

A scenic view of a lake at sunset. The sky is filled with orange and yellow clouds, reflecting on the calm water. In the foreground, the bow of a wooden canoe is visible, pointing towards the center of the frame. The shoreline is lined with dense green trees.

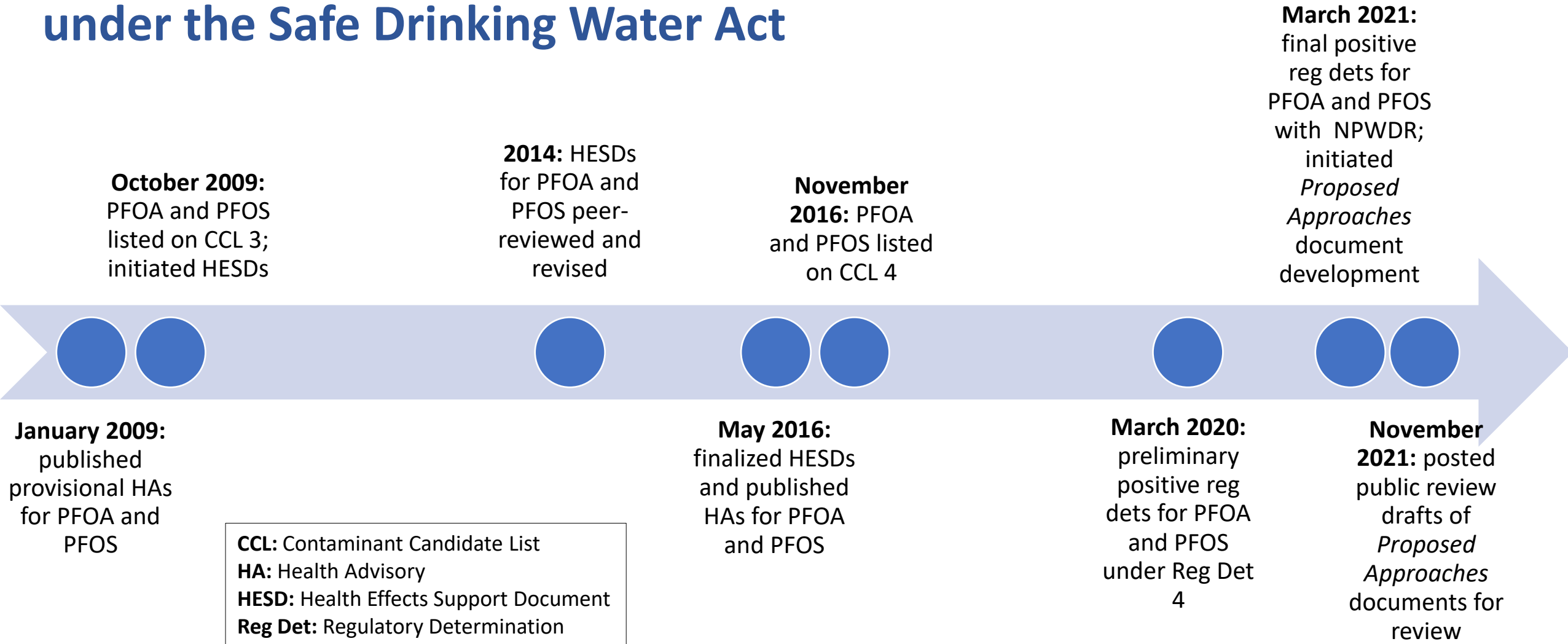
Proposed Approaches for Developing Maximum Contaminant Level Goals for Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonic Acid (PFOS) in Drinking Water

SAB PFAS Panel Meeting
December 16, 2021
Brittany Jacobs, Ph.D.

Presentation Overview

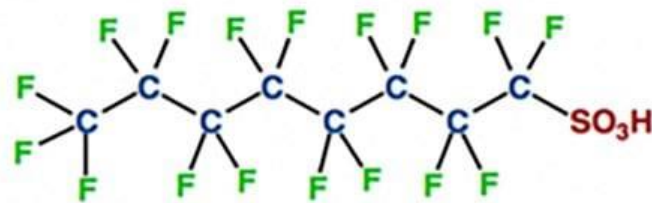
- **Background.** History of PFOA and PFOS under SDWA, Purpose
- **Approach.** Procedures/Guidance, Systematic Literature Review
- **Results.** Health Effects Literature Search and Review; Update to TK Models; POD_{HED} Derivation
- **Draft Input Values for Deriving MCLGs.** Candidate RfD Selection, CSF Derivation, Cancer Classifications, and RSCs
- **Conclusions.**

EPA's Assessment of PFOA and PFOS under the Safe Drinking Water Act

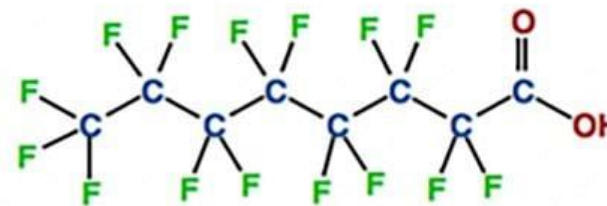


Purpose and Scope of the Proposed Approaches Drafts

- Purpose: Support development of the Maximum Contaminant Level Goals for the PFAS National Primary Drinking Water Regulation (NPDWR)
- Scope:
 - Synthesis of the available toxicological and epidemiological health effects information after exposure to PFOA and PFOS
 - Derive inputs – toxicity values and relative source contribution - needed to support maximum contaminant level goal (MCLG) development
 - These documents do not include derivation of the MCLGs.



PFOS - perfluorooctanesulfonic acid



PFOA - perfluorooctanoic acid

Document Development Approach

- 1) Formation of cross-EPA science Working Group (WG) to leverage EPA scientific expertise and tools
 - Led by OST scientists with active participation from across EPA (OW, ORD, OCHP, OLEM, OCSPP)
 - 6 subgroups tasked with development of different areas of interest depending on expertise (>25 scientists from across 4 EPA offices participated)
- 2) Action Development Process (ADP) workgroup for the National Primary Drinking Water Regulation (NPDWR)
- 3) Use of the best available science
 - Used systematic review methods to conduct literature screens and study quality evaluations (U.S. EPA, 2020)
 - Used cutting-edge software to conduct reviews, extract data, study quality evaluation, model data, and develop visualizations (DistillerSR, *litstream*TM, HAWC, Tableau, BMD Software v3.2)
 - Quantitatively considered epidemiological studies
- 4) Consistent with EPA human health risk assessment guidance and methods to derive -
 - Non-cancer reference doses (RfDs) (U.S. EPA, 2002; U.S. EPA, 2012; U.S. EPA, 2019)
 - Cancer Classifications and cancer slope factors (CSFs, if applicable) (U.S. EPA, 2005; U.S. EPA, 2019)

Methodologies – Literature Identification & Review

- Incorporation of Data from 2016 HESDs into 2021 Drafts
 - 2016 HESDs predate current IRIS systematic review process:
 - Literature searches included literature through 2015
 - Study quality was evaluated using current EPA risk assessment best practices (U.S. EPA, 2002) at that time
 - Therefore, many of the studies described in 2016 HESDs were summarized qualitatively in the 2021 *Approaches* drafts
 - New study quality evaluation method (i.e., HAWC) was only performed for the animal studies that were considered for RfD development in 2016; these studies were considered quantitatively
- Updated Systematic Review, 2013-Sept. 2020
 - Health Effects literature:
 - Literature sources included peer-reviewed journal articles, “gray” literature, and manual review of references cited in ATSDR *Toxicological Profile for Perfluoroalkyls* (ATSDR, 2021) and CalEPA’s *Proposed PHGs* (CalEPA, 2021)
 - Consistent with draft IRIS Handbook (U.S. EPA, 2020), used ORD approach for identifying, evaluating study quality, and synthesizing literature
 - Human exposure literature for RSC development:
 - Literature sources included peer-reviewed journal articles and “gray” literature
 - Used systematic review method described in Deluca et al. (2021) modified from draft IRIS Handbook (U.S. EPA, 2020)

Methodologies – PECO

- 3 PECO statements to identify -

1) Dose-response studies and PBPK models

- Initial screen tagged toxicokinetic and mechanistic studies as supplemental (see below)

2) Mechanistic data and conduct relevancy screens

- Performed a data – lite extraction on 405 studies

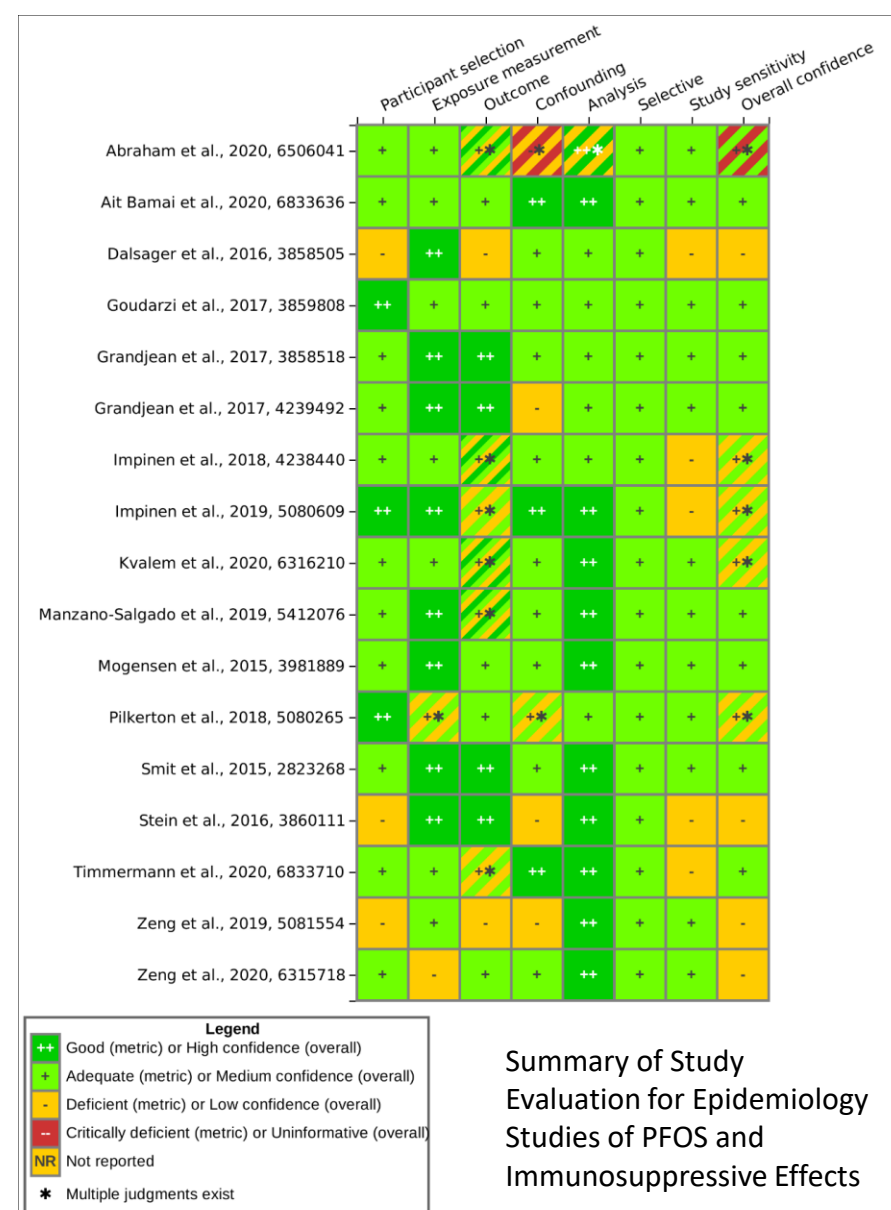
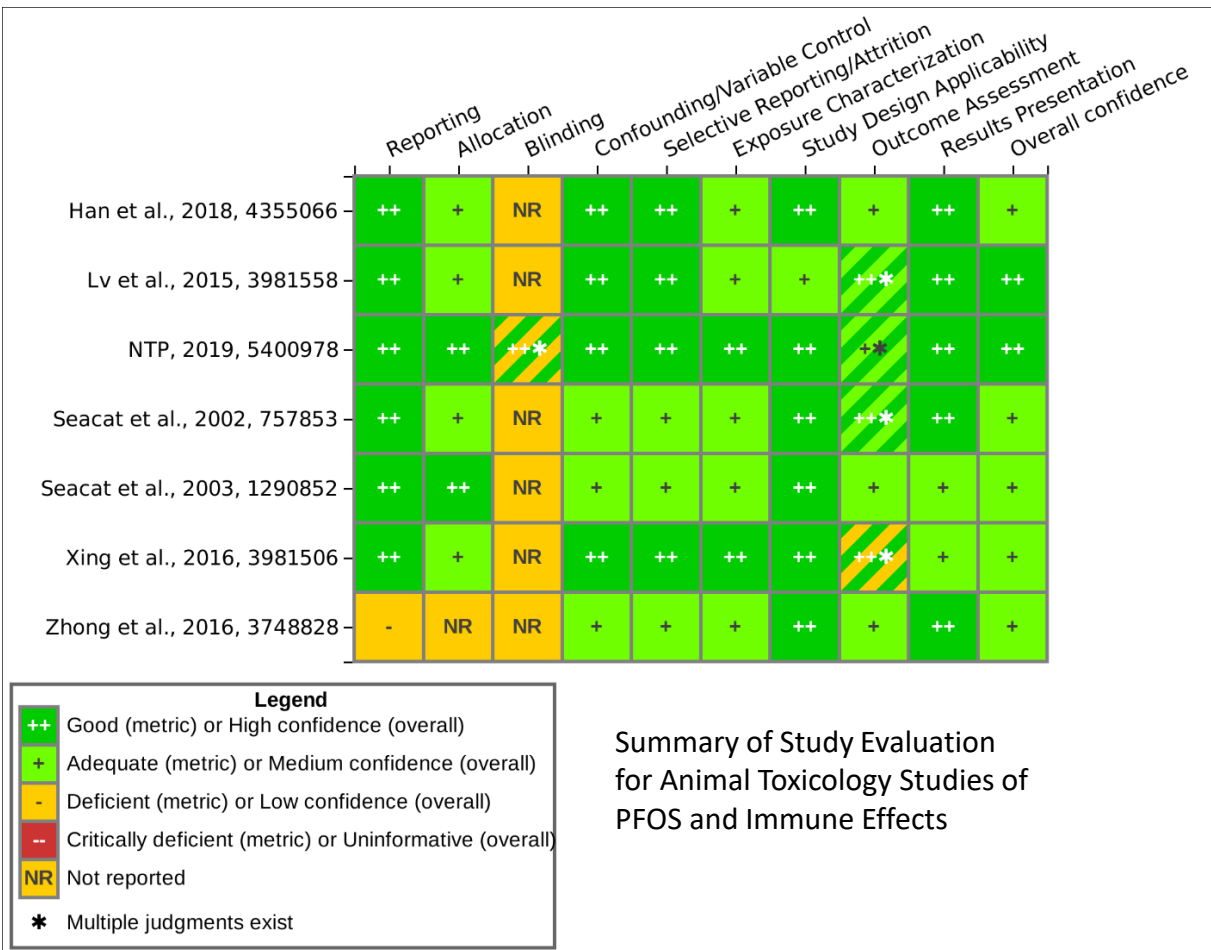
3) Toxicokinetic data (ADME) and conduct relevancy screens

- Performed a data-lite extraction on 114 studies
- Developed an updated ADME summary

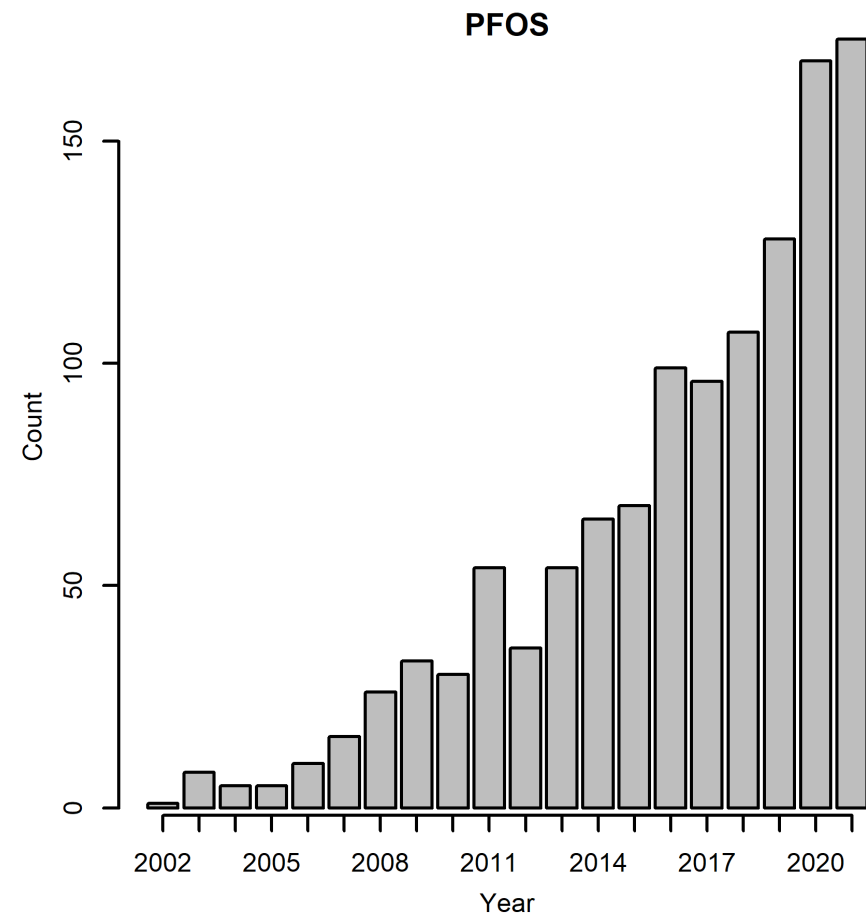
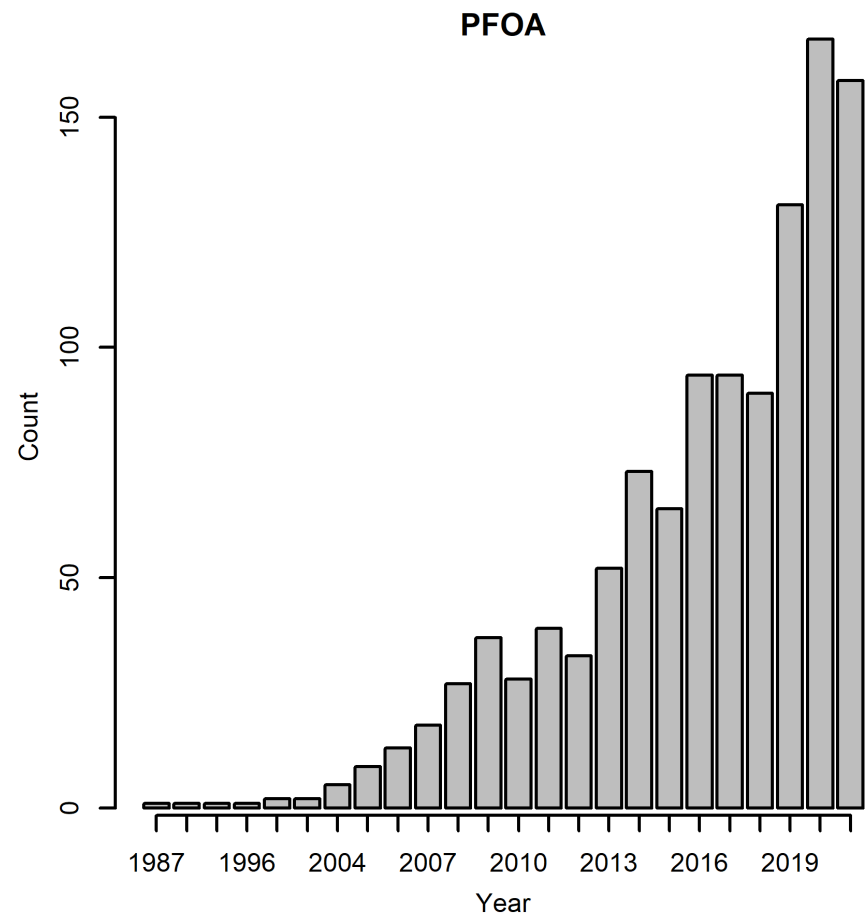
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PECO Element	Inclusion Criteria
Population	<p>Human: Any population and life stage (occupational or general population, including children and other sensitive populations).</p> <p>Animal: Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages). In vitro/cell studies or in silico/modeling toxicity studies should be tagged as supplemental</p>
Exposure	<p>Relevant forms: PFOA (CAS number 335-67-1). Other names: perfluorooctanoate, perfluorooctanoic acid, perfluorooctanoic acid, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoic acid, Pentadecafluoro-1-octanoic acid, Pentadecafluoro-n-octanoic acid, Octanoic acid, pentadecafluoro-, Perfluorocaprylic acid, Pentadecafluorooctanoic acid, perfluoroheptanecarboxylic acid</p> <p>PFOS (CAS number 1763-23-1). perfluorooctane sulfonate, perfluorooctanesulfonic acid, perfluorooctane sulfonic acid, perfluorooctane sulphonate, perfluorooctane sulfonate, perfluorooctanyl sulfonate, Heptadecafluorooctane-1-sulphonic, Heptadecafluoro-1-octanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-octanesulfonic acid</p> <p>Human: Any exposure to PFOA or PFOS via oral routes. Other exposure routes, including inhalation, dermal or unknown/multiple routes, will be tracked during title and abstract screening and tagged as “potentially relevant supplemental information.”</p> <p>Animal: Any exposure to PFOA or PFOS via oral routes. Other exposure routes, including inhalation, dermal, injection or unknown/multiple routes, will be tracked during title and abstract screening and tagged as “potentially relevant supplemental information.” Studies involving exposures to mixtures will be included only if they include exposure to PFOA OR PFOS alone. Studies with less than 28 days of dosing, with the exception of reproductive or developmental studies, should be tagged as supplemental.</p>
Comparator	<p>Human: A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of PFOA or PFOS, or exposure to PFOA or PFOS for shorter periods of time. Case reports and case series will be tracked as “potentially relevant supplemental information.”</p> <p>Animal: A concurrent control group exposed to vehicle-only treatment or untreated control.</p>
Outcome	All health outcomes (both cancer and noncancer).
PBPK Models	Studies describing physiologically-based pharmacokinetic (PBPK) models will be included

Methodologies – Study Quality Evaluation

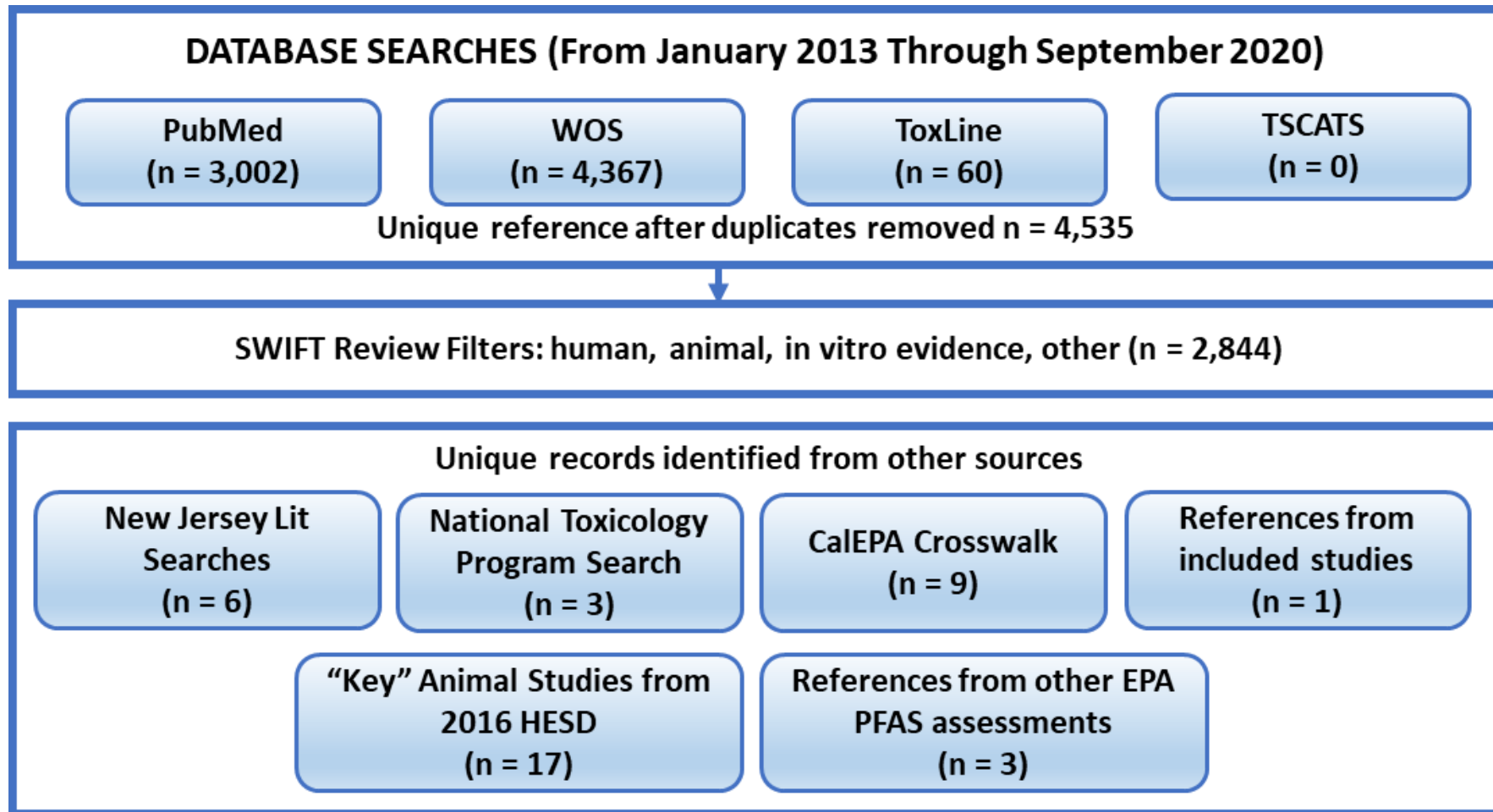


PFOA and PFOS Health Effects Literature: Increases Over Time

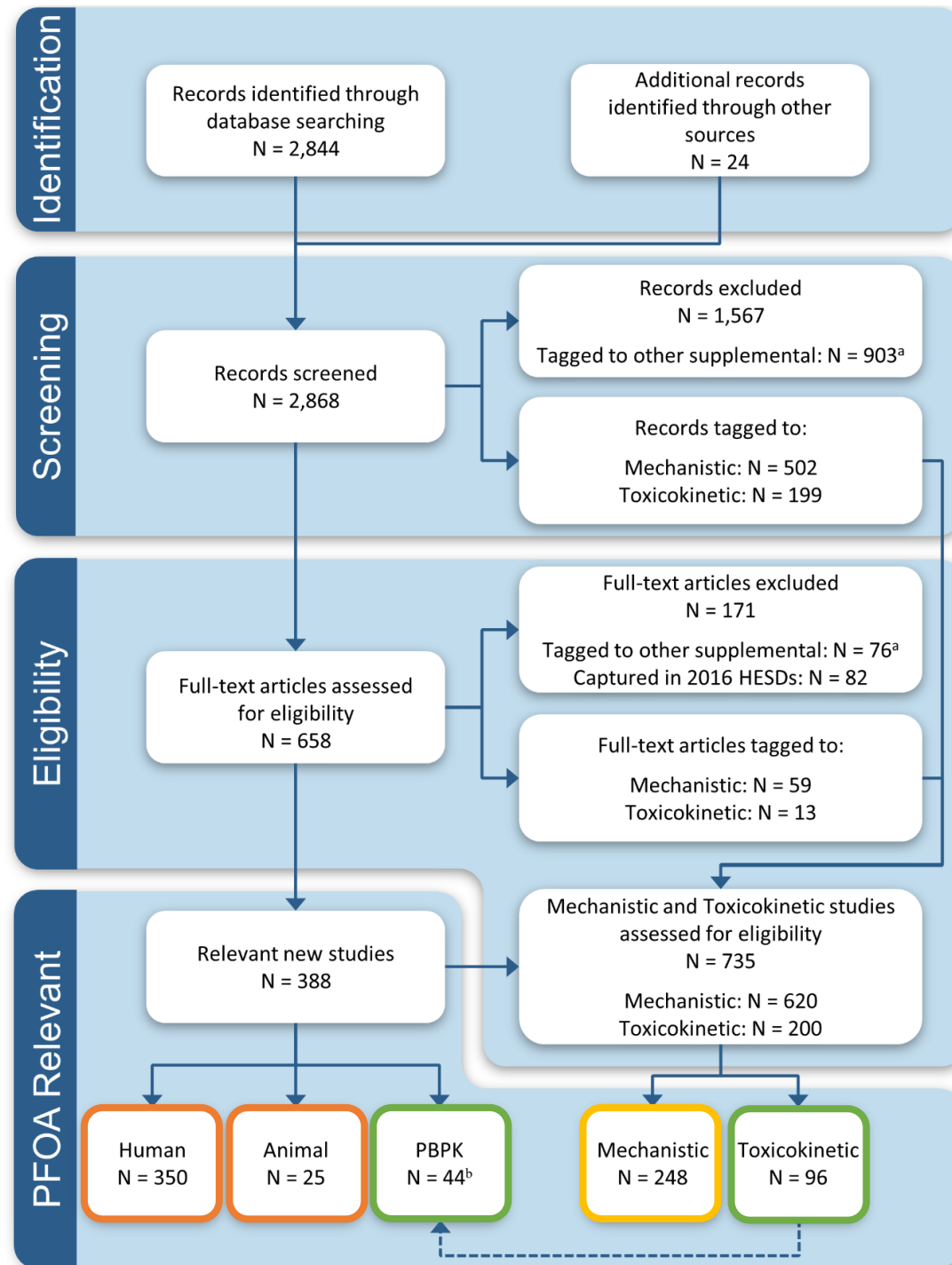


Source: PubMed health effects PFOA and PFOS literature search results

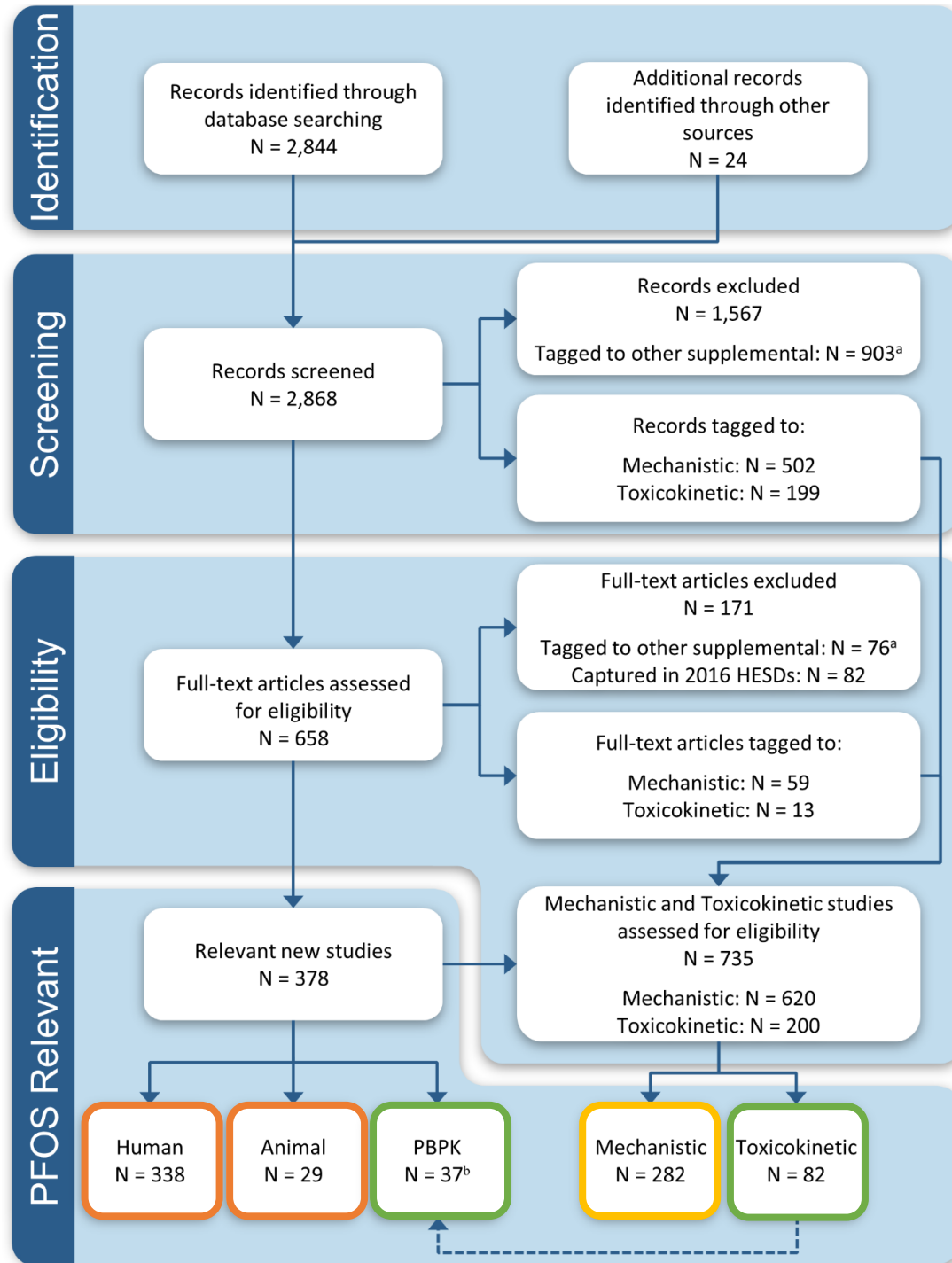
Results – Updated Literature Search



Results – PFOA Systematic Literature Review



Results – PFOS Systematic Literature Review



Results – Systematic Literature Review

	PFOA	PFOS
# of new animal tox studies	25 relevant studies	29 relevant studies
# of new human epi studies	350 relevant studies	338 relevant studies
# of new cancer studies – epi; tox	13 (8 medium or high quality); 1	11 (8 medium or high quality); 0
Health effects observed	immune, developmental, cardiovascular, hepatic, reproductive, nervous, endocrine, and metabolic effects and cancer	immune, developmental, cardiovascular, reproductive, endocrine, metabolic, and hepatic effects and cancer
# of new PK or PBPK studies	44 relevant studies	37 relevant studies

PFOA Noncancer Studies: Critical Studies & Endpoint Selection

Endpoint	Study Reference; Study Quality	Strain/Species/Sex
Immune Effects		
Reduced Antibody Concentrations for Diphtheria and Tetanus in Children	Developmental Studies Grandjean et al., 2012, 1248827; Grandjean et al., 2017, 3858518; Grandjean et al., 2017, 4239492; Budtz-Jørgensen & Grandjean, 2018; Medium confidence	Human (male and female children)
Reduced immunoglobulin M (IgM) Response	Adult Studies Loveless et al., 2008, 988599; DeWitt et al., 2008, 1290826; Medium confidence	C57BL/6N mice (females), Crl:CD-1(ICR)BR mice (males)

Developmental Effects		
Decreased Birth Weight	Chu et al., 2020, 6315711; Govarts et al., 2016, 3230364; Sagiv et al., 2018, 4238410; Starling et al., 2017, 3858473; Wikström et al., 2020, 6311677; High confidence	Human (male and female infants)
Decreased Offspring Survival	Song et al., 2018, 5079725; Medium confidence	Kunming mice (F ₁ males and females)
Decreased Fetal Body Weight	Li et al., 2018, 5084746; Medium confidence	Kunming mice (F ₁ males and females)
Developmental Scores for the Mammary Gland	Macon et al., 2011, 1276151; Medium confidence	CD-1 mice (F ₁ females)
Delayed Time to Eye Opening	Lau et al., 2006, 1276159; Medium confidence	CD-1 mice (F ₁ males and females)
Increased Placental Lesions	Blake et al., 2020, 6305864; Medium confidence	CD-1 mice (parental females)

PFOA Noncancer Studies: Critical Studies & Endpoint Selection (cont.)

Endpoint	Study Reference; Study Quality	Strain/Species/Sex
Serum Lipid (Cardiovascular) Effects		
Increased Total Cholesterol	Dong et al., 2019, 5080195; Medium confidence	Human (male and female)
Hepatic Effects		
Necrosis (focal, individual cell, both) in the Liver	Loveless et al., 2008, 7330145; Medium confidence, NTP, 2020, 7330145; High confidence	Crl:CD-1(ICR)BR mice (males), Sprague-Dawley rats (males)
Endocrine Effects		
Increased TSH	NTP, 2019, 5400977; High confidence	Sprague-Dawley rat (females)
Decreased Free T4	NTP, 2019, 5400977; High confidence	Sprague-Dawley rats (male)
Reproductive Effects		
Reduced Number of Leydig Cells	Song et al., 2018, 5079725; Medium confidence	Kunming mice (male)
Increased Length of Diestrus	Zhang et al., 2020, 6505878; Medium confidence	ICR mice (female)

PFOA Cancer Study & Endpoint Selection

Tumor Location/Type	Study Reference; Study Quality	Strain/Species/Sex
Renal Cell Carcinomas (RCCs)	Shearer et al. (2021) 7161466; Medium confidence	Human, male and female 55-74 years
Leydig Cell Adenomas in the Testes (LCTs)	Butenhoff et al., 2012, 2919192, Medium confidence	Male Sprague-Dawley
Hepatocellular Adenomas or Carcinoma	NTP, 2020, 7330145, High confidence	F1 Male Sprague-Dawley Rats, Perinatal (300 PPM) and Postweaning Exposure
Pancreatic Acinar Cell Adenoma (PACTs)	NTP, 2020, 7330145, High confidence	F1 Male Sprague-Dawley Rats, Perinatal (300 PPM) and Postweaning Exposure

PFOS Noncancer Critical Study & Endpoint Selection

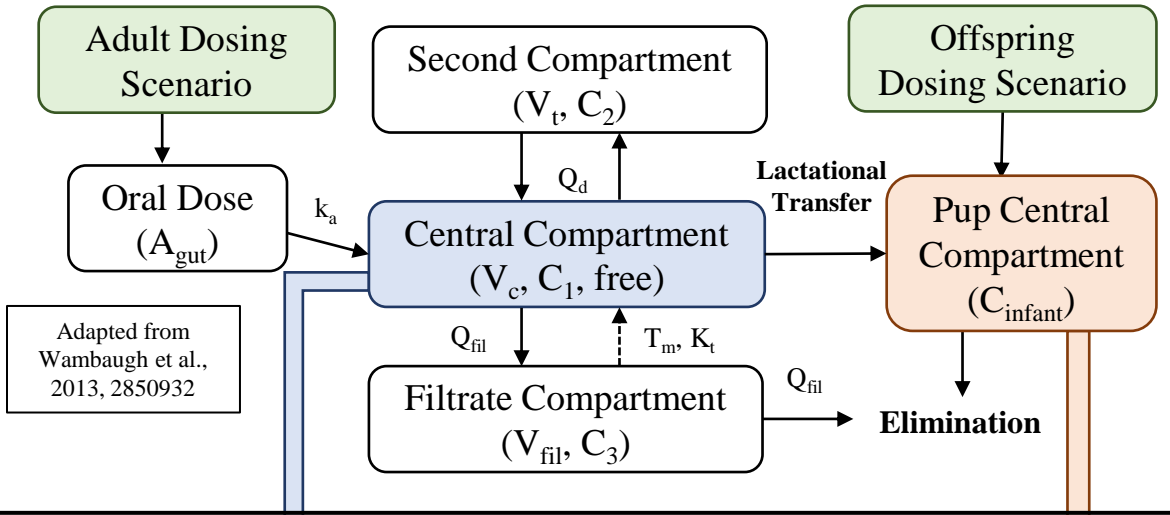
Endpoint	Study Reference; Study Quality	Strain/Species/Sex
Immune Effects		
Reduced Antibody Concentrations for Diphtheria and Tetanus	Developmental Immune Studies Grandjean et al., 2012, 1248827; Grandjean et al., 2017, 3858518; Grandjean et al., 2017, 4239492; Budtz-Jørgensen & Grandjean, 2018; Medium confidence	Human (male and female children)
Extramedullary Hematopoiesis in the Spleen	Adult Immune Studies NTP 2019, 5400978; High confidence	Sprague-Dawley Rats, male and female
Decreased Plaque Forming Cell (PFC) Response to SRBC	Adult Immune Studies Zhong et al., 2016, 3748828; Medium confidence	C57BL/6 Mice, F ₁ males
Developmental Effects		
Decreased Birth Weight	Chu et al., 2020, 6315711; Sagiv et al., 2018, 4238410; Starling et al., 2017, 3858473; Wikström et al., 2020, 6311677; High confidence	Human, male and female infants
Decreased Fetal Body Weight	Lee et al., 2015, 2851075; Medium confidence	CD-1 Mice, F ₁ males and females
Decreased Pup Body Weight	Luebker et al., 2005, 757857; Medium confidence	Sprague-Dawley Rats, F ₁ male and female
Increased Number of Dead Fetuses	Lee et al., 2015, 2851075; Medium confidence	CD-1 Mice, females
Serum Lipid (Cardiovascular) Effects		
Increased Total Cholesterol	Dong et al., 2019, 5080195; Medium confidence	Human (male and female)

PFOS Noncancer Critical Study & Endpoint Selection (cont.)

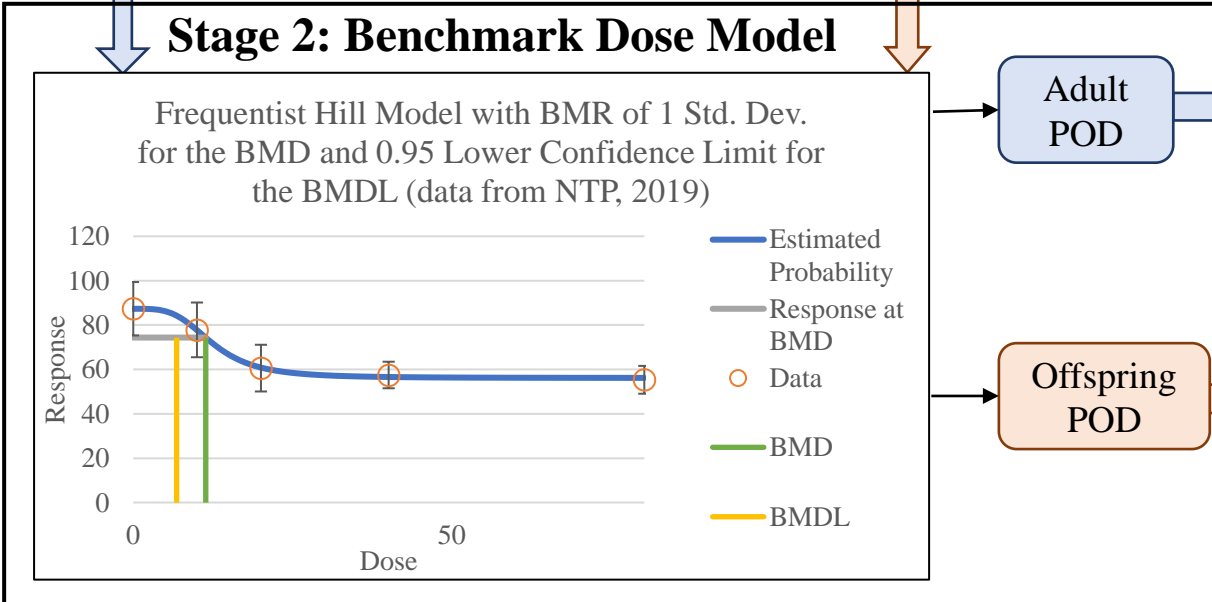
Endpoint	Study Reference; Study Quality	Strain/Species/Sex
Hepatic Effects		
Individual Cell Necrosis in the Liver	Butenhoff et al., 2012, 1276144; High confidence	Sprague-Dawley Rats, females
Endocrine Effects		
Decreased Free T4	NTP, 2019, 5400978; High confidence	Sprague-Dawley Rats, male and female
Decreased Total T4	NTP, 2019, 5400978; High confidence	Sprague-Dawley Rats, male and female
Decreased Total T3	NTP, 2019, 5400978; High confidence, Seacat et al., 2002, 757853; Medium confidence	Sprague-Dawley Rats, male and female; Cynomolgus Monkeys, male and female
Nervous System Effects		
Decreased Performance on the Object Location Recognition Memory Test	Mshaty et al., 2020, 6833692; Medium confidence	C57BL/6J Mice, F ₁ males

Results – Modeling Workflow

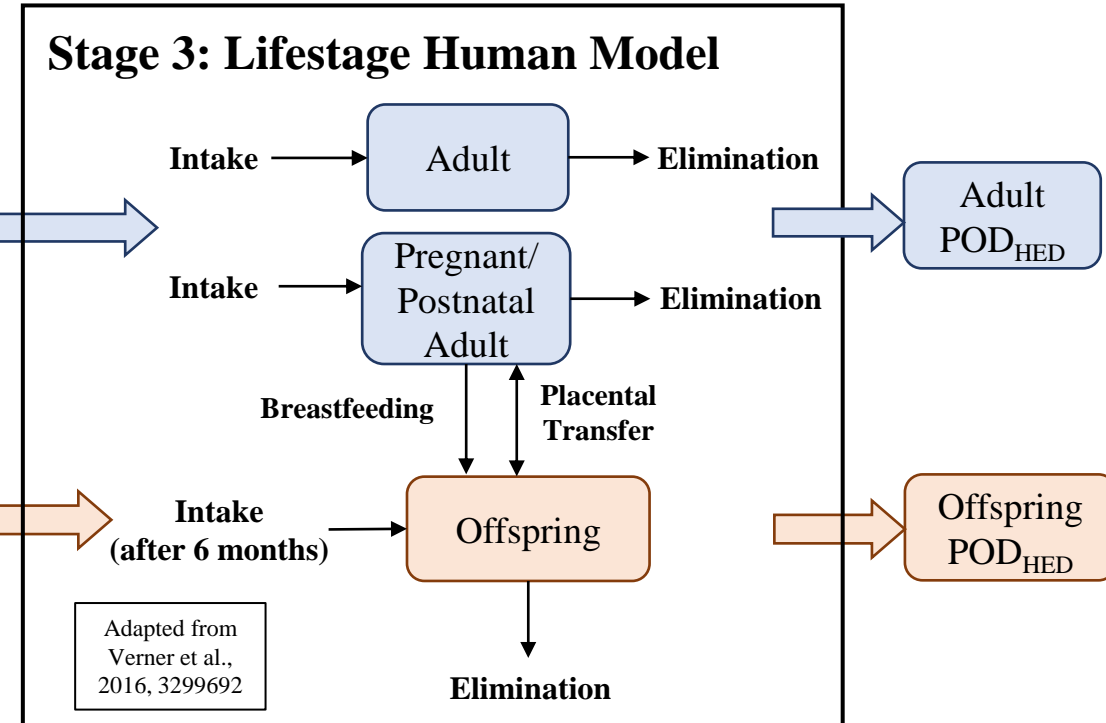
Stage 1: Lifestage Animal Model



Stage 2: Benchmark Dose Model



Stage 3: Lifestage Human Model



Results – Selected Toxicokinetic Modeling Approaches

- Subject Matter Experts evaluated new literature identified in the updated literature search as well as literature discussed in the 2016 HESDs
- Animal TK Approach –
 - Used Wambaugh et al. (2013) model (previously selected in 2016 HESDs) to predict dose metrics associated with NOAELs and LOAELs identified from animal studies
 - Updated Wambaugh model to account for gestation, lactation, and postweaning (Kapraun et al., *in prep.*)
- Human TK Approach –
 - Used Verner et al. (2016) one-compartment model to calculate a human equivalence dose from PODs (NOAEL, LOAEL, BMDL) from selected animal studies and simulate chronic doses resulting in internal PODs obtained from selected epidemiological studies
 - Updated Verner model to use bodyweight curves and incorporate new literature on PFOA/PFOS concentrations in cord blood and breastmilk

PFOA Noncancer POD_{HED} Derivation

Endpoint	Species, Strain, Sex	POD Type, Model	POD _{HED} (mg/kg-day)	Candidate RfD (mg/kg-day)	Study Reference; Study Quality
Immune Effects					
Decreased serum anti-tetanus antibody concentration in children	Human epidemiology, male and female	BMDL _{5RD} , piecewise	1.49×10^{-8}	1.5×10^{-9}	Grandjean, (2012, 1248827); Grandjean, (2017, 3858518); Grandjean, (2017, 4239492); Budtz-Jørgensen and Grandjean (2018); Medium confidence
Decreased serum anti-diphtheria antibody concentration in children	Human epidemiology, male and female	BMDL _{5RD} , piecewise	1.75×10^{-8}	1.8×10^{-9}	Grandjean, (2012, 1248827); Grandjean, (2017, 3858518); Grandjean, (2017, 4239492); Budtz-Jørgensen and Grandjean (2018); Medium confidence
Decreased IgM response to SRBC	C57BL/6N Mice, Females Study 1	BMDL _{1SD} , Polynomial 4	3.20×10^{-3}	Not calculated	Dewitt et al., 2008, 1290826, Medium
Decreased IgM response to SRBC	C57BL/6N Mice, Females Study 2	BMDL _{1SD} , Hill	6.19×10^{-3}	Not calculated	Dewitt et al., 2008, 1290826, Medium
Decreased IgM response to SRBC	CD-1(ICR)BR Mice, Males	BMDL _{1SD} , Exponential 3	1.09×10^{-2}	Not calculated	Loveless et al., 2008, 988599, Medium

PFOA Noncancer POD_{HED} Derivation

Endpoint	Species, Strain, Sex	POD Type, Model	POD _{HED} (mg/kg-day)	Candidate RfD (mg/kg-day)	Study Reference; Study Quality
Developmental Effects					
Decreased Birth Weight	Human epidemiology, male and female	BMDL _{5RD} , Hybrid	1.00 x 10 ⁻⁶	1.0 x 10 ⁻⁷	Chu et al., 2020, 6315711, High Confidence
Decreased Birth Weight	Human epidemiology, male and female	BMDL _{5RD} , Hybrid	4.62 x 10 ⁻⁸	4.6 x 10 ⁻⁹	Govarts et al., 2016, 3230364, High Confidence
Decreased Birth Weight	Human epidemiology, male and female	BMDL _{5RD} , Hybrid	4.74 x 10 ⁻⁶	4.7 x 10 ⁻⁷	Sagiv et al., 2018, 4238410, High Confidence
Decreased Birth Weight	Human epidemiology, male and female	BMDL _{5RD} , Hybrid	9.47 x 10 ⁻⁷	9.5 x 10 ⁻⁸	Starling et al., 2017, 3858473, High Confidence
Decreased Birth Weight	Human epidemiology, male and female	BMDL _{5RD} , Hybrid	1.10 x 10 ⁻⁶	1.1 x 10 ⁻⁷	Wikström et al., 2020, 6311677, High Confidence
Decreased Offspring Survival	Kunming Mice, F1 males and females	BMDL _{0.5SD} , Polynomial 3rd degree	4.59 x 10 ⁻⁴	Not calculated	Song et al., 2018, 5079725; Medium confidence
Decreased Fetal Body Weight	Kunming Mice, F1 males and females	NOAEL	1.50 x 10 ⁻³	Not calculated	Li et al., 2018, 5084746; Medium confidence

PFOA Noncancer POD_{HED} Derivation

Endpoint	Species, Strain, Sex	POD Type, Model	POD _{HED} (mg/kg-day)	Candidate RfD (mg/kg-day)	Study Reference; Study Quality
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Developmental Effects (Continued)

Developmental Scores for the Mammary Gland	CD-1 Mice, F1 females	BMDL _{1SD} , Exponential 4	1.49×10^{-5}	Not calculated	Macon et al., 2011, 1276151; Medium confidence
Delayed Time to Eye Opening	CD-1 Mice, F1 males and females	BMDL _{1SD} , Polynomial 2	1.67×10^{-3}	Not calculated	Lau et al., 2006, 1276159; Medium confidence
Increased Placental Lesions	CD-1 Mice, parental females	BMDL _{1SD} , Logistic	3.19×10^{-3}	Not calculated	Blake et al., 2020, 6305864; Medium Confidence

Serum Lipid (Cardiovascular) Effects

Increased Total Cholesterol	Human epidemiology, male and female	BMDL _{10RD} , Hybrid	6.72×10^{-7}	Not calculated	Dong et al., 2019, 5080195; Medium confidence
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Endocrine Effects

Increased TSH	Sprague-Dawley Rats, females	BMDL _{1SD} , Hill	2.00×10^{-4}	Not calculated	NTP, 2019, 5400977; High confidence
Decreased Free T4	Sprague-Dawley Rats, males	LOAEL	3.75×10^{-3}	Not calculated	NTP, 2019, 5400977; High confidence

PFOA Noncancer POD_{HED} Derivation

Endpoint	Species, Strain, Sex	POD Type, Model	POD _{HED} (mg/kg-day)	Candidate RfD (mg/kg-day)	Study Reference; Study Quality
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Hepatic Effects

Focal Necrosis	Crl:CD-1(ICR)BR Mice, males	BMDL _{10RD} , Log-Probit	1.64×10^{-3}	Not calculated	Loveless et al., 2008, 7330145; Medium confidence,
Necrosis	Sprague-Dawley Rats (males); Perinatal and Postweaning, males	BMDL _{10RD} , Log-logistic	3.23×10^{-3}	Not calculated	NTP, 2020, 7330145; High confidence

Reproductive Effects

Reduced Number of Leydig Cells	Kunming mice, males	BMDL _{1SD} , Polynomial Degree 2	2.4×10^{-4}	Not calculated	Song et al., 2018, 5079725; Medium confidence
Increased Length of Diestrus	ICR mice, females	BMDL _{1SD} , Polynomial Degree 3	1.81×10^{-3}	Not calculated	Zhang et al., 2020, 6505878; Medium confidence

PFOA Cancer POD_{HED} Derivation

Endpoint	Species, Strain, Sex	POD Type, Model	POD _{HED}	Candidate CSF	Study Reference; Study Quality
Renal cell carcinoma (RCC)	Human epidemiology, male and female 55-74 years, general population	CSF serum in adults (per ng/mL of serum PFOA); central tendency slope	--	0.01483 (ng/kg/day) ⁻¹	Shearer et al. (2021) 7161466; <i>Medium</i> confidence
Renal cell carcinoma (RCC)	Human epidemiology, male and female 55-74 years, general population	CSF serum in adults (per ng/mL of serum PFOA); upper limit of the 95% CI	--	0.0352 (ng/kg/day) ⁻¹	Shearer et al. (2021) 7161466; <i>Medium</i> confidence
Leydig Cell Adenomas in the Testes	Male Sprague-Dawley	BMDL _{4RD} , Multistage Model 3	3.20 x 10 ⁻³ mg/kg/day	12.2 (mg/kg/day) ⁻¹	Butenhoff et al., 2012, 2919192, <i>Medium</i> confidence
Hepatocellular Adenomas or Carcinoma	F1 Male Sprague-Dawley Rats, Perinatal (300 PPM) and Postweaning Exposure	BMDL _{10RD} , Multistage 2	1.1 x 10 ⁻² mg/kg/day	9.4 (mg/kg/day) ⁻¹	NTP, 2020, 7330145, <i>High</i> confidence
Acinar Cell Adenoma	F1 Male Sprague-Dawley Rats, Perinatal (300 PPM) and Postweaning Exposure	BMDL _{10RD} , Multistage 1	1.9 x 10 ⁻² mg/kg/day	53 (mg/kg/day) ⁻¹	NTP, 2020, 7330145, <i>High</i> confidence

PFOS Noncancer POD_{HED} Derivation

Endpoint	Species, Strain, Sex	POD Type, Model	POD _{HED} (mg/kg-day)	Candidate RfD (mg/kg-day)	Study Reference; Study Quality
Immune Effects					
Decreased serum anti-tetanus antibody concentration in children	Human epidemiology, male and female	BMDL _{5RD} , piecewise	1.05×10 ⁻⁷	1.1 x 10 ⁻⁸	Grandjean, (2012, 1248827); Grandjean, (2017, 3858518); Grandjean, (2017, 4239492); Budtz-Jørgensen and Grandjean (2018); Medium confidence
Decreased serum anti-diphtheria antibody concentration in children	Human epidemiology, male and female	BMDL _{5RD} , piecewise	7.91×10 ⁻⁸	7.9 x 10 ⁻⁹	Grandjean, (2012, 1248827); Grandjean, (2017, 3858518); Grandjean, (2017, 4239492); Budtz-Jørgensen and Grandjean (2018); Medium confidence
Decreased Plaque Forming Cell (PFC) Response to SRBC	C57BL/6 Mice, F ₁ males	BMDL _{1SD} , Hill	2.01×10 ⁻⁴	Not calculated	Zhong et al., 2016, 3748828; Medium confidence
Extramedullary Hematopoiesis in the Spleen	Sprague-Dawley Rats, female	BMDL _{10RD} , Multistage Degree 2	4.63×10 ⁻⁴	Not calculated	NTP 2019, 5400978; High confidence
Extramedullary Hematopoiesis in the Spleen	Sprague-Dawley Rats, male	BMDL _{10RD} , Logistic	1.21×10 ⁻³	Not calculated	NTP 2019, 5400978; High confidence

PFOS Noncancer POD_{HED} Derivation

Endpoint	Species, Strain, Sex	POD Type, Model	POD _{HED} (mg/kg-day)	Candidate RfD (mg/kg-day)	Study Reference; Study Quality
Developmental Effects					
Decreased Birth Weight	Human epidemiology, male and female	BMDL _{5RD} , Hybrid	1.65×10 ⁻⁶	1.7 x 10 ⁻⁷	Chu et al., 2020, 6315711, High confidence
Decreased Birth Weight	Human epidemiology, male and female	BMDL _{5RD} , Hybrid	8.95×10 ⁻⁶	8.9 x 10 ⁻⁷	Sagiv et al., 2018, 4238410, High confidence
Decreased Birth Weight	Human epidemiology, male and female	BMDL _{5RD} , Hybrid	1.26×10 ⁻⁶	1.3 x 10 ⁻⁷	Starling et al., 2017, 3858473, High confidence
Decreased Birth Weight	Human epidemiology, male and female	BMDL _{5RD} , Hybrid	1.72×10 ⁻⁶	1.7 x 10 ⁻⁷	Wikström et al., 2020, 6311677, High confidence
Decreased Fetal Body Weight	CD-1 Mice, F ₁ males and females	BMDL _{5RD} , Exponential 5	1.05×10 ⁻⁴	Not calculated	Lee et al., 2015, 2851075; Medium confidence
Decreased Pup Body Weight	Sprague-Dawley Rats, F ₁ male and female	BMDL _{0.5SD} , Exponential 4	8.74×10 ⁻⁴	Not calculated	Luebker et al., 2005, 757857; Medium confidence
Increased Number of Dead Fetuses	CD-1 Mice, females	LOAEL	3.32×10 ⁻⁴	Not calculated	Lee et al., 2015, 2851075; Medium confidence

PFOS Noncancer POD_{HED} Derivation

Endpoint	Species, Strain, Sex	POD Type, Model	POD _{HED} (mg/kg-day)	Candidate RfD (mg/kg-day)	Study Reference; Study Quality
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Endocrine Effects

Decreased Free T4	Sprague-Dawley rats, male	LOAEL	3.75×10^{-3}	Not calculated	NTP, 2019, 5400978; High confidence
Decreased Free T4	Sprague-Dawley rats, female	BMDL _{1SD} , Exponential 4	4.98×10^{-4}	Not calculated	NTP, 2019, 5400978; High confidence
Decreased Total T4	Sprague-Dawley rats, female	BMDL _{1SD} , Exponential 4	3.39×10^{-4}	Not calculated	NTP, 2019, 5400978; High confidence
Decreased Total T3	Sprague-Dawley rats, male	BMDL _{1SD} , Hill	8.72×10^{-4}	Not calculated	NTP, 2019, 5400978; High confidence
Decreased Total T3	Sprague-Dawley rats, female	BMDL _{1SD} , Hill	2.06×10^{-3}	Not calculated	NTP, 2019, 5400978; High confidence
Decreased Total T3	Cynomolgus Monkeys, male	LOAEL	1.04×10^{-3}	Not calculated	Seacat et al., 2002, 757853; Medium confidence
Decreased Total T3	Cynomolgus Monkeys, female	BMDL _{1SD} , Exponential 4	9.07×10^{-4}	Not calculated	Seacat et al., 2002, 757853; Medium confidence

PFOS Noncancer POD_{HED} Derivation

Endpoint	Species, Strain, Sex	POD Type, Model	POD _{HED} (mg/kg-day)	Candidate RfD (mg/kg-day)	Study Reference; Study Quality
Serum Lipid (Cardiovascular) Effects					
Increased Total Cholesterol	Human epidemiology, male and female	BMDL _{10RD} , Hybrid	3.08×10 ⁻⁶	Not calculated	Dong et al., 2019, 5080195; Medium confidence
Hepatic Effects					
Individual Cell Necrosis in the Liver	Sprague-Dawley rats, females	BMDL _{10RD} , Multistage 3	3.13×10 ⁻³	Not calculated	Butenhoff et al., 2012, 1276144; High confidence
Nervous Effects					
Decreased Performance on the Object Location Recognition Memory Test	C57BL/6J, F ₁ mice, males	NOAEL	9.97×10 ⁻⁵	Not calculated	Mshaty et al., 2020, 6833692; Medium confidence

Conclusions – Noncancer Candidate RfD Selection

	PFOA	PFOS
Critical Studies	Budtz-Jorgensen and Grandjean (2018); Supporting studies: Grandjean et al. (2012), Grandjean et al. (2017a), and Grandjean et al. (2017b)	Budtz-Jorgensen and Grandjean (2018); Supporting studies: Grandjean et al. (2012), Grandjean et al. (2017a), and Grandjean et al. (2017b)
Critical Effect(s)	Developmental immune; decreased serum anti-tetanus antibody concentration in children	Developmental immune; decreased serum anti-diphtheria antibody concentration in children
Study type	Human epidemiology	Human epidemiology
UF_L	1	1
UF_S	1	1
UF_A	1	1
UF_H	10	10
UF_D	1	1
UF_{TOTAL}	10	10
RfD	Candidate: 1.5 X 10⁻⁹ mg/kg/day	Candidate: 7.9 X 10⁻⁹ mg/kg/day

Conclusions – Cancer Candidate CSF Derivation

	PFOA	PFOS
Cancer Classification	<i>Likely</i> to be carcinogenic to humans based on new studies since 2016 HA	<i>Suggestive</i> evidence of carcinogenic potential
Studies and Candidate CSFs	<ul style="list-style-type: none"> Butenhoff et al., (2012; male Sprague-Dawley rats) – <ul style="list-style-type: none"> Leydig cell adenomas: 12.2 (mg/kg/day)⁻¹ NTP (2020; male Sprague-Dawley rats) - <ul style="list-style-type: none"> Hepatocellular adenomas or carcinomas: 9.4 (mg/kg/day)⁻¹ Pancreatic acinar cell adenomas: 53 (mg/kg/day)⁻¹ Shearer et al. (2021; adults aged 55-78, general population epidemiology study) - <ul style="list-style-type: none"> Renal cell carcinomas: <ul style="list-style-type: none"> 0.0352 (ng/kg/day)⁻¹ (renal cell carcinomas (95% CI upper limit), Shearer; [35,200 (mg/kg/day)⁻¹]) 	NA

Relative Source Contribution

- EPA applies an RSC when calculating the MCLG to provide a margin of safety that an individual's total exposure from a contaminant does not exceed the RfD.
 - RSC is the portion of an exposure for an individual in the general U.S. population estimated to equal the RfD that is attributed to drinking water (directly or indirectly in beverages like coffee tea or soup); the remainder is allocated to other potential sources.
- In the case of PFOA and PFOS, other potential sources include diet, ambient and indoor air, incidental soil/dust ingestion, consumer products and others.



80% RSC: Exposure is primarily from drinking water; reserve 20% for other sources

20% RSC: Exposure is primarily from other sources (e.g., diet, dust, air, soil, etc.); reserve 80% for other sources

Conclusions – Relative Source Contribution

- EPA followed its Exposure Decision Tree approach found in the *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health* (2000) and considered the following:
 - The adequacy of data available for each relevant exposure source and pathway.
 - The availability of sufficient information to characterize the likelihood of exposure to relevant sources.
 - Whether there are significant known or potential uses/sources other than the source of concern (i.e., drinking water).
 - Whether information on each source is available to characterize exposure.
- Studies suggest that diet is the major contributor to total PFOA/PFOS exposure among adults, typically with drinking water and/or dust as important additional exposure routes, especially for sensitive subpopulations.
- Estimates of relative exposure from different sources support a **20%** RSC for drinking water.

Conclusions

- **Noncancer RfDs:** Compared with EPA (2016) Health Advisories, PFOA and PFOS draft noncancer RfDs derived from the available data are **several orders of magnitude lower** –
 - **PFOA:** 1.5×10^{-9} mg/kg/day (draft) compared to 2×10^{-5} mg/kg/day (2016)
 - **PFOS:** 7.9×10^{-9} mg/kg/day (draft) compared to 2×10^{-5} mg/kg/day (2016)
 - Critical effects are developmental immune health outcomes from epidemiological studies; sensitive lifestage - children
 - Justification for selection of critical effect: Most health protective values among medium and high confidence studies; Multiple studies corroborate antibody response outcome after PFOA/S exposure; Developmental/growth and cardiovascular health outcomes in other epidemiology studies associated in $\sim 10^{-7}$ to 10^{-8} mg/kg/day PFOA/S dose range
 - Updated toxicokinetic models
- **Cancer:**
 - **PFOA:** cancer classification change to ***‘likely’*** compared with 2016 Health Advisory (HA)/HESD based on new medium quality studies; multiple candidate CSFs derived and based on EPA analysis, Shearer renal cell carcinomas provides the greatest health protection
 - **PFOS:** cancer classification of ***‘suggestive’*** which is not a change from the 2016 Health Advisory (HA)/HESD

Implications of Results – Anticipated Driver of MCLGs

PFOA

- **MCLG driven by cancer effects**

- Additional evidence supporting the carcinogenicity of PFOA and subsequent update of the Cancer Classification to “Likely”
- Typically, the MCLG for likely or known human carcinogens is set at zero because it is assumed there is no known threshold for carcinogenicity in the absence of data suggesting otherwise

PFOS

- **MCLG driven by noncancer effects**

- Candidate RfD = 7.9×10^{-9} mg/kg/day PFOS based on decreased serum anti-diphtheria antibody concentration in children
- Studies identified since the 2016 assessments do not provide additional clarity on the association between PFOS and cancer; maintain conclusion that of **suggestive** evidence of carcinogenic potential in humans

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Charge Questions

Charge Questions

1. Study Identification and Inclusion

- EPA used systematic review methods consistent with the current ORD systematic review practice to ensure transparency and completeness of literature identification, sorting, and study quality evaluation. Is the process clearly described? Please identify additional peer-reviewed studies that the panel is aware of that could inform toxicity value derivation.

2. Noncancer Hazard Identification

- Please comment on the health effect/outcome categories identified from the review of the available literature. Do you agree with the strong vs. suggestive evidence designations for the various health outcome categories? Do any other health systems or endpoints need to be considered for POD derivation?

Charge Questions

3. Noncancer Hazard Identification (continued)*

- Elevation of liver serum biomarkers in humans is frequently used as an indication of liver injury, although it has not been shown to be as specific as functional tests, such as histology findings and liver disease (Boone, 2005, HERO ID: 782862). However, greater than 2-fold increases in alanine aminotransferase (ALT) activity, the most sensitive test of hepatocellular injury in humans, above the upper limit of normal are considered indicative of hepatocellular injury. EPA concluded that the available data in adults show a consistent positive association between PFOA and/or PFOS exposure and increased serum ALT levels in the epidemiological literature. However, this response was not selected for dose response modeling because 1) the magnitude of the effect was not large compared to control levels; and 2) concerns about the clinical relevance of the findings and non-specificity of the biomarkers relationship to adverse liver injury and disease.
 - a) Does the SAB panel agree with EPA's rationale for not considering the ALT endpoint reported in the epidemiological studies for the derivation of a POD for the liver health effects? Please provide your justification and if you suggest that EPA consider this endpoint for POD derivation, please provide your recommendations for a modeling approach.
 - b) Are you aware of additional studies that support the ALT levels as markers of adverse liver effects? Please provide citations.
 - c) Are there other adverse liver endpoints identified in the epidemiological literature that need to be considered?

*note that this question was mistakenly split into two questions on the charge document

Charge Questions

4. Cancer

a. Cancer classification for PFOA/PFOS

- i. PFOA: Based on new cancer studies identified since the 2016 PFOA Health Advisory (HA), EPA concludes that the available cancer data for PFOA indicate a 'likely carcinogen' categorization which is a change from 'suggestive' in the 2016 HA. Does the panel agree with the 'likely' designation based on the new evidence? If yes, is the rationale clearly described? If no, please provide an explanation for arriving at a different conclusion.
- ii. PFOS: Based on a small number of new cancer studies identified since the 2016 PFOS HA, EPA concludes that the available cancer data for PFOS indicate a 'suggestive' categorization which is unchanged from the categorization identified in the 2016 HA. Does the panel agree that the new studies do not change the designation? If yes, is the rationale clearly described? If no, please provide an explanation for arriving at a different conclusion.

- b. Cancer Slope Quantification: EPA used the Shearer et al., 2021 epidemiological study to quantify a cancer slope factor using peak exposure for PFOA. Has EPA adequately justified the use of this study and peak exposure for the quantification of a cancer slope factor for PFOA? If no, please describe alternate approaches that SAB recommends. [Does SAB support the selection of this CSF in the derivation of a risk specific dose for PFOA \(i.e., the concentration of PFOA in drinking water that would have a one-in-1-million chance of an increased cancer risk\)? If not, please provide input on the strengths and weaknesses of the other candidate CSFs that EPA derived.*](#)

* additional question not in the original charge

Charge Questions

5. Human Toxicokinetic Model

- a. For endpoints observed in adults, EPA used a steady-state approach to calculate the HED, which assumes a relatively constant exposure and clearance during adulthood. Please comment on this method of HED calculation. Are there alternative approaches that EPA should consider? If so, please describe the rationale for recommending this approach(es).
- b. Two key parameters are the half-life and volume of distribution, which were used to calculate clearance. Half-life and volume of distribution were assumed to be constant across sex and age groups because of a lack of strong quantitative data to parametrize changes across sex and age. Please comment on the strengths and weakness of the use of this assumption and the choice of these parameters by the EPA. Please describe the rationale for alternative recommended approaches. For endpoints observed in human neonates or children, EPA used a one-compartment TK model to simulate dosimetry during pregnancy and a two-compartment TK model (one-compartment models for the mother and the child) to simulate dosimetry during lactation, to calculate the HED for each POD. Please comment on the strengths and weaknesses of this choice of model structure for the task of predicting dosimetry in the human fetus and child compared to dosimetry in mice and rats in the similar lifestages. Please provide the rationale for any alternative recommended approaches.
- c. The key chemical-specific parameters that describe the transfer of the chemical from the mother to the child during gestation and lactation are the maternal to fetal serum ratio and the ratio of maternal serum to milk PFOA/S concentration. These ratios were assumed to be constant during gestation and lactation, respectively. Another important parameter is the rate of milk ingestion, which is chemical-independent and varies throughout lactation. Please comment on the strengths and weaknesses of the choice of parameters for fetal to maternal partitioning and partitioning into breastmilk, as well as the choice for lactation rate. Please also comment on the choice to assume that fetal to maternal partitioning and partitioning to breastmilk did not vary in time. Please describe whether there are other methods you would recommend to account for these changes over time and across development.

Charge Questions

6. Animal Toxicokinetic Model

- a. After a review of the available toxicokinetic models for PFOA/S predictions in laboratory animals, EPA selected the Wambaugh et al. (2013) model because it was parametrized using all species of interest, demonstrated good agreement with training and test datasets, and used a single, biologically motivated, model structure across all species. Does the panel agree with selecting this model? If not, please describe the rationale for alternative recommended approaches for the calculation of the internal dose metrics in adult animals.
- b. The animal model parameters were obtained through a Bayesian inference parameterization which produced wide credible intervals for some parameter values, but relatively tight credible intervals for the predicted serum concentration. Does the panel agree with using the median values of the estimated animal parameter distributions for prediction of serum concentration and internal dose metrics?
- c. Based on visual inspection of model predictions to the calibration datasets, EPA utilized sex-independent parameters for PFOS. The male-specific parameters were used for all rat-specific PFOS predictions including predictions in pregnant and nursing dams and the female-specific parameters were used for all mouse-specific PFOS predictions because the parameter values obtained from fitting the female-specific rat data and male-specific mouse data were not consistent with the overall TK parameters for PFOS and produced poor fits to the training and test datasets. Does the panel agree with this approach and justification for this assumption for PFOS? If not, please describe other approaches that could be considered?

Charge Questions

6. Animal Toxicokinetic Model (cont.)

- d. EPA assumed a one compartment model for the developing infant based on the lack of infant-specific toxicokinetic data from rats and mice. This model utilizes averages of half-life and volume of distribution from the literature coupled with physiologically relevant lactational parameters for pup nursing. Does the panel agree with the decision to use this model structure for infant animals? If not, please provide data on infant-specific changes during the animal lactational-period that could be used to account for toxicokinetic differences between the adult and infant rats and mice.
- e. Several parameters dictate the transfer of chemical from the mother to her pup. Does the panel agree with the selection of these parameters for the animal model? If not, please provide your justification and alternative parameters.
- f. For neonatal animals, EPA assumed no sex differences in clearance in neonatal animals based on the lack of identification of sex-dependent differences in PFOA/S toxicokinetics from the available data. Does the panel agree with this assumption? If not, please provide your justification and available data on sex differences in neonatal rats.

Charge Questions

7. Epidemiological Study RfD Derivation

- a. EPA evaluated potential confounding as part of their study quality evaluation of the epidemiological studies and selected only 'medium' and 'high' quality studies for POD derivation. Have the epidemiological studies that were selected for dose-response modeling sufficiently addressed confounding? If not, are there key additional analyses that could be performed to further address the potential confounding of PFAS exposures in these studies?
- b. Studies of developmental immune health outcomes (Grandjean et al., 2012 [HERO ID: 1248827]; Grandjean et al. 2017 [HERO ID: 3858518]; Grandjean et al., 2017 [HERO ID: 4239492]; and Budtz-Jorgensen and Grandjean, 2018 [HERO ID: 5083631]) after PFOA/S exposure identified associations with very low doses of either PFOA or PFOS with developmental immune effects. The RfD for this outcome was selected as the critical effect because it was the lowest among the candidate RfDs for PFOA or PFOS and can result in severe illness. Does the panel agree with the selection of the critical study and critical effect for the derivation of chronic RfDs for PFOA and PFOS?
 - i. If so, please explain your justification.
 - ii. If not, please provide your rationale and detail an alternative critical study and/or critical effect you would select to support the derivation of chronic RfDs.
 - iii. Are any additional analyses or rationales needed to increase the confidence in the chronic RfDs for PFOA and PFOS?

Charge Questions

7. Epidemiological Study RfD Derivation (cont.)

- c. The health outcomes identified in the critical studies were decreased antibody response, specifically in serum anti-tetanus and anti-diphtheria, in children after vaccination (Grandjean et al., 2012 [HERO ID: 1248827]; Grandjean et al. 2017 [HERO ID: 3858518]; Grandjean et al., 2017 [HERO ID: 4239492]; and Budtz-Jorgensen and Grandjean, 2018 [HERO ID: 5083631]). This health outcome represents an increased susceptibility to a disease that can cause very severe symptoms, including lethality. Furthermore, children who are immunocompromised may mount a lower antibody response and in turn, be more susceptible to contracting the disease, if exposed than healthy children. Because this health outcome has the potential for severe illness and was assessed in children (i.e., EPA guidelines [US EPA, 1991] support a 5% BMR for developmental effects), a benchmark response (BMR) of 5% was selected for benchmark dose modeling. While some clinical findings are available, the clinical relevance of a 5% decrease in antibody response is not clear. Given the need to protect sensitive subpopulations (e.g., children, individuals with pre-existing conditions) and the available clinical data (i.e., antibody response clinical level), does the SAB support the 5% BMR selection for modeling to identify the POD? If not, please recommend the BMR level and a scientific rationale for an alternative selection.
- d. 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 PFOA and PFOS.
 - i. Has uncertainty been adequately accounted for in the derivation of the RfDs? Please describe and provide suggestions, if needed.
 - ii. Does the provided scientific rationale support the application of the selected uncertainty factors? Please explain.

Charge Questions

8. Relative Source Contribution

- a. EPA applies a Relative Source Contribution (RSC) when calculating the MCLG to provide a margin of safety that an individual's total exposure from a contaminant does not exceed the RfD. The RSC is the portion of an exposure for an individual in the general U.S. population estimated to equal the RfD that is attributed to drinking water; the remainder of the exposure equal to the RfD is allocated to other potential sources. Based on the physical properties, detected levels, and available exposure information, there are significant potential sources other than drinking water ingestion for PFOA and PFOS; however, information is not available to quantitatively characterize exposure from these different sources. EPA followed Agency guidance on how to derive an RSC (U.S. EPA, 2000; available online at: <https://www.epa.gov/sites/default/files/2018-10/documents/methodology-wqc-protection-hh-2000.pdf>) and recommends an RSC of 20 percent (0.20) for PFOA and PFOS. This RSC is the same as what was used in the 2016 HAs for PFOA and PFOS.
 - i. Are you aware of additional relevant exposure data that EPA should consider in developing the RSCs for PFOA and PFOS? If so, please provide citations.
 - ii. Please provide comment on whether the recommended RSC of 20 percent (0.20) for PFOA and PFOS is adequately supported and clearly described.



QUESTIONS ?