba	/ (2000)-5412700 muzi et al. (2019)-5387078 muzi et al. (2020)-6512125 t Bamai et al. (2020)-6833636 erina et al. (2021)-7410155 ch et al. (2015)-3981559 ch et al. (2015)-3981559 ch et al. (2016)-3981534 injabi et al. (2020)-6833613 io et al. (2017)-3860099 irrett et al. (2015)-2850382 irg et al. (2015)-2851002									
	Birth defects Blood pressure Cardiovascular Gestational hyp Preeclampsia Serum lipids Ventricular geo Null	6 4 . 1 . 1 . 1	1 3 1 4 4	1 1 2 1 3	1 10 3 2 1 17 1 1	Grand Total 17 Overall Study Confidence Some references have more than one overall High/Medium 10 Low 12 Uninformative 1	Cross- Grand	-sectional   Total <i>rating.</i>	11 17	Be Re (Al Qu (Al Ra	rg et al. (2016)-3350759 rk et al. (2014)-2713574 ralth Effect Category II) ticome II) ting	Rationale	Confidence Label*	Confidence Detail Sour-multiverite early pregnancy wit conditional specific analyses Flastin pe	5 ogistic regression h GH, PE, and over ation methods was tragression (detai	was used to examinate applied to handlet	re associations de models. Multiple i the missing data o	mputation with ful all covariates use	evers m ly d for the onsures
Epidemiolo Reference Averina et al. (2021)	gical Study De Sub- Chemical popul PFHpA	ation Outcom Serum li	e ipids	Measured Effect/Endpoints Serum lipids (TC, LC HDL, TG) (nmol/L)	N )L, 940	Comparison regression coefficient (per 1-log10 ng/mL increase)	Effect Estimate Null	e Ci Lcl Null	Ci Uci Null 🗲		II)   AS-RN  II)  Complete I			within models, and were In-transforme restricting to wome with normal prepre- reported as ORs and	restricted cubic sp d because of skewr n enrolled at ≤ 16 v gnancy BM, or by a d 95% confidence ir	ine regression was less.Sensitivity and weeks' gestation, ri dding the season o itervals.	used to assess no alyses included sea estricting to nullip f birth, or for comp	n-linear relationshi isonal variation of i arous women and v lete case analyses.	ips. PFASs HDP, or vomen Results
-	PFHpS PFUnDA	Serum li	ipids ipids	Serum lipids (TC, LL HDL, TG) (nmol/L) Apolipoprotein A1 (g/L) Apolipoprotein B (g/L)	940 940 940	regression coefficient (per 1-log10 ng/mL increase) regression coefficient (per 1-log10 ng/mL increase) regression coefficient (per 1-log10 ng/mL increase)	Null 0.10 0.05	Null 0.05 0.01	Null 6 0.15 6 0.09 6	OU 8:2 NE PF PF PF	2-FTOH 1 EtFOSE 1 EDDA 1 EDBS 2 HppA 55			Good. Pearson corre log2-transformed. I binary classification fold increase in each chosen a priori as th constituity analysis	elations between d Aultivariate logisti n of total, internali: n of the prenatal PF ne cut-off to indicat	ifferent SDQ measu c regression was u zing, and externaliz AS exposure; an ou e difficulties. Cut-c- tho outcome class	ures were evaluate sed to estimate the ing difficulties in t itcome score above off scores are show disction. In additio	d. PFAS concentrat odds ratios and 9 the offspring accord the 90% percentil n in the supplemen-	ions were 5% CI for ding to 2- e was t. A