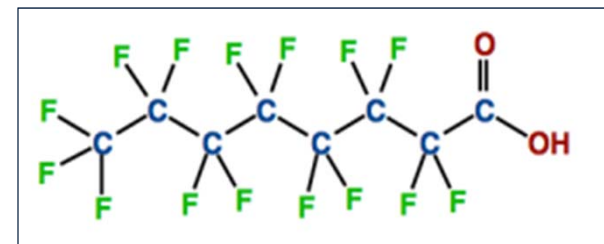
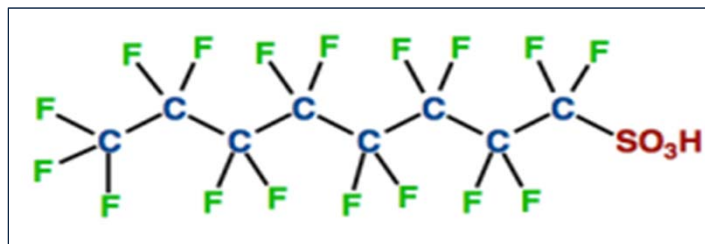


PER- AND POLY-FLUOROALKYL SUBSTANCES (PFASs)

Addressing Limited Toxicity Data in Site Characterization



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Battelle
11th International Conference
Remediation of Chlorinated and Recalcitrant Compounds
April 8-12 2018

OVERVIEW



Toxicity Data in Site Characterization

Analytical Capability vs Toxicity Data

Current Regulatory Strategies

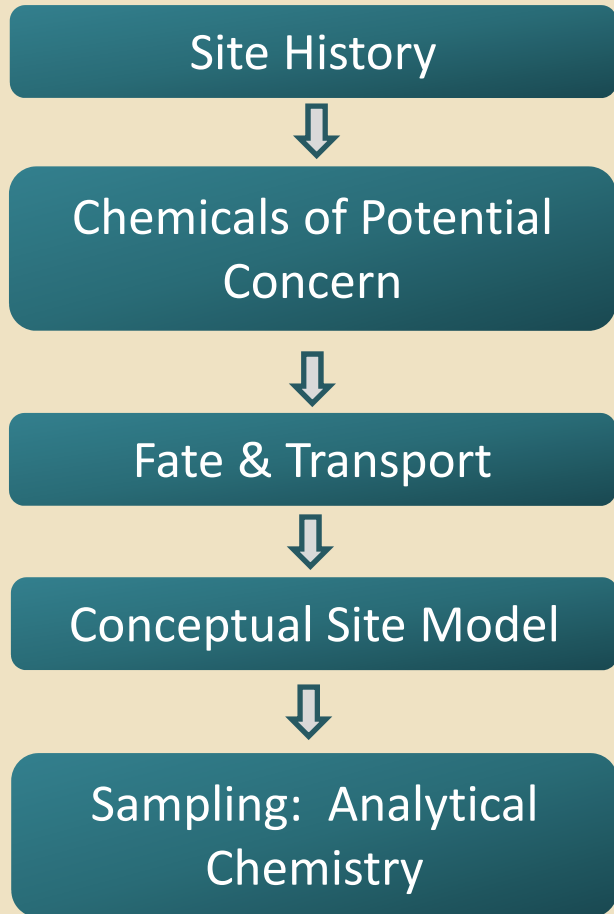
PFAS Toxicity and Modes of Action

Summary and Conclusions

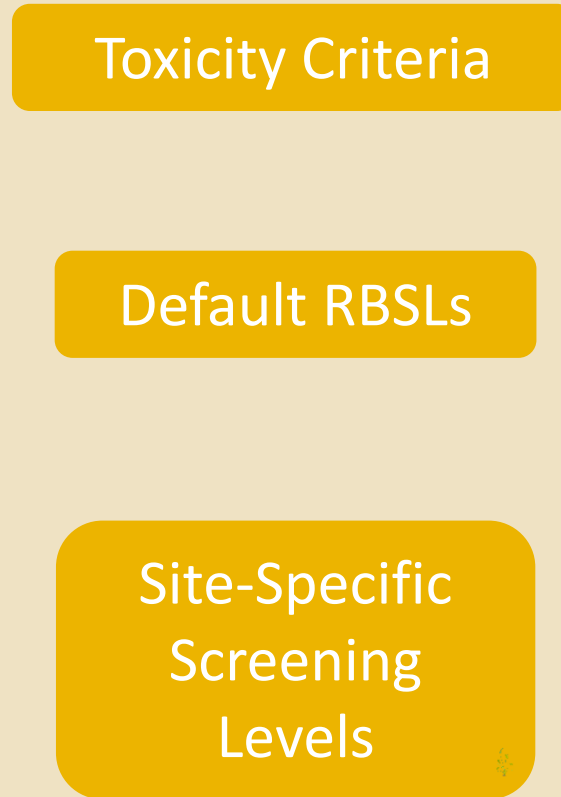
TOXICITY DATA IN SITE CHARACTERIZATION & REMEDIATION



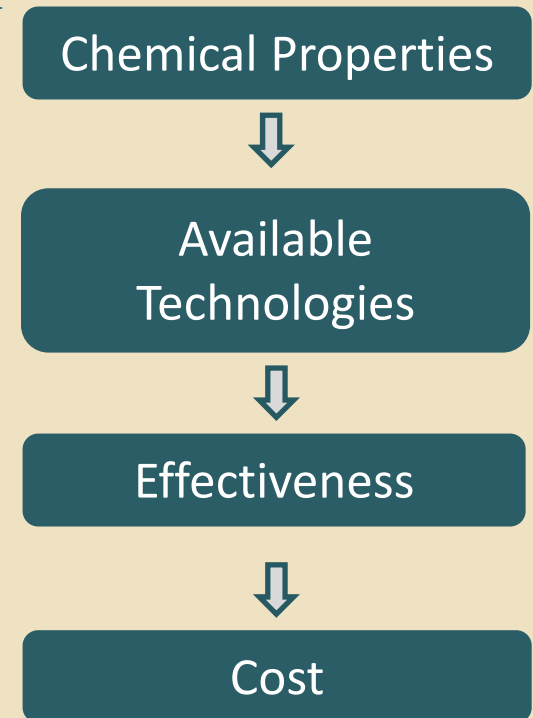
Site Characterization



Applicable Criteria



Remediation



PFAS ANALYTICAL CAPABILITY HAS OUTPACED TOXICOLOGY



PFAS Category	Commercial Analytical Capability by PFAS Category	No. of Toxicity Studies – Individual PFASs in Category ¹
Perfluoroalkyl Carboxylates, Acids	12	0 ↓ > 100
Perfluoroalkyl Sulfonates, Sulfonic Acids	4	0 ↓ > 100
Perfluoroalkyl Phosphonic Acids	None	None
Perfluorooctane Sulfonamide and Derivatives	6	0 ↓ 10
Fluorotelomer Sulfonates, Acids	3	1
Fluorotelomer Alcohols	None	0 ↓ 10
Polyfluorinated Alkyl Phosphates	10	1

¹ Mammalian data; peer-reviewed literature

TOXICITY WEIGHTING AS INTERIM STRATEGY?

Basis

- Shared toxicological mode of action (MOA)
 - Additivity of effects
 - Linearity of dose-response
 - MOA endpoint protective of other effects

Examples

- Polychlorinated dibenzodioxins/furans; PCBs, PAHs

Dioxin	TEF
2,3,7,8-TCDD	1.0
1,2,3,4,7,8-HxCDD	1.0
1,2,3,4,6,7,8-HpCDD	0.01
OCDD	0.0003

Van den Berg et al 2006

Purpose

- Identify interim toxicity criteria for PFAS with limited data
- Support site characterization; risk assessment; remediation

CURRENT STRATEGIES TO ADDRESS UNCERTAINTY IN MOA - US













Agency	PFAS	Surrogate Toxicity	Additivity?
USEPA	PFOA, PFOS	No	✓
CO DPHE	PFOA, PFOS, PFHpA	✓ Yes PFHpA = PFOA or PFOS	✓
CT DEEP	PFOA, PFOS PFHpA, PFNA, PFHxS	✓ Yes PFHpA, PFNA, PFHxS = PFOA or PFOS	✓
TX CEQ	PFOA, PFOS, PFBA, PFBS PFNA, PFDeA PFOSA PFHxS PFDoA PFPeA PFHxA PFHpS PFDS PFUA PFTTrDA PFTeDA	No No ✓ Yes = PFOA TK = PFOS TK = PFOA ✓ Yes = PFHxS ✓ Yes = PFHxS ✓ Yes = to PFOS ✓ Yes = PFDoA ✓ Yes = PFDoA ✓ Yes = PFDoA ✓ Yes = PFDo	No

CURRENT STRATEGIES TO ADDRESS UNCERTAINTY IN MOA - INTERNATIONAL

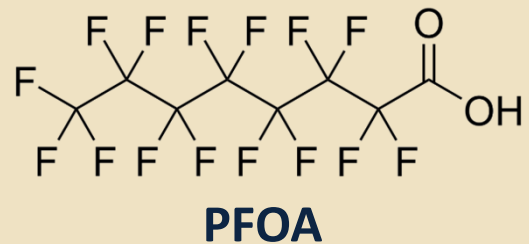


Country	PFAS (excluding PFOA/PFOS)	Surrogate Toxicity	Assumed Additivity?
Sweden	PFHpA, PFNA, PFHxS, PFBS, PFHxA, PFPeA	✓ = PFOS	✓
Denmark	PFHpA, PFNA, PFHxS, PFBA, PFBS, PFHxA, PFPeA, PFOSA, PFDA, 6:2 FTS	✓ = PFOS	✓
Canada	PFBA, PFBS, PFHxS, PFPeA, PFHxA, PFHpA, PFNA	✓ = PFOA = PFOS	✓ PFOA PFOS only

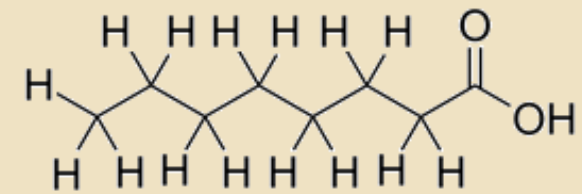
PFAAs - ADVERSE EFFECTS

System	Species	Health Effect
Hepatic & Metabolic		↑ cholesterol
		↓ cholesterol, liver hypertrophy
Developmental & Reproductive		low birth weight, delayed onset of puberty
		↓ pup body weight, pup survival; develop. delays
Immune System		reduced vaccine response
		reduced thymus & spleen weights
Carcinogenicity		kidney and testes
		liver, pancreas, testes
Endocrine System		reduced thyroid hormone & testosterone levels
		activation of Estrogen Receptor α

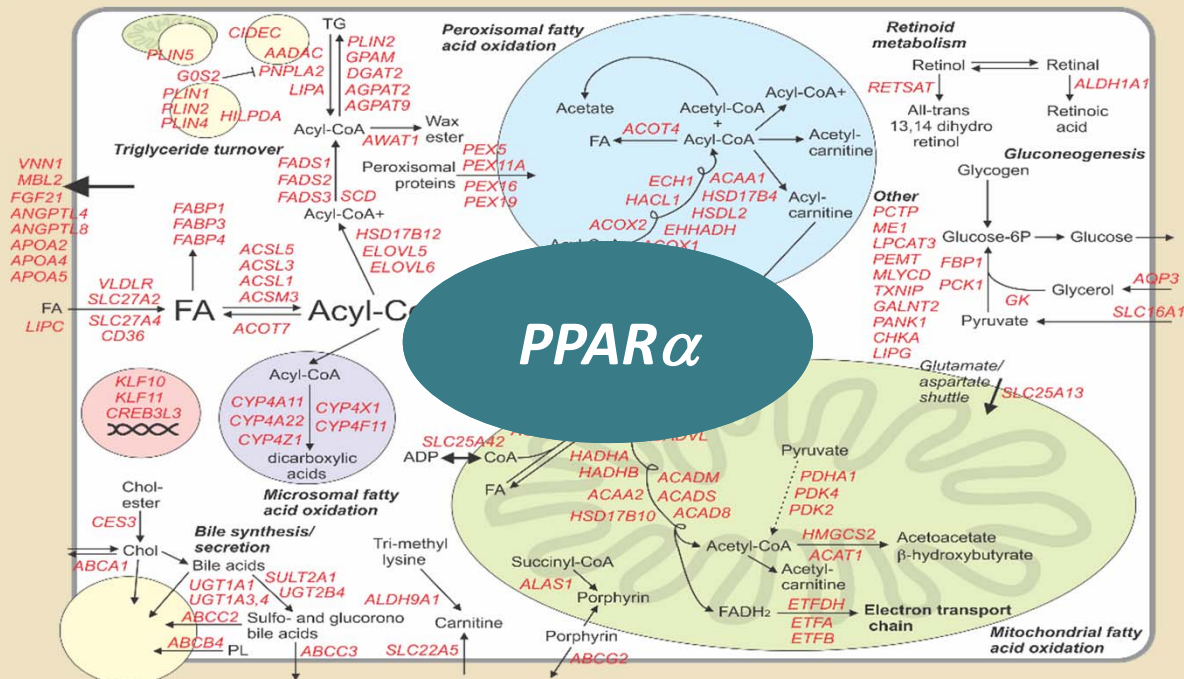
PFAAs – MODES OF ACTION



*Structural Analogs
of Fatty Acids*



Nuclear Receptors (Gene Regulators)



PFAAs – TOXICITY VS MODE OF ACTION

PPAR α ¹

- Dominant nuclear receptor of those studied

PPAR α

- PFOA, PFOS, PFNA, PFHxS
- ~75% of genes

*Other Receptors*¹

- Significant but variable no. of genes

PPAR γ

ER α

CAR

- PFHxS
 - 22-24% of genes
- PFOA, PFOS, PFNA
 - 10-17% of genes

¹Rosen et al. 2017

PPAR_A ACTIVATION IN VITRO

Perfluorocarboxylic Acids (PFCA)

- ↑ activity with fluorinated chain length
 - Cos-1 (mouse, human PPAR α)¹
 - Rat, human liver²

PFBA	PFPeA	PFHxA	PFOA	PFHpA	PFOA	PFNA	PFUNA
C4	C5	C6	C8	C7	C8	C9	C11
1	1.4	1.6	4.7	5	6.5	6.8	0.9

Wolf et al., 2008; 2012

- Rodent cells > responsive than human cells

Perfluorosulfonic acids (PFSA):

- PFSAs << PFCAs
- Activation not well correlated to fluorinated chain length

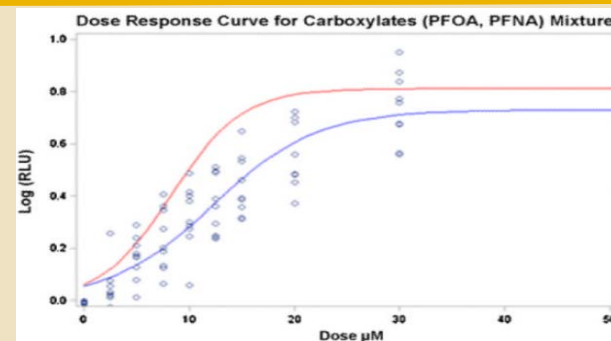
¹ Wolf et al., 2008; 2012

² Bjork and Wallace, 2009

ARE PFAS_s EFFECTS ADDITIVE IN VITRO?

PPAR α Activation^{1,2}

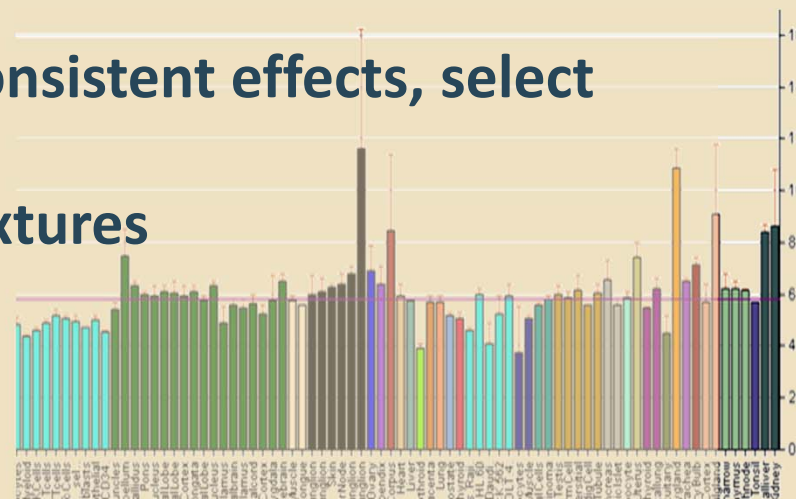
- Additivity
 - only at low concentrations
 - non-linear
- PFOA, PFNA, PFOS, PFHxS (in pairs & combined)¹
- PFOA + [PFNA or PFHxA or PFOS or PFHxS]²



Carr et al.2013

Different genes activated by mixtures³

- Individual PFCAs, (PFOS; FTOH); consistent effects, select genes
 - Unique gene expression by mixtures
 - PFCAs \neq PFOS or 8:2 FTOH
 - PFOA:PFOS mixture \neq PFOA \neq PFOS



^{1,2} Carr et al.2013; Wolf et al. 2014

³ Wei et al. 2009 .

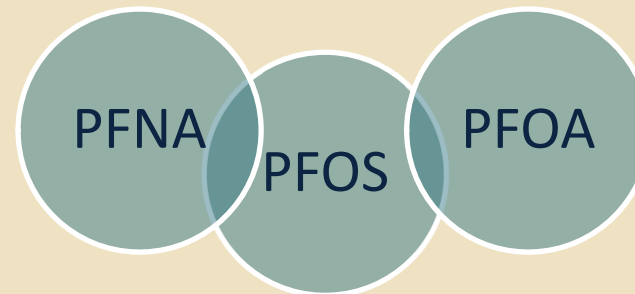
Do in vivo PPAR_α data support toxicity weighting?

Developmental Toxicity

- PPAR_α-dependent: PFNA > PFOA >>> PFBA
- PPAR_α-Independent: PFOS, PFHxS, PFBS

Hepatic Toxicity (non-cancer)

- PPAR_α-dependent
- PPAR_α-Independent



- **Multiple MOAs for PFAS toxicity**
 - **PPAR α activation the dominant MOA**
 - **Role of other nuclear receptors not well-characterized**
 - **Many key toxicity endpoints are PPAR α -dependent, but many are PPAR α -independent**
- **Additivity of PFASs uncertain**
 - **In vitro data support limited additivity, PFCAs when PPAR α -mediated**
 - **Data do not necessarily support additivity of PFCAs and PFSA**

CONCLUSIONS

- **MOA data are currently not adequate for development of interim toxicity weighting strategy**

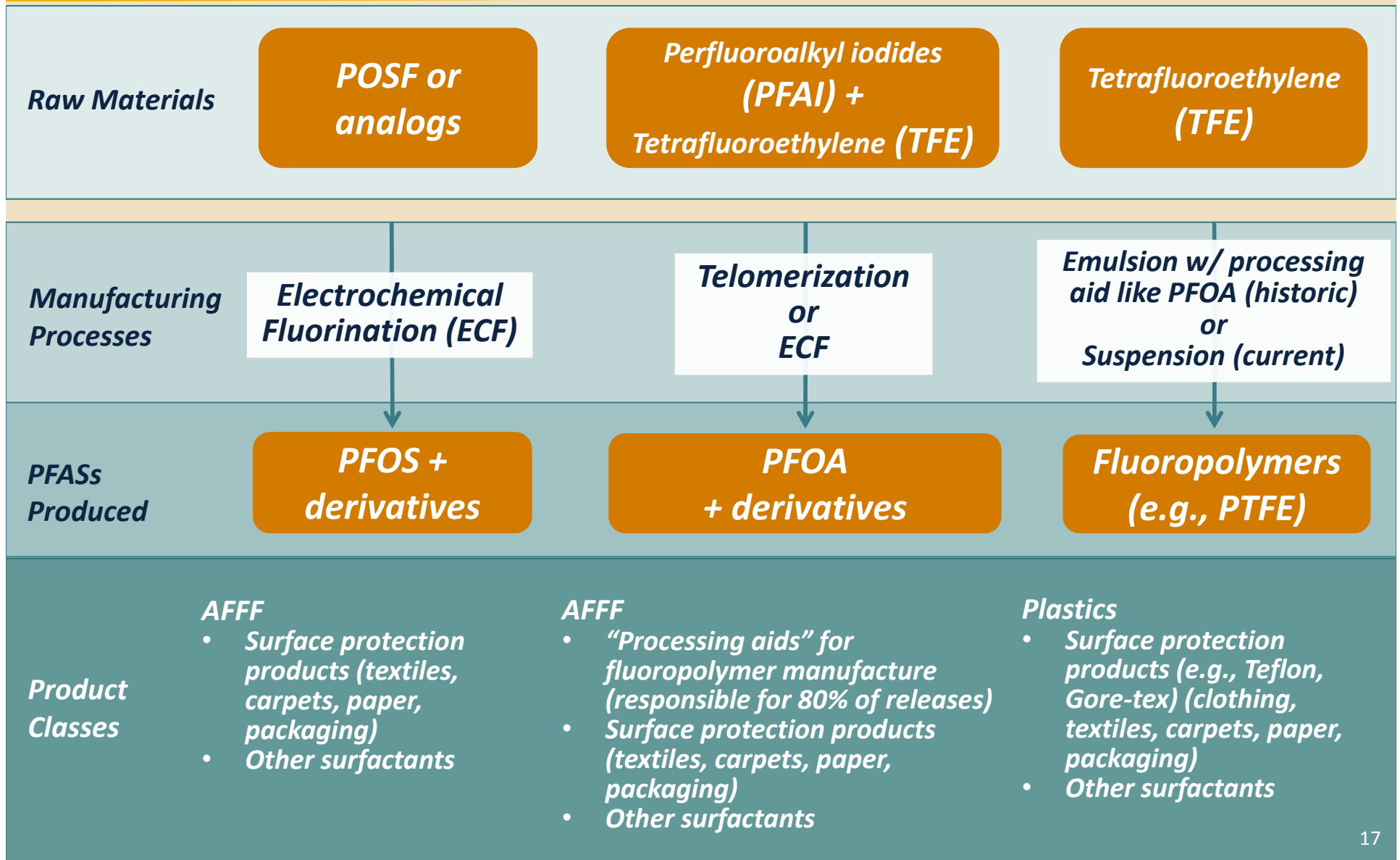
- **Implications for Site Characterization:**
 - **Continued use of surrogate toxicity supported by Precautionary Principle**
 - **But many questions on additivity of environmental mixtures.....**

QUESTIONS?



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PFAS: HISTORIC PRODUCTION AND USE



PFAAs – TOXICITY VS MODE OF ACTION

*Peroxisome
Proliferator-
Activated
Receptor alpha
(PPAR α)*

- Hepatic toxicity
- Lipid regulation and metabolism
- Immunotoxicity
- Developmental toxicity
- Rodent tumors (liver) pancreas? testes ?

- Hepatic toxicity
- Immunotoxicity
- Developmental toxicity
- Endocrine (thyroid hormone levels, metabolic effects)

