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Comparison of Approaches for Evaluating Relative Toxicity and Risk of PFAS Without Regulatory Toxicity Values

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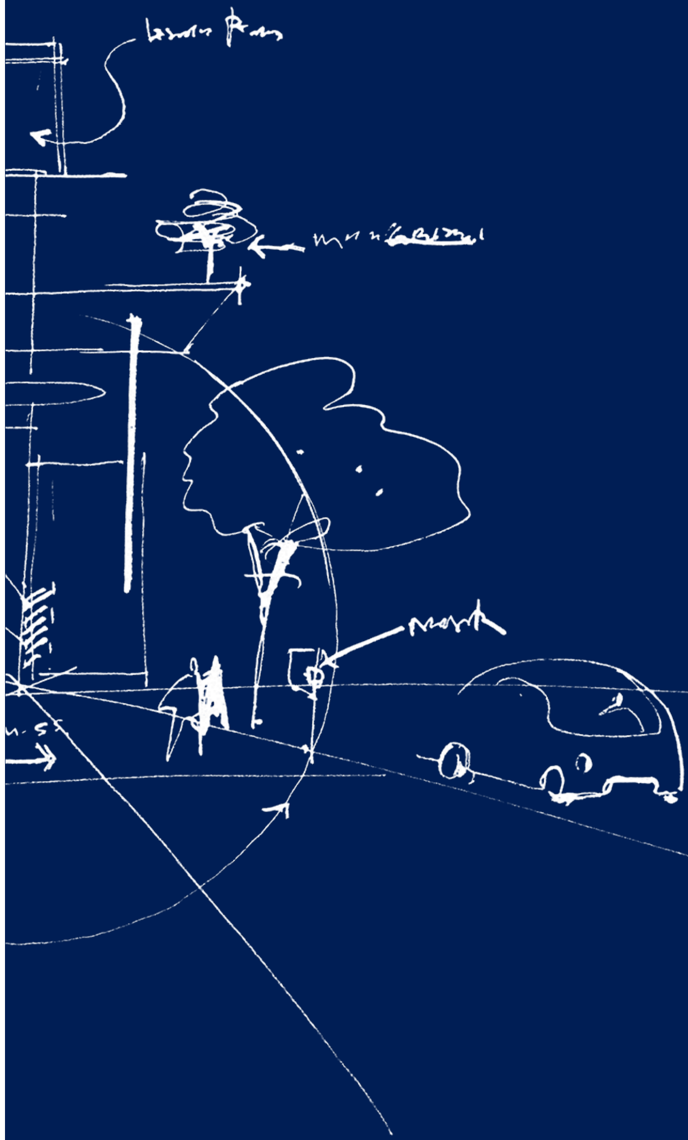
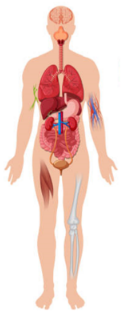
Agenda

- Background information on PFAS toxicity values & assessing toxicity of chemical mixtures
- Approaches for assessing PFAS without regulatory toxicity values
- Case study
  - Estimate toxicity values for 4 PFAS using various approaches
  - Compare results with EPA toxicity values
- Summary



Background - PFAS toxicity values & assessing toxicity of chemical mixtures

There are many PFAS but few published toxicity values



- **Thousands** of PFAS
- Potential exposure to **hundreds** of PFAS
- **Few** with well-understood/accepted toxicity

RfD – estimate of the daily oral exposure at which a non-cancer health effect is not expected

Blue font = in EPA documents
Red font = in EPA RSL table

PFAS Toxicity Values Identified or Currently Used by EPA

PFAS	Status	RfD (mg/kg-day) / Health Effect	Source/Date
GenX	Final	3x10^{-6}/liver	EPA OW (10/21)
PFBA	Final	1x10^{-3}/liver; 1x10^{-3}/thyroid; 6x10^{-3}/developmental	EPA IRIS (12/22)
PFBS	Final	3x10^{-4}/thyroid	EPA ORD (4/21)
PFDA	Draft	4x10^{-10}/immune; 3x10^{-10}/developmental; 7x10^{-7}/liver; 5x10^{-6}/male reproductive; 3x10^{-6} female reproductive	EPA IRIS (4/23)
PFDoDA	Tier 3	5x10^{-5}/endocrine	EPA RSL (WI) (5/24)
PFHxA	Final	4x10^{-4}/liver; 5x10^{-3}/blood; 5x10^{-4}/developmental	EPA IRIS (4/23)
PFHxS	Draft	2x10^{-5}/thyroid	ATSDR MRL (3/20)
PFNA	Final	3x10^{-6}/developmental	ATSDR MRL (3/20)
PFOA	Final	3x10^{-8}/immune, developmental, cardiovascular	EPA OW (4/24)
PFODA	Tier 3	4x10^{-2}/body weight, pancreas	EPA RSL (WI) (5/24)
PFOS	Final	1x10^{-7}/developmental, cardiovascular	EPA OW (4/24)
PFPrA	Final	5x10^{-4}/liver	EPA ORD (9/23)
PFTetA	Tier 3	1x10^{-3}/body weight	EPA RSL (WI) (5/24)
PFUDA	Tier 3	3x10^{-4}/reproductive	EPA RSL (WI) (5/24)

ATSDR – Agency for Toxic Substances and Disease Registry; IRIS – Integrated Risk Information System; MRL = Minimal risk level; ORD – Office of Research & Development; OW – Office of Water; RfD – Reference dose; RSL – Regional Screening Level; WI – Wisconsin

Toxicity values are needed for more PFAS

- EPA Method 1633 includes 40 PFAS
- 1000s of PFAS but only 14 with draft/final toxicity values identified or currently used by EPA
- Traditional way of developing toxicity values using animal/human studies cannot meet the needs for PFAS
- An EPA goal is to reduce animal testing
- Need to generate more toxicity data rapidly
- Reduce concerns about unaddressed PFAS
- Avoid rework at sites undergoing investigation & cleanup

Need to consider mixtures when addressing risks from exposure

- Laws require it: CERCLA, SARA, CAA, SDWA, FQPA
- Exposure is rarely to a single chemical (e.g., in groundwater)
- Multiple chemicals typically detected and many/all may cause health effects
- Need to account for chemical mixtures to avoid underestimating exposure/risk
- EPA's *Risk Assessment Guidance for Superfund Part A* (1989) - cumulative risk
- EPA's *PFAS National Primary Drinking Water Regulation* (2024)
  - MCL based on mixture (4 PFAS: PFHxS, PFNA, PFBS, HFPO-DA [GenX])

CERCLA – Comprehensive Environmental Response, Compensation, and Liability Act
SARA – Superfund Amendments and Reauthorization Act; CAA – Clean Air Act; SDWA – Safe Drinking Water Act
FQPA – Food Quality Protection Act

Mixtures are typically assessed using methods for individual chemicals

- Developed due to the lack of whole-mixture toxicity data
- 3 methods presented in EPA's *Draft Mixtures Framework for PFAS* (2023)
  - Hazard Index (HI)
    - Common approach in HHRA; *RAGS Part A 1989*; goal is ≤1
    - Requires individual chemical toxicity values (e.g., RfDs)
  - Relative Potency Factor (RPF)
    - Common approach in HHRA for carcinogenic PAHs (1993) & dioxins/furans (1989)
    - Compare the toxicity of a chemical to a well-studied chemical with toxicity data/values
    - The toxicity is expressed as a "relative potency factor" (RPF) relative to a well-studied chemical
    - Requires toxicity data indicating similar target organ (e.g., liver) or health effect
    - Assumes individual chemical dose-response relationships are similar
  - Mixture Benchmark Dose
    - Assumes individual chemical dose-response relationships are not similar
- Based on a simplified and conservative assumption: doses are additive
  - Produce a common health effect without enhancing or diminishing toxicity

$$Tox_1 + Tox_2 + Tox_3 + Tox_x = \text{Mixture toxicity}$$

Need chemical-specific toxicity data to assess mixtures… but have limited data

HHRA – human health risk assessment

Approaches for assessing PFAS without regulatory toxicity values

RPF + carbon chain length approach for PFAS missing toxicity values

- RPFs published by Zeilmaker et al.
- Scaled in relation to PFOA (“*reference compound*”) for liver toxicity
  - RPFs estimated based on lab studies in rats/mice where available
  - If no relevant studies, identified **surrogate** RPF range based on carbon chain length
    - Assumes toxicity related to chain length (ATSDR 2021)
- Used by Hawai’i DOH (2024) for 10 PFAS
- Uncertainties related to limited # (6) of PFAS predicted, assumes toxicity related to carbon chain length, based on data to 2018, liver endpoint only

Surrogate – a substitute/estimate when lacking data

PFAS	RPF	Estimated RfD (mg/kg-day)
PFBS	0.001	2×10^{-2}
PFPeS	0.001 ≤RPF ≤0.6	$2 \times 10^{-2} \leq$ RfD $\leq 3.3 \times 10^{-5}$
PFHxS	0.6	3.3×10^{-5}
PFHpS	0.6 ≤RPF ≤2	$3.3 \times 10^{-5} \leq$ RfD $\leq 1 \times 10^{-5}$
PFOS	2	1×10^{-5}
PFDS	2	1×10^{-5}
PFBA	0.05	4×10^{-4}
PFPeA	0.01 ≤RPF ≤ 0.05	$2 \times 10^{-3} \leq$ RfD $\leq 4 \times 10^{-4}$
PFHxA	0.01	2×10^{-3}
PFHpA	0.01 ≤RPF ≤1	$2 \times 10^{-3} \leq$ RfD $\leq 2 \times 10^{-5}$
PFOA	1	2×10^{-5}
PFNA	10	2×10^{-6}
PFDA	4 ≤RPF ≤10	$5 \times 10^{-6} \leq$ RfD $\leq 2 \times 10^{-6}$
PFUnDA	4	5×10^{-6}
PFDoDA	3	6.7×10^{-6}
PFTrDA	0.3 ≤RPF ≤3	$6.7 \times 10^{-5} \leq$ RfD $\leq 6.7 \times 10^{-6}$
PFTeDA	0.3	6.7×10^{-5}
PFHxDA	0.02	1×10^{-3}
PFODA	0.02	1×10^{-3}

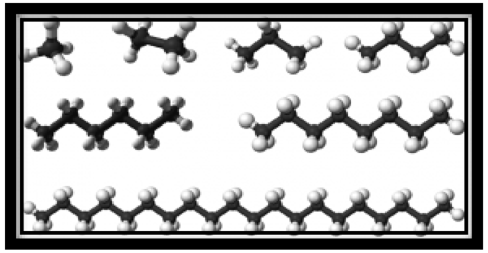
Red = surrogate range

RPF Source: Zeilmaker et al. 2018. *Mixture exposure to PFAS: A Relative Potency Factor approach.* RIVM Report 2018-007. National Institute for Public Health and the Environment, Bilthoven, The Netherlands.

Carbon chain length (only) approach for PFAS missing toxicity values

- For PFAS missing toxicity data & values:
  - Use surrogate toxicity values for PFAS with same/longer carbon chain length
- Used by Texas Commission on Environmental Quality (TCEQ) (2023)
  - Ongoing evaluation by TCEQ of latest data
  - Uncertainties related to limited # (6) of PFAS predicted, assumes toxicity related to carbon chain length only (ATSDR 2021)

PFAS Missing Toxicity Data		Surrogate Used		
Name	Carbon Chain Length	Name	Carbon Chain Length	RfD (mg/kg-day)
PFPeA	5	PFHxA	6	5.0×10^{-4}
PFHpA	7	PFOS	8	2.3×10^{-5}
PFDS	10	PFDoA	14	1.2×10^{-5}
PFUA	11	PFDoA	14	1.2×10^{-5}
PFTrDA	14	PFDoA	14	1.2×10^{-5}
PFTeDA	14	PFDoA	14	1.2×10^{-5}



ATSDR 2021 - *Toxicological Profile for Perfluoroalkyls*

Extrapolation from closest most conservative PFAS on a molar basis for PFAS missing toxicity values

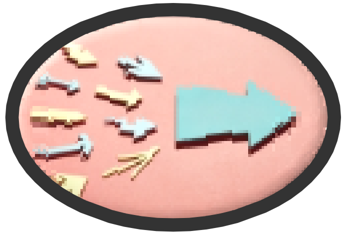
- For PFAS missing toxicity data & values:
  - Used most potent PFAS when comparing equal molar amounts
  - Uncertainties related to limited # (7) of PFAS predicted, based on data to 2013, liver & reproductive endpoints only
- Used qualitatively in risk assessments in Australia
  - Relative toxicity of detected PFAS with missing toxicity values
  - Available toxicity: PFOA & PFOS
  - PFHxS assumed to be as toxic as PFOS
  - Other PFAS 10-100 times less toxic than PFOA and PFOS (except PFNA)

PFAS Missing Liver Toxicity Data	Surrogate Used
PFOSA	PFOS
PFDS	PFOS
PFPeA	PFOA
PFUnDA	PFNA
PFTriDA	PFNA
PFTeDA	PFNA
6:2 FTS	PFOS

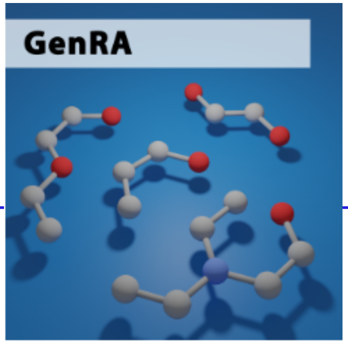
Source: Borg et al. 2013 (Cumulative health risk assessment of 17 perfluoroalkylated and polyfluoroalkylated substances (PFASs) in the Swedish population)

New Approach Methods (NAMs) for PFAS missing toxicity values

- NAMs – Methods that avoid/reduce use of animal testing
- EPA's Generalized Read-Across (GenRA) tool
  - Uses chemical structure data to identify "similar" (surrogate) chemicals
    - Many publications on relationship between structure and toxicity
    - Chain length, branching, and functional groups (e.g., carboxylates) can affect toxicity
  - Identifies multiple (max. of 15) surrogate chemicals
  - Uses *in-vivo* data of surrogates to predict toxicity
    - Final toxicity estimate weighted based on the degree of similarity of surrogates
  - GenRA database contains information on 1,000s of chemicals
    - Periodically updated to reflect most recent scientific data
- Use NTP's ICE tool to adjust for absorption/ distribution/ excretion



In-vivo – in a living animal or human

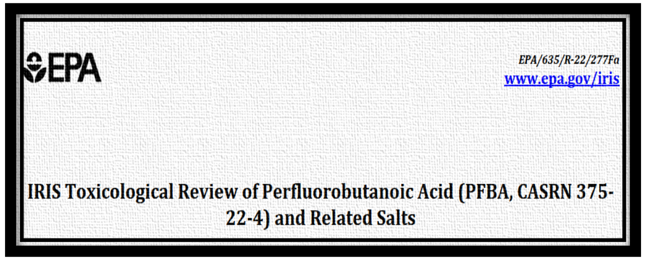


Available at https://comptox.epa.gov/genra/

Case Study: Surrogate Toxicity Values for PFAS Using Various Approaches

Case Study – goal & overall approach

- Goal – Evaluate how various approaches perform in estimating surrogate toxicity values for liver effects
  - Identify PFAS with draft/final EPA toxicity values for liver effects
  - Compare estimated surrogate toxicity values to EPA's values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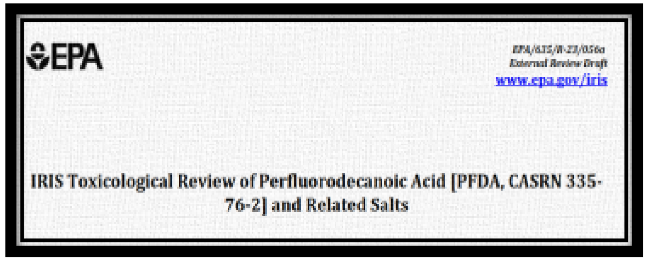
IRIS Toxicological Review of Perfluorobutanoic Acid (PFBA, CASRN 375-22-4) and Related Salts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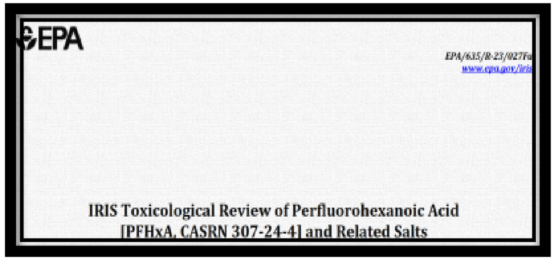
External Review Draft
www.epa.gov/iris
IRIS Toxicological Review of Perfluorodecanoic Acid [PFDA, CASRN 335-76-2] and Related Salts

PFAS Toxicity Values Identified by EPA (Liver Effects)

PFAS	Status	RfD (mg/kg-day)	Source/Date
PFBA	Final	$1x10^{-3}$	EPA IRIS (12/22)
PFDA	Draft	$7x10^{-7}$	EPA IRIS (4/23)
PFHxA	Final	$4x10^{-4}$	EPA IRIS (4/23)
PFPrA	Final	$5x10^{-4}$	EPA ORD (9/23)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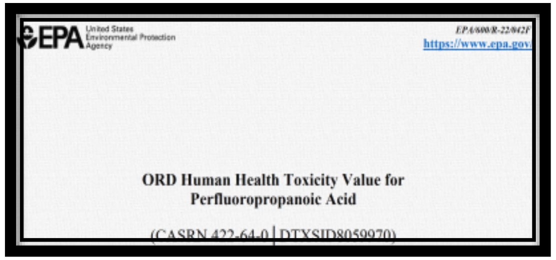
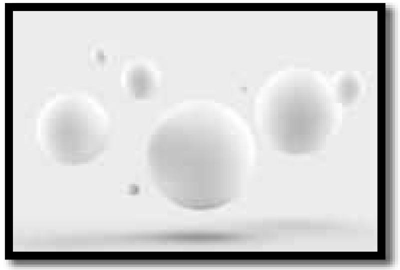

EPA United States Environmental Protection Agency
EPA/600/R-22/042F
https://www.epa.gov/
ORD Human Health Toxicity Value for Perfluoropropanoic Acid
(CASRN 422-64-0 | DTXSID8059970)

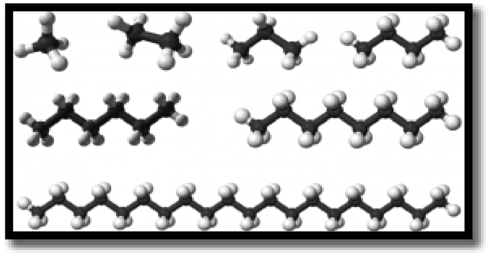
Two approaches (carbon chain length [only] & extrapolation using closest most conservative PFAS) did not identify surrogates for the 4 PFAS, so not used in case study.

Case Study – RPF + carbon chain length approach - results

PFAS	RPF in relation to PFOA	Surrogate RfD (mg/kg-day)	EPA RfD (mg/kg-day)	Surrogate RfD in relation to EPA's RfD
PFBA	0.05	$4x10^{-4}$	$1x10^{-3}$	2.5x higher
PFDA	4 ≤RPF ≤10	$5x10^{-6} \leq$ RfD $\leq 2x10^{-6}$	$7x10^{-7}$	~3x to ~7x lower
PFHxA	0.01	$2x10^{-3}$	$4x10^{-4}$	5x lower
PFPrA	-	-	$5x10^{-4}$	-

- Not included in the list of PFAS evaluated by Zeilmaker et al.





Surrogate RfDs are ± 2.5 to 7 times the RfDs identified by EPA; limited # of PFAS included

RPF Source: Zeilmaker et al. 2018. *Mixture exposure to PFAS, A Relative Potency Factor approach.* RIVM Report 2018-0070. National Institute for Public Health and the Environment, Bilthoven, The Netherlands.

Case Study – NAMs approach using GenRA tool & NTP's ICE tool

Overall steps in calculating GenRA toxicity values

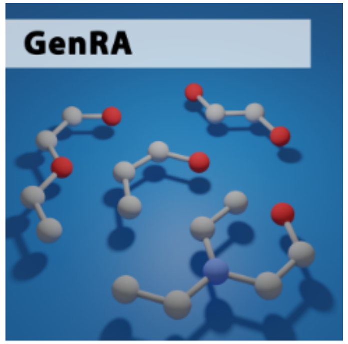
Use GenRA to identify surrogates based on structural similarity	→	Obtain *in-vivo* POD toxicity data for surrogates	→	Use surrogates to predict toxicity of target chemical for liver effects
Identifies surrogates; calculates SI for each surrogate based on chemical structure		From EPA toxicity documents or GenRA toxicity database		GenRA weights surrogates to provide a merged toxicity estimate. Use NTP's ICE tool to adjust for absorption/ distribution/ excretion. Apply UFs.

Point of departure (POD): the point on a dose-response curve corresponding to an estimated low effect level or no effect level
Similarity index (SI) : prediction of relative toxicity (or potency) between target chemical & surrogate (a ratio)

ICE - Integrated Chemical Environment (ICE); NTP – National Toxicology Program; UF – uncertainty factor

Case Study – NAMs approach - results

PFAS	NAMs Approach RfD (mg/kg-day)	EPA RfD (mg/kg-day)	NAMs Approach RfD in relation to EPA's RfD
PFBA	5×10^{-4}	1×10^{-3}	2x higher
PFDA	2×10^{-6}	7×10^{-7}	2.8x lower
PFHxA	6×10^{-4}	4×10^{-4}	1.5x lower
PFPrA	3×10^{-3}	5×10^{-4}	6x lower

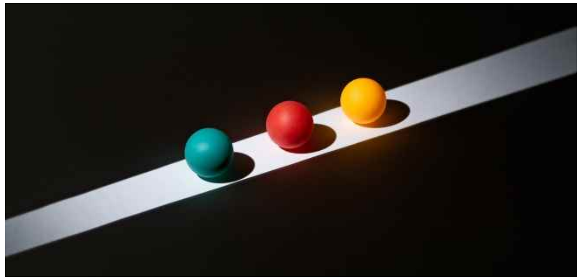


Surrogate RfDs are ± 1.5 to 6 times the RfDs identified by EPA; able to estimate RfD for PFPrA

Case Study – comparison of results

	Surrogate RfD in relation to EPA's RfD	
PFAS	RPF + Carbon Chain Length Approach	NAMs Approach
PFBA	2.5x higher	2x higher
PFDA	~3x to ~7x lower	2.8x lower
PFHxA	5x lower	1.5x lower
PFPrA	-	6x lower

- Not estimated



The NAMs approach estimates RfDs closer to EPA's RfDs than the RPF + carbon chain length approach & provides surrogate RfD for PFPrA

Key differences in approaches for assessing PFAS missing toxicity values

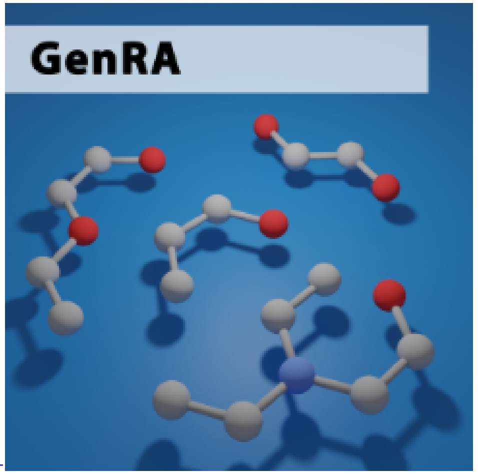
Aspects Incorporated	RPF + Carbon Chain Length Approach	Carbon Chain Length (Only) Approach	Extrapolation Approach	NAMs Approach
# PFAS predicted	6	6	7	unlimited
PFAS grouping/ subgrouping	N	N	N	Y
Carbon chain length	Y	Y	Y	N
Blood serum data	N	N	Y	Y
Toxicity data	To 2018	To 2023	To 2013	To 2024
Health endpoints	Liver	All applicable	Liver & reproductive	All applicable
Other Challenges/ uncertainties	RPFs based on liver endpoint only; assumes toxicity related to carbon chain length	Assumes toxicity related to carbon chain length	Based on liver & reproductive endpoints only	Ongoing updates & refinement of tools & databases

Y – yes; N – No

Uncertainties associated with all approaches; NAMs approach uses most updated toxicity data & can address the most PFAS

Summary for addressing PFAS missing toxicity values

- For now, individual PFAS assessed in the mixture
  - Need toxicity & health effect (e.g., liver, thyroid) data for each PFAS
  - Without health effect data, conservatively assume all PFAS cause same effect
- Various approaches can be used for PFAS with missing regulatory toxicity values
  - Use a relative potency factor (RPF) + carbon chain length approach
  - Use surrogate toxicity values from PFAS with similar carbon chain length (only)
  - Qualitatively discuss the relative toxicity
  - Generate toxicity values using NAMs (GenRA/ICE tools)
- NAMs GenRA/ICE tools can be used to estimate toxicity values
  - Can address more PFAS than other approaches due to database
  - Incorporates more than one surrogate in toxicity estimates
    - More robust estimate of toxicity
  - Ongoing updates/refinement of tool & databases
    - Reflect state of the science for PFAS



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