Overview of risk assessment approaches for mixtures

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SOILveR Online PFAS Contaminated Sites Risk Assessment workshop, November 9, 2020

Outline

- Strategies for grouping PFAS
  - focus on risk assessment
- Mixture risk assessment: decision flow chart
- Exposure assessment
- Effects assessment (“mixture toxicity”)
- Conclusions
- The way forward

Strategies for Grouping PFAS

- Motivation:
  - Grouping strategies are needed for PFAS because it would be time and resource intensive to test and regulate the thousands of PFAS on the global market on a chemical-by-chemical basis.
- Two main categories of grouping strategies, those that:
  1. are based on the intrinsic properties or structure of PFAS and
  2. **inform risk assessment through estimation of cumulative exposure and/or effects**


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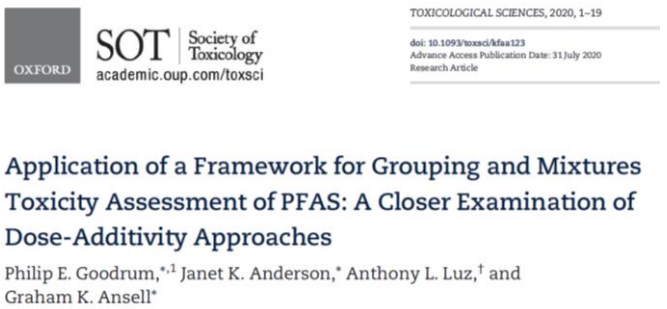
Strategies for grouping per- and polyfluoroalkyl substances (PFAS) to protect human and environmental health

Ian T. Cousins, Jamie C. DeWitt, Juliane Glüge, Gretta Goldenman, Dorte Herzke, Rainer Lohmann, Mark Miller, Carla A. Ng, Martin Scheringer, Lena Vierke and Zhanyun Wang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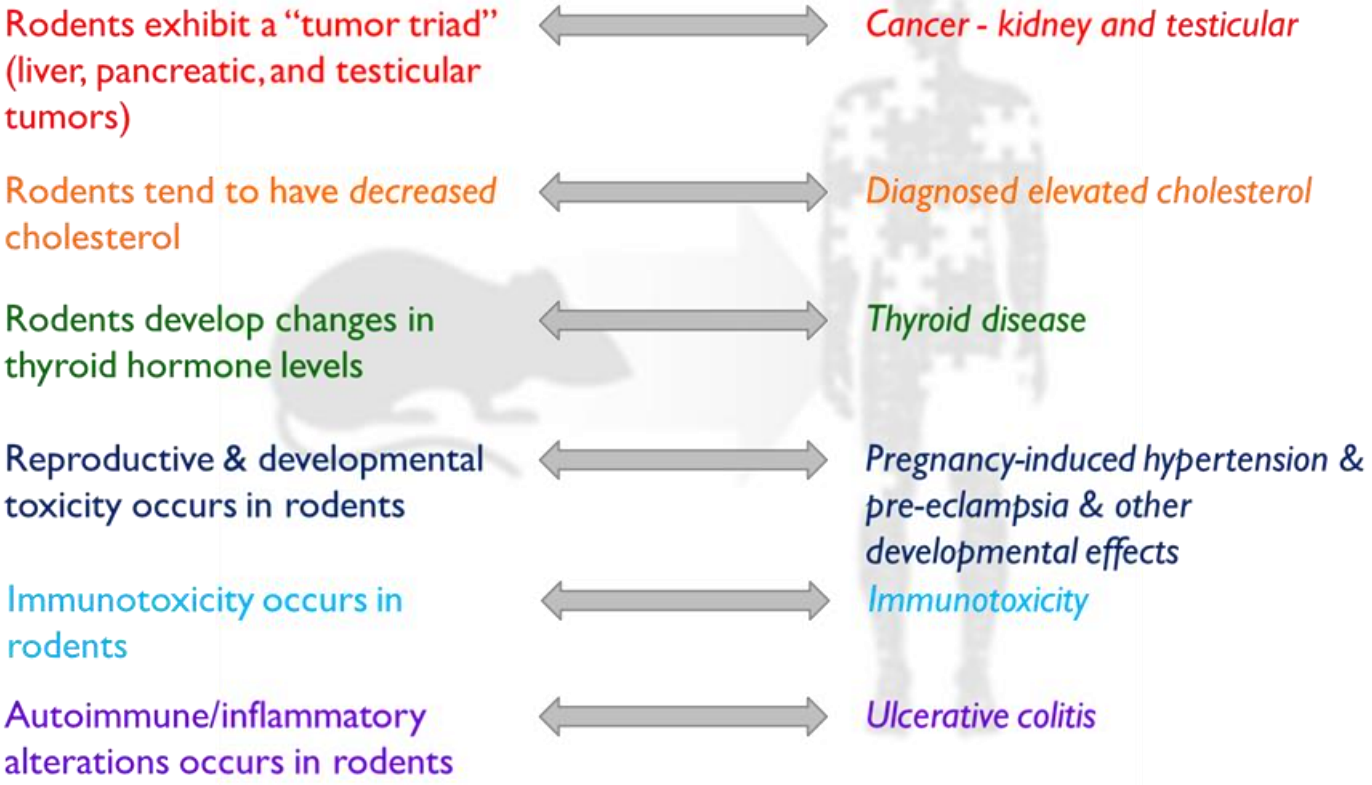
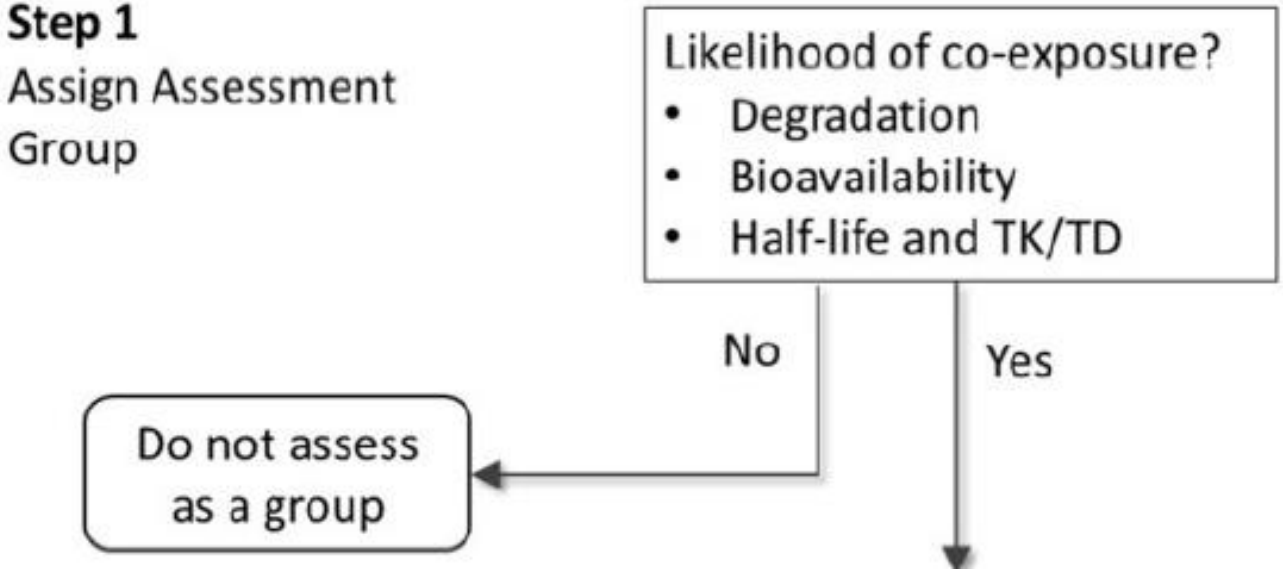


- No consensus on a single critical adverse effect
- Few adverse effects studied for multiple PFAS, and even fewer mixture toxicity studies
- Even if common effects for multiple PFAS, common mode of action is not established

Decision Flow Chart – Mixture Risk Assessment: Step 1



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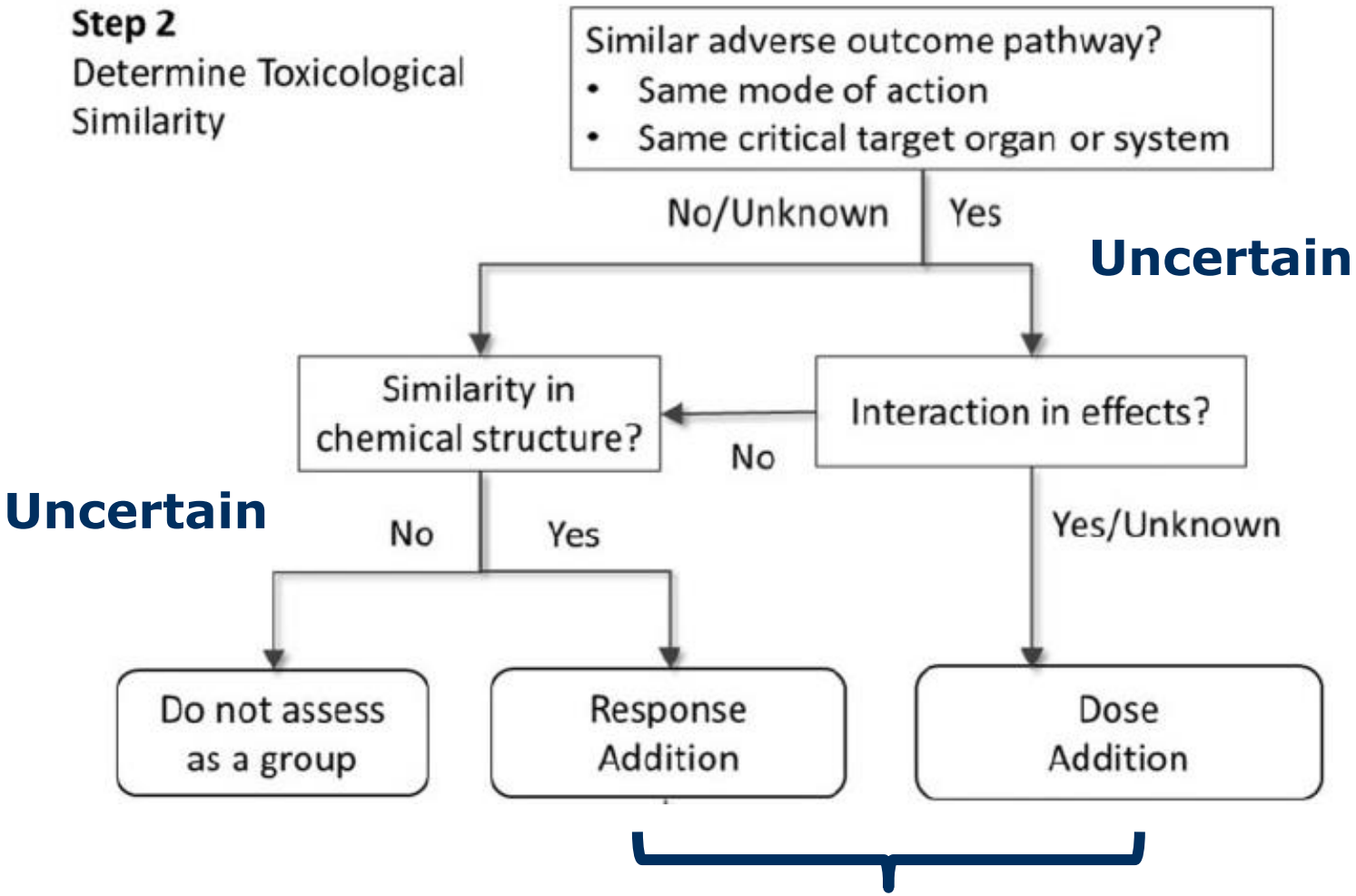
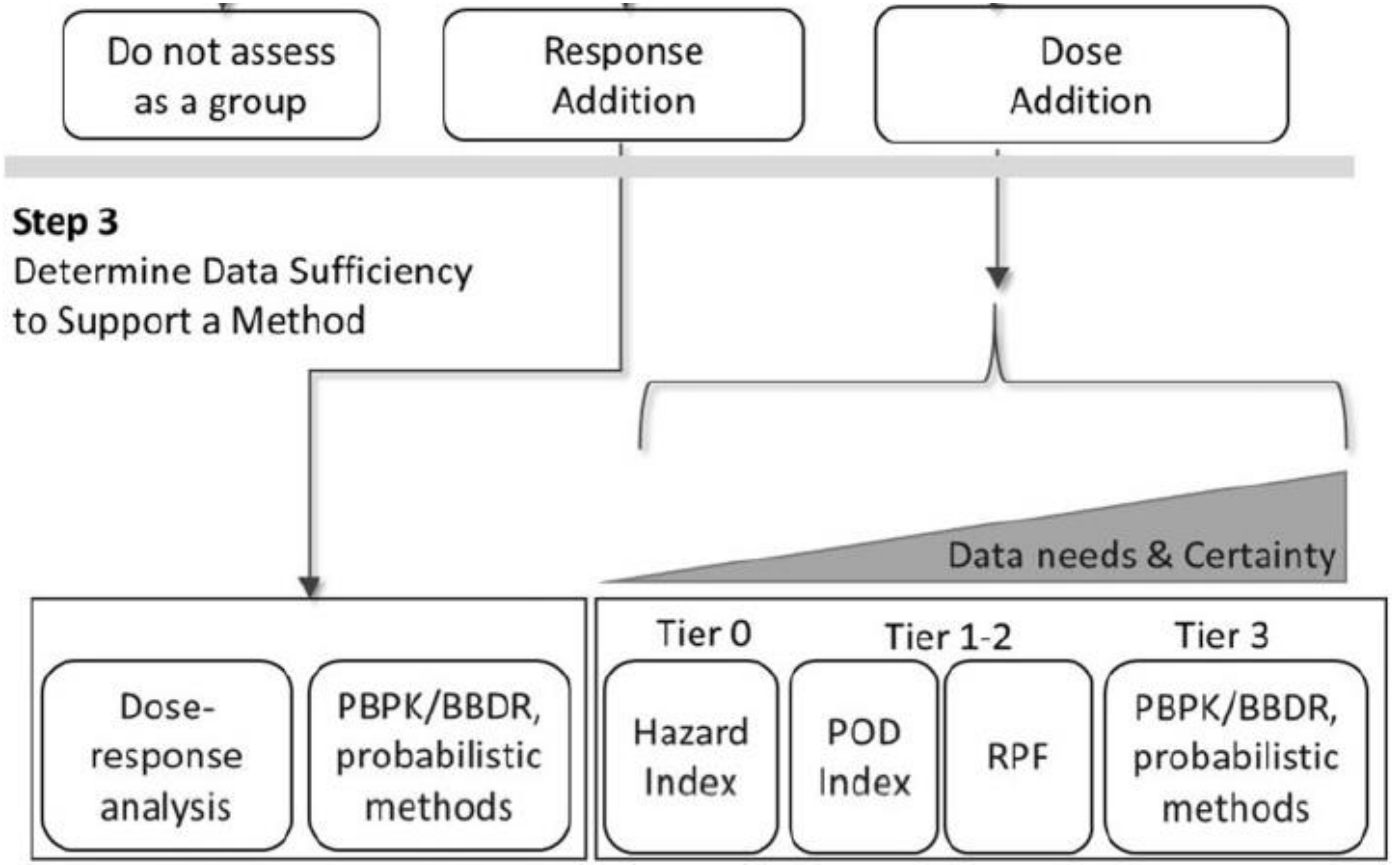
Decision Flow Chart – Mixture Risk Assessment: Step 2



Decision Flow Chart – Mixture Risk Assessment: Step 3



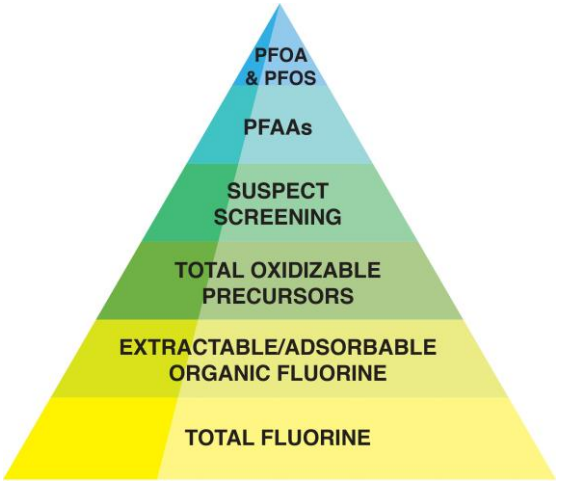
Exposure assessment for PFAS mixtures

Ideal Exposure Assessments vs Reality

- Accurate measurements of all relevant PFAS in exposure media in time and space
  - Can be complex especially if behaviours are accounted for
- Want to make probabilistic estimates of exposure (rather than single points “deterministic”)
- External and internal exposure measured
- Reality
  - We only measure a few PFAS compared to those present and only in a few places and certain times
  - Precursors and PFAAs present

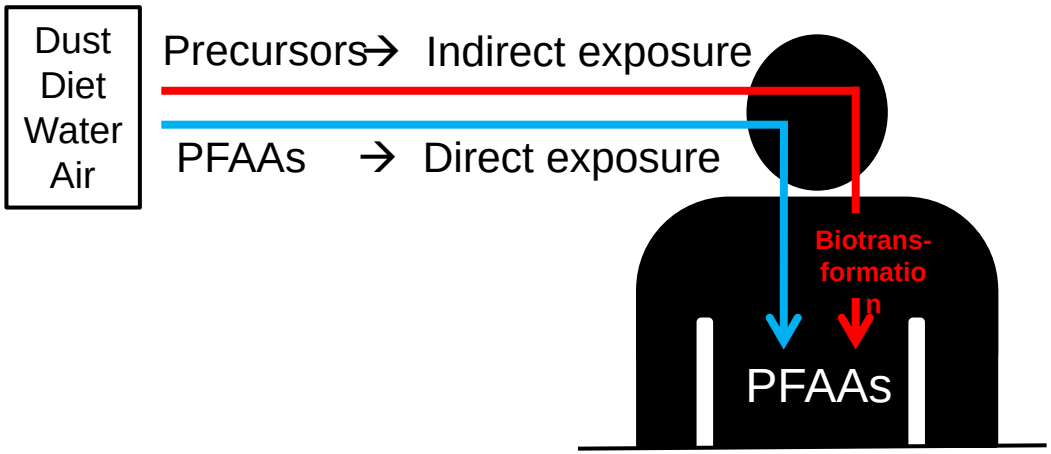
Total Organofluorine Approach

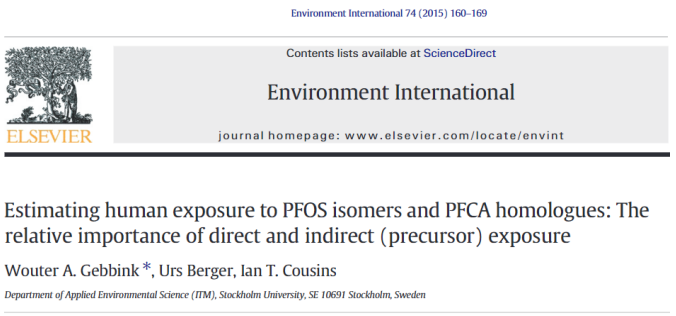
- TF/EOF/AOF – surrogates for PFAS cumulative exposure
- EU 'PFAS total' limit of 500 ng/L set in a recast of the Drinking Water Directive
  - EOF/AOF could be used to pre-screen samples
- Uncertainties in translating the EOF/AOF measurements into risk-based guidelines
  - Which PFAS are represented?
  - EOF/AOF would capture non-PFAS derived organic fluorine
- Still maybe promising as pre-screening approach



Precursor exposure?

- Lack of methods for measuring all relevant precursors to a specific PFAA
- Total oxidizable precursor assay (TOPA)?
- Levels of PFAAs in samples could be compared to guidelines after applying TOPA
- TOPA does not accurately simulate metabolism
- Precursor contribution can be modelled if precursors measured in exposure media

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Estimating human exposure to PFOS isomers and PFCA homologues: The relative importance of direct and indirect (precursor) exposure

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Effects assessment for PFAS mixtures or "Mixture toxicity"

Simple Additive Toxicity: "tier 0"

- Assumes multiple PFAS have the equivalent toxicity of a "lead PFAS" (often PFOS or PFOA)
  - Guideline set based on sum of multiple PFAS (mostly PFAAs) in sample
  - Used in drinking water guidelines in Sweden (11 PFAS), Denmark (12 PFAS), US states, etc.
- Limitations:
  1. the identified critical adverse effects, as well as modes of action vary
  2. elimination kinetics vary
  3. mixture toxicity may not be simply additive
  4. many PFAS are neglected

Hazard Index: "tier 0"

$$\mathrm{HI} = \sum_{i=1}^{n} HQ_i \qquad HQ_i = \frac{Dose_i}{Rfd_i}$$

Where HI is the Hazard Index and HQ_i is the Hazard Quotient for component *i*

$Dose_i$ is the average daily dose (mg/kg/d) and Rfd_i can be any relevant toxicity reference dose (mg/kg/d) (liver, development, kidney, etc.)

- No common critical effect needed at tier 0!
- Screening level risk assessment

Hazard Index Application

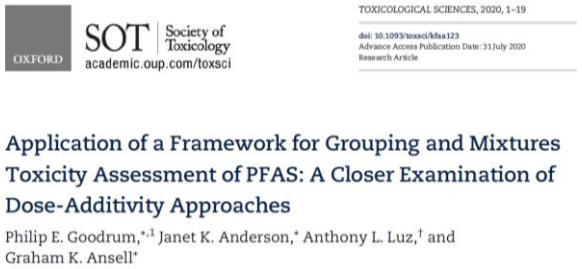
Stockholm University

Table 3. Hypothetical Example Illustrating Application of the HI Approach for Infants Consuming Drinking Water

Chemical	C (ng/l)	DW (l/day)	BW (kg)	EF (days/year)	Dose[a] (mg/kg/day)	Oral RfD (mg/kg/day)	Critical Effect Target Organ	HQ[b]	Source for RfD
PFNA	11	0.78	15	350	5.5E-07	2E-06	liver	0.3	Health Canada (2019)
PFOA	43	0.78	15	350	2.1E-06	2E-05	development	0.1	USEPA (2016b)
PFHxA	87	0.78	15	350	4.3E-06	0.25	kidney	0.00002	Luz *et al.* (2019)
PFOS	446	0.78	15	350	2.2E-05	2E-05	development	1	USEPA (2016a)
PFHxS	92	0.78	15	350	4.6E-06	6E-05	liver	0.1	Health Canada (2019)
PFBS	21	0.78	15	350	1.0E-06	2E-03	kidney	0.0007	USEPA (2014)
Sum:	700						Sum (HI):	1.6	

Abbreviations: BW, infant body weight; C, concentration; DW, infant drinking water ingestion rate; EF, exposure frequency; HQ, hazard quotient.
[a]Dose = $(C/1 \times 10^6) \times DW \times (EF/365)/BW$.
[b]HQ = dose/RfD.

- HI > 1 so more refined risk assessment needed



Higher tier mixture risk assessments?

- Mixture toxicity methods should ideally be applied to same critical organ/system
- Hepatocellular hypertrophy and kidney effects remain the only endpoints for which there are similar toxicity data from similar study designs, for multiple PFAS
  - Kidney data not amenable for dose-response modelling
  - But liver hypertrophy data are
  - Applied by RIVM in Relative Potency Factor (RPF) Approach

RPF approach "tier 1-2"

$$RPF_i = \frac{BMD_{PFOA}}{BMD_i}$$

$$C_{PFOA\,Equ} = \sum_{i=1}^{n} RPF_i * C_i$$

$$HQ = \frac{C_{PFOA\,Equ}}{POD_{PFOA}}$$

- Liver hypertrophy
- 22 PFAS rat, oral
- Congruent dose-response curves

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Hazard/Risk Assessment

Risk Assessment of Per- and Polyfluoroalkyl Substance Mixtures: A Relative Potency Factor Approach

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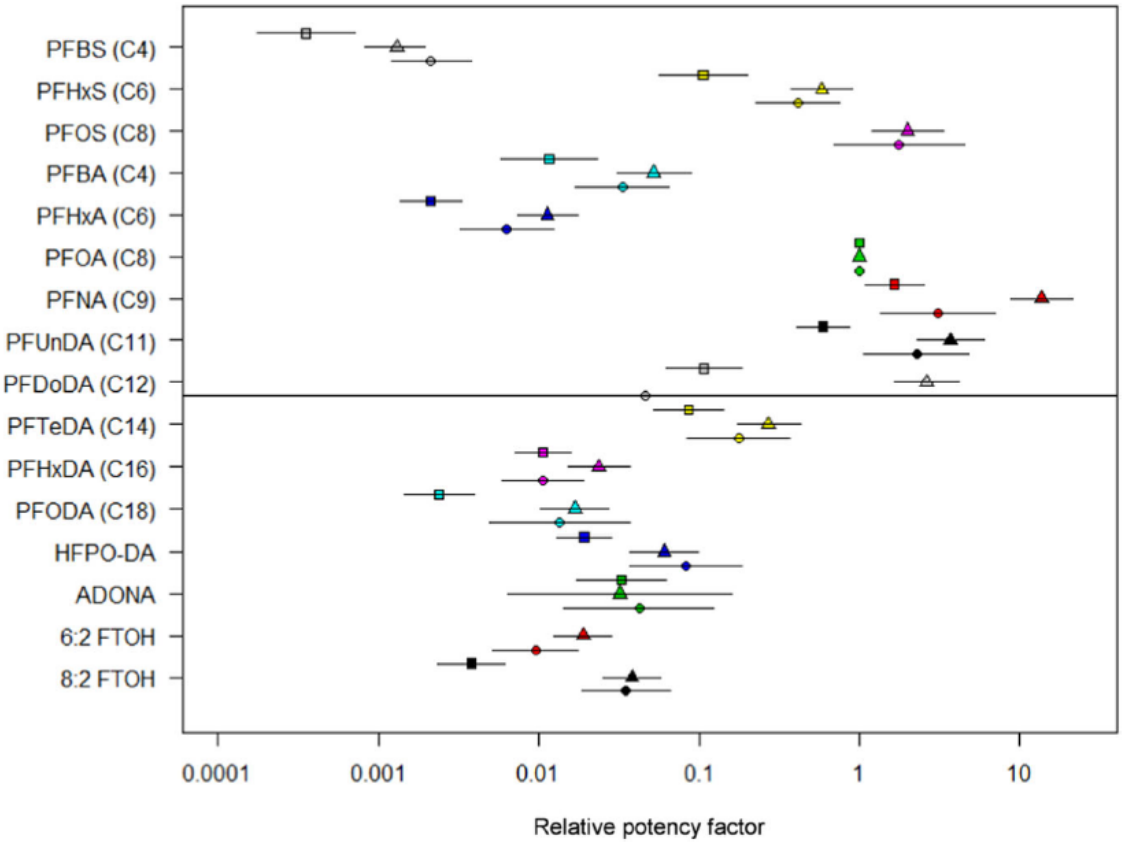
RPFs for multiple PFAS



- Differences in RPFs largely explained by elimination rates
- Internal dose normalization indicated similar potencies for all PFAAs (Gomis et al., 2015)

RPF approach: application to drinking water

Stockholm University

TABLE 2: The occurrence of per- and polyfluoroalkyl substances in drinking water in Rotterdam, The Netherlands, as presented in Brandsma et al. (2019) and the resulting sum of perfluorooctanoic acid equivalents based on the relative potency factors

Per- and polyfluorinated congeners	Concentration (ng/L)	RPF	PEQ[c] (ng/L)	PEQ[d] (ng/L)
PFBS	4.8	0.001	0.0048	0.0048
PFHxS	0.6[b]	0.6	0.36	0.36
PFHpS	0.5[a]	$0.6 \leq RPF \leq 2$	$0.3 \leq PEQ \leq 1$	NA
PFOS	1.3[b]	2	2.6	2.6
PFBA	5.0[a]	0.05	0.25	NA
PFPeA	5.1[b]	$0.01 \leq RPF \leq 0.05$	$0.051 \leq PEQ \leq 0.26$	$0.051 \leq PEQ \leq 0.26$
PFHxA	5.6	0.01	0.056	0.056
PFHpA	3.1[b]	$0.01 \leq RPF \leq 1$	$0.031 \leq PEQ \leq 3.1$	$0.031 \leq PEQ \leq 3.1$
PFOA	3.9	1	3.9	3.9
PFNA	0.5[a]	10	5	NA
PFDA	0.5[a]	$4 \leq RPF \leq 10$	$2 \leq PEQ \leq 5$	NA
PFUnDA	0.5[a]	4	2	NA
PFDoDA	0.5[a]	3	1.5	NA
HFPO-DA	5.9	0.06	0.35	0.35
Sum PEQ			$18 \leq PEQ \leq 25$[e]	$7.4 \leq PEQ \leq 11$[e]

- PFOA equivalent concentration 25 ng/L which is under the drinking water guideline limit for PFOA in the Netherlands of 87.5 ng/L

EFSA opinion: mixture approach

- Tolerable weekly intake (TWI) of 8 ng/kg BW for sum of 4 PFAS (PFOA, PFNA, PFHxS and PFOS)
- Decreased response of the immune system to vaccination was used as the critical human health effect in determining the new TWI value
- 4 PFAS have similar elimination half-lives
- Immunotoxicity effects observed for all four PFAS although potencies inconsistent
- Mode of action unknown
- Pragmatic protective approach adopted

Conclusions

- Strictly, for mixture risk assessment, one should only group PFAS that have the same mode of action, accounting for PK differences
  - Then grouping PFAS is challenging!
  - “Strictness” varies between jurisdictions
- Huge data gaps have caused progressive regulators to make pragmatic and protective solutions
  - Precaution warranted given high persistence and multiple PFAS that are not included
- RPF approach only “higher tier” method available for mixture risk assessment, and only for liver
  - but no consensus on common critical effect for PFAAs

The way forward

- US EPA and NTP testing 150 PFAS for hepatotoxicity, immunotoxicity, developmental toxicity, mitochondrial toxicity, developmental neurotoxicity, hepatic clearance, and toxicokinetics with high-throughput in vitro assays
  - By maximizing structural diversity, this research may inform mixture risk assessment
- In the meantime, precautionary mixture risk assessment approaches are warranted
  - But there are clean-up cost implications
- Restriction of PFAS uses based on problematic intrinsic properties (especially high persistence)
  - REACH restriction by 5 European countries (D, DK, N, NL, SE)

Thank you for your attention!

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