(Eco)toxicology of PFAS: A few highlights

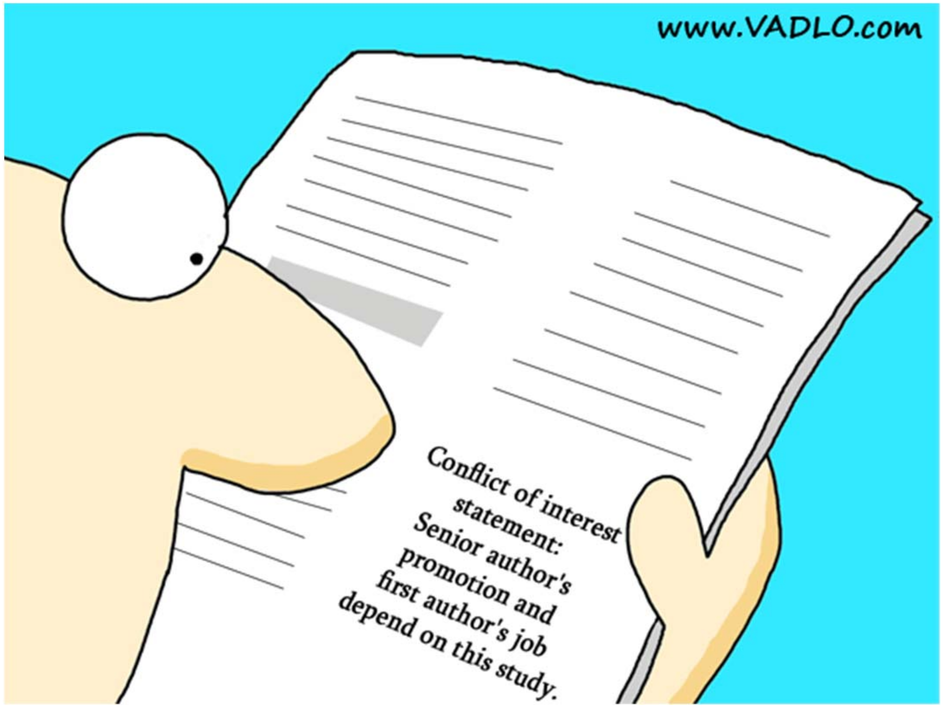
Jamie DeWitt, PhD, DABT
Department of Pharmacology & Toxicology
Brody School of Medicine
East Carolina University
Greenville, NC
dewittj@ecu.edu

Europe's PFAS problem: situation briefings by independent experts
Session 2 Webinar: September 14, 2020

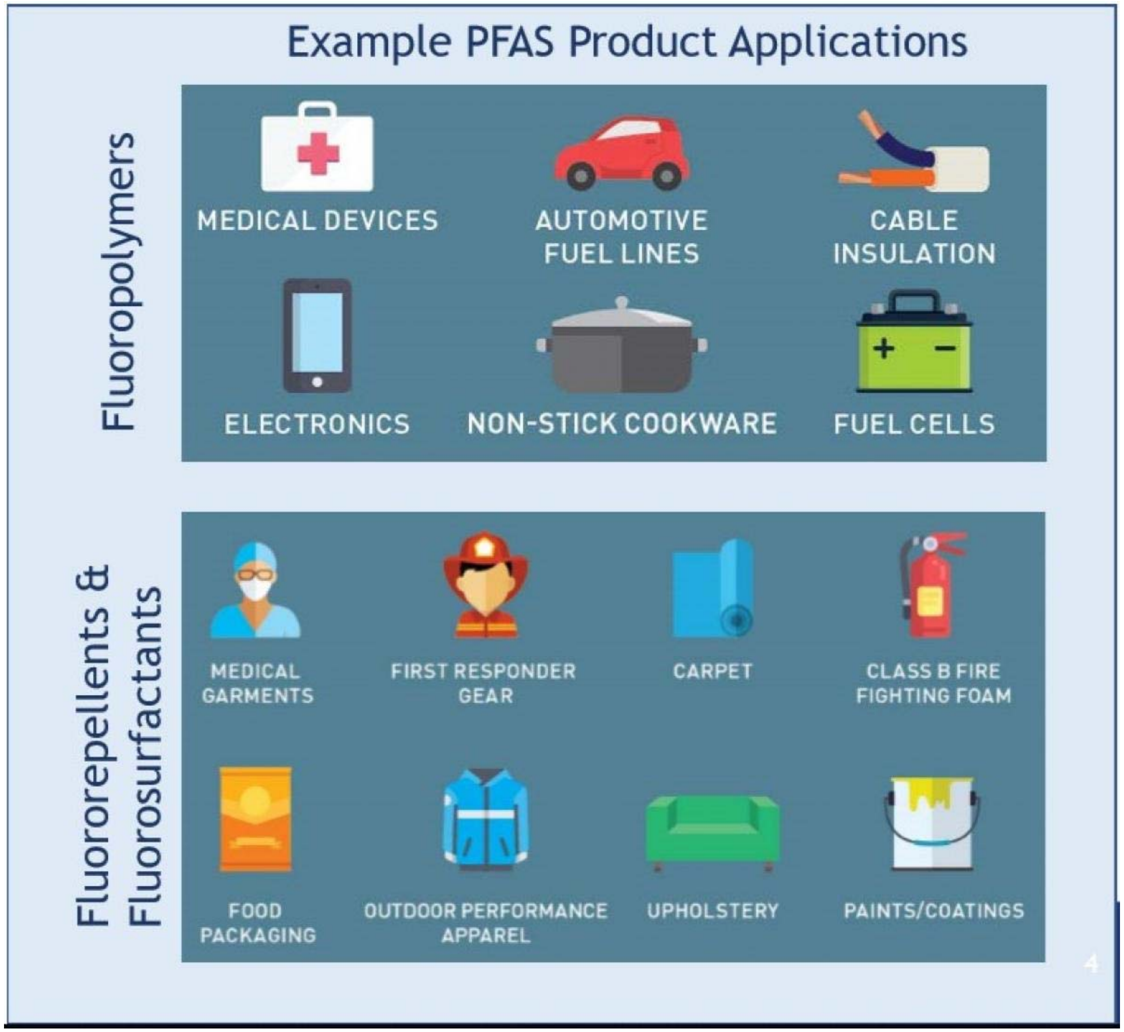
Conflict of Interest Statement:

I currently am funded to study immune system effects of PFAS.

I have spoken publicly about my understanding of PFAS toxicity, serve/have served as a plaintiff's expert witness, and advocate for the need to protect the public from their exposures to PFAS.



PFAS – quick reminders

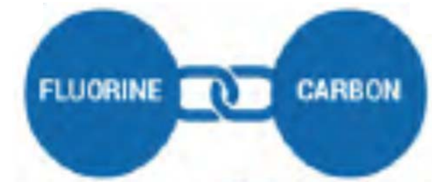


PFAS

- A class of >4,000 substances
- Produced and used since 1940s
- Chemical properties that make them useful in a wide range of applications, especially as surfactants and surface protectors

Image source: https://www.oaklodgewaterservices.org/surface-water/page/public-information-brief-pfas.

PFAS – quick reminders



"The use and manipulation of this bond gives FluoroTechnology its distinct properties of strength, durability, heat resistance and stability."

But also…

- Persistence
- Bioaccumulation potential
- Mobility (some)
- Toxicity (those studied)

PFAS images source: Hopkins et al. 2018. Fluorine-carbon bond and quote from the FluoroCouncil.

PFAS persistence in perspective

TABLE 17.2 The persistence of various chemicals in the environment, measured in terms of their half-life

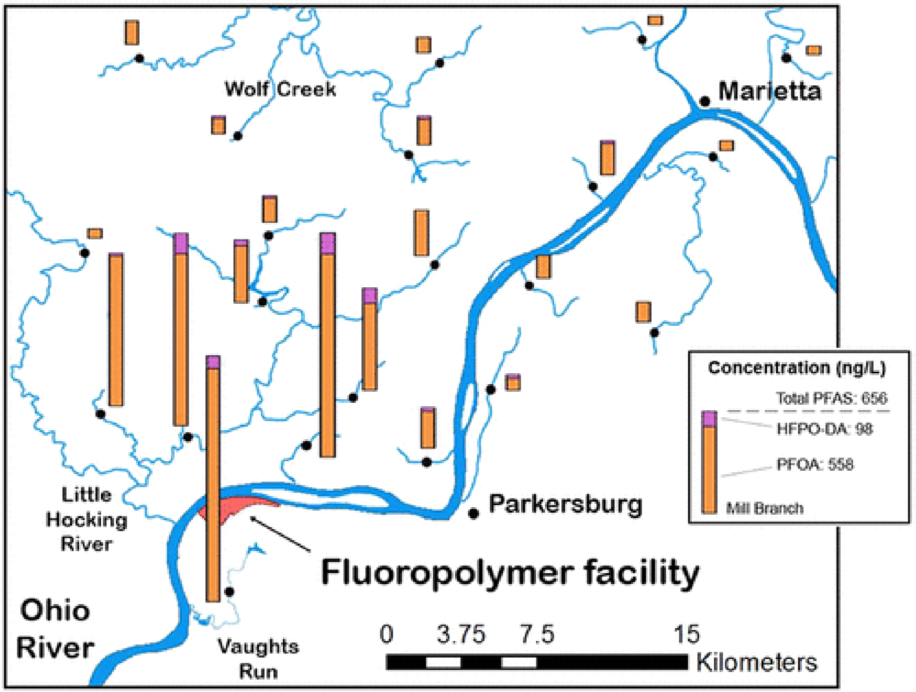
Chemical	Half-life
Malathion insecticide	1 day
Radon	4 days in air
Vinyl chloride	4.5 days in air
Phthalates	4.5 days in water
Roundup herbicide	7 to 70 days in water
Atrazine herbicide	224 days in wetland soils
Polychlorinated biphenyls (PCBs)	8 to 15 years in water
DDT	30 years in soil

Source: Hazardous Substances Data Bank, http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB/.

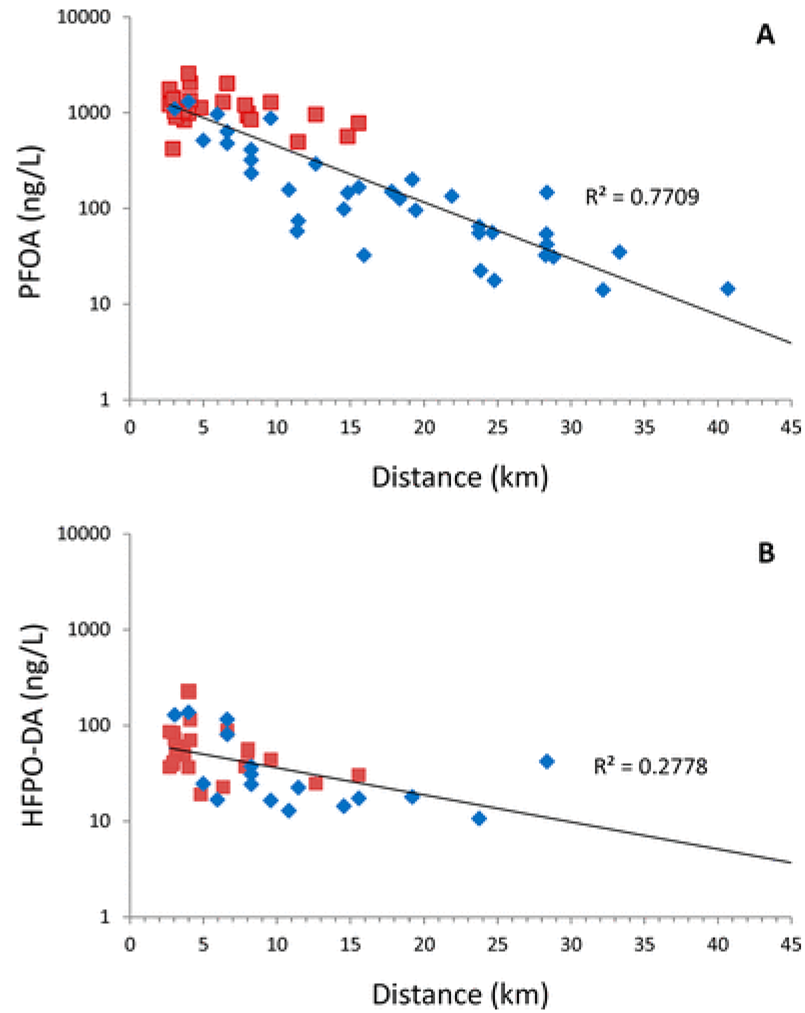
Table 17.2
Environmental Science

PFAS	>30 years? >100 years?

PFAS mobility is not limited to short-chains



Galloway et al. (2020) demonstrated that atmospheric transport of both PFOA and HFPO-DA ("GenX") has occurred from a point source and *that the boundaries of the impact zone have not yet been fully delineated.*



Red dots = 2016; Blue dots = 2018

Image source: Galloway et al. 2020.

PFAS exposure sources and pathways

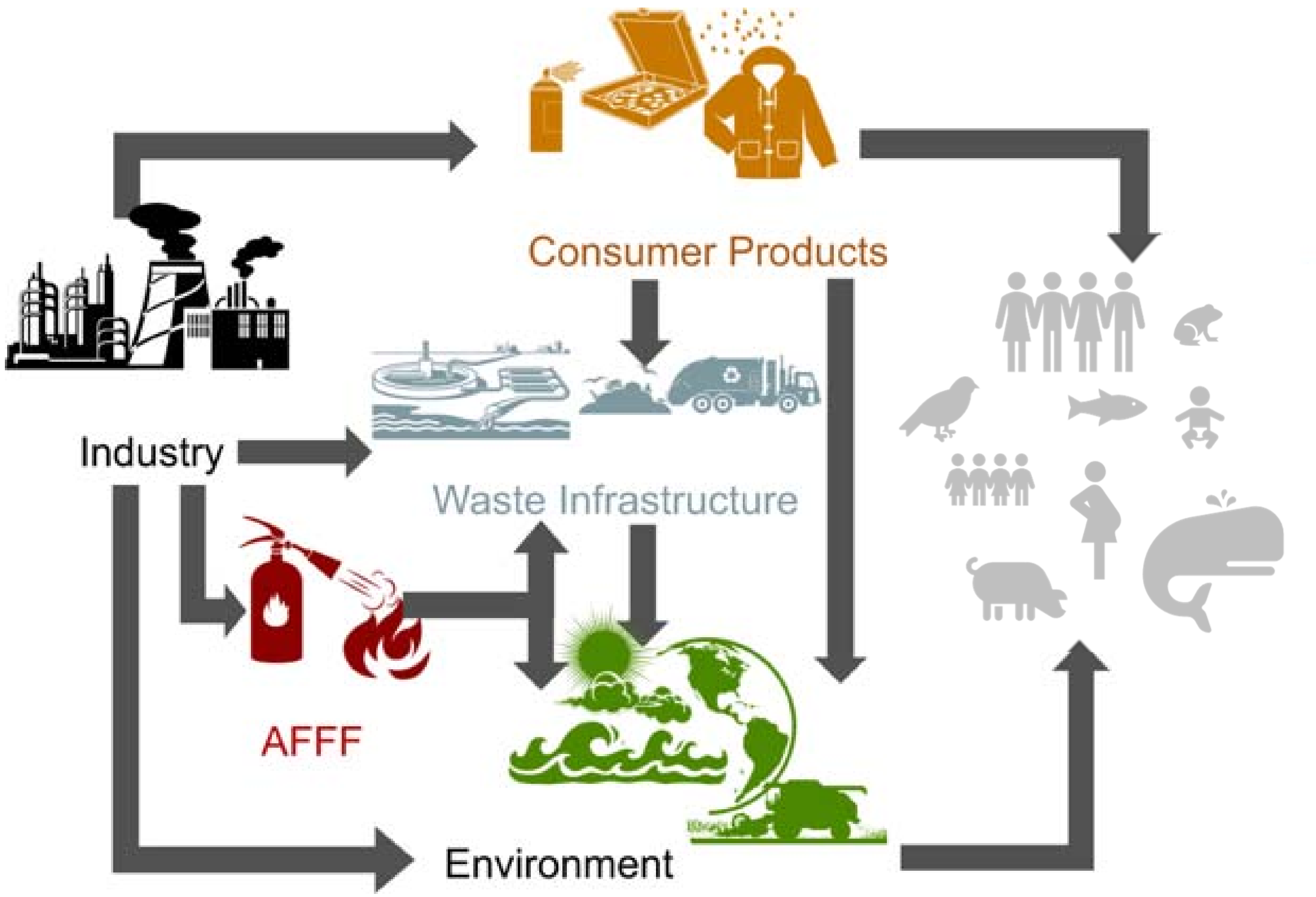
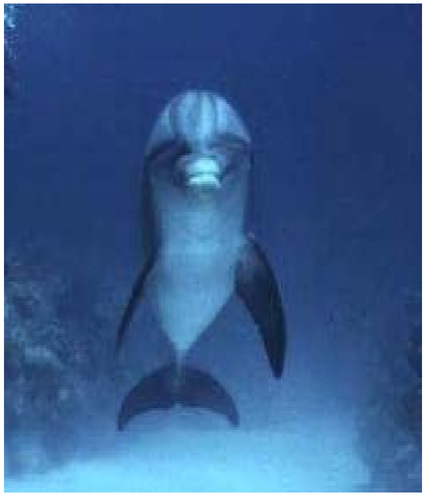


Image modified from: Sunderland et al. 2018.

PFAS accumulation in wildlife



Vertebrate wildlife [max PFOS]

Up to 3073 ng/mL in plasma of **Bottlenose dolphin**

Up to 1325 ng/g in liver of **polar bear**

Up to 96.8 ng/mL in plasma of **Loggerhead sea turtle**

Up to 450 ng/mL in plasma of **Herring gulls**

Up to 176 ng/mL in plasma of **rockfish**

(DeWitt et al., 2012)

Images from various sources.

PFAS accumulation in wildlife

Invertebrate wildlife

0.1 – 10 mg/kg PFOA and PFOS in marine and freshwater invertebrate tissue (Houde et al., 2011)

Up to 280 mg/kg of PFOS, PFCAs, and PFOSA in invertebrates from Lake Ontario (Martin et al., 2004)

Accumulation in soil invertebrates (i.e., earthworms) appears to be low.

Data from: https://pfas-1.itrcweb.org/6-media-specific-occurrence/#6_5

PFAS accumulation in humans

PFOA and PFOS in human serum

On average, serum concentrations of PFOA and PFOS in general populations from the US and European countries appear to be below 10 ng/mL (CDC & EFSA).

However, people living in areas with point sources and those who work with PFAS, have blood concentrations 100s to 1000s times higher than concentrations of those in the general population.

But PFAS exposure also persists

	PFBS (C4)		PFHxS (C6)		PFOS (C8)		PFBA (C4)		PFHxA (C6)		PFOA (C8)		PFNA (C9)	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Rat	4.0 hours	4.5 hours	? Shorter than M	16-29 days	62-71 days	38-41 days	1.0-1.8 hours	6-9 hours	0.4-0.6 hours	1.0-1.6 hours	2-4 hours	4-6 days	1.4 days	30.6 days
Mouse			25-27 days	28-30 days	31-38 days	36-43 days	3 hours	12 hours	~1.2 hours	~1.6 hours	16 days	22 days	26-68 days	34-69 days
Rabbit											7 hours	5.5 hours		
Dog											8-13 days	20-30 days		
Cattle												19.2 hours		
Chick						15-17 days						3.9 days		
Monkey	3.5 days	4.0 days	87 days	141 days	110 days	132 days	1.7 days		0.1-0.8 days	0.2-1.5 days	30 days	21 days		
Humans	28 days		8.5 years		4.3-5.0 years		3 days		32 days		2.1-3.8 years			

Image source: Courtesy of C. Lau. US EPA.

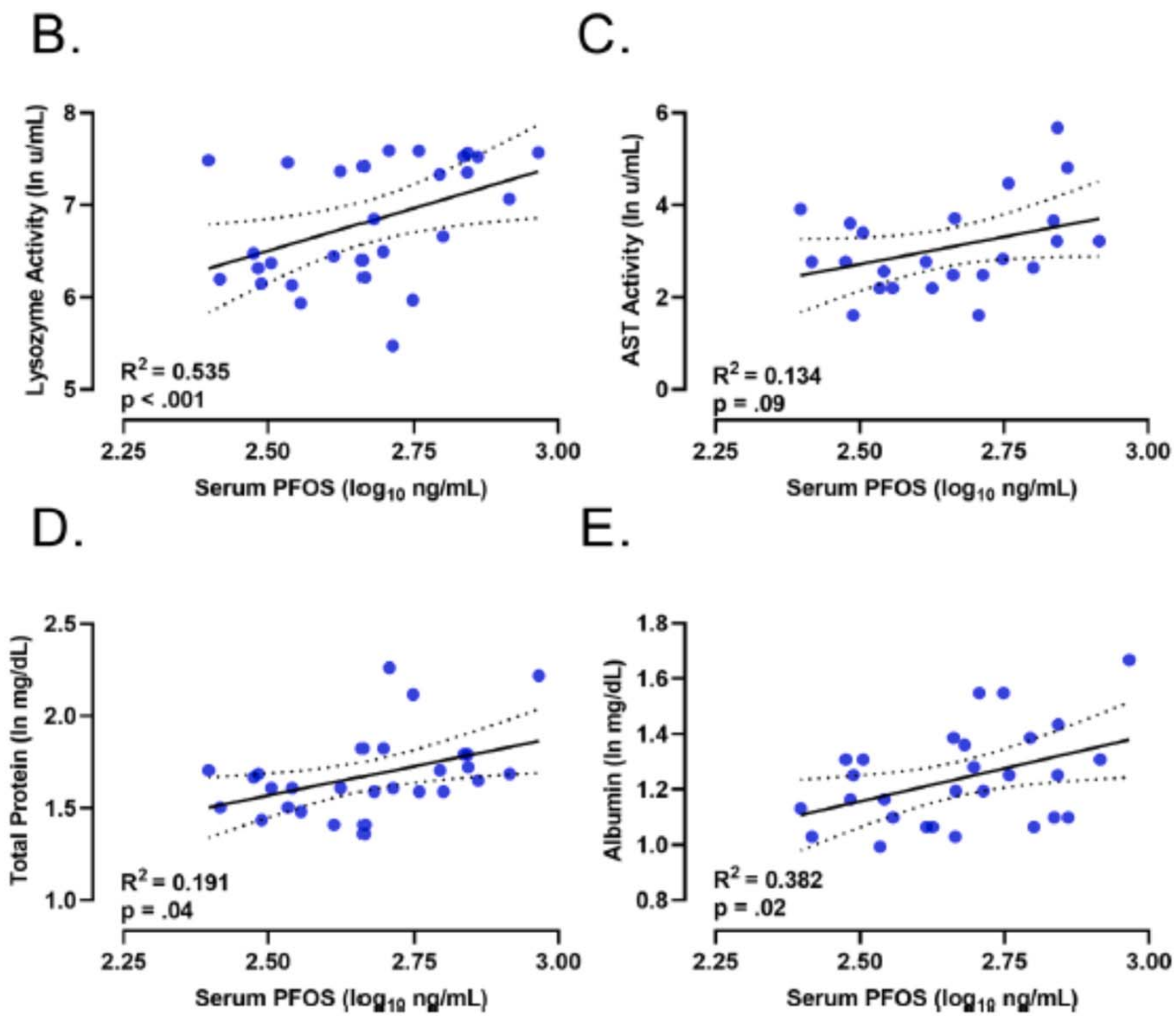
PFAS toxicity reported in wildlife

Species	Summary Of Findings	Reference
Sea otter *Enhydra lutris*	Higher PFOS/PFOA concentrations in liver samples found in diseased otters versus nondiseased group	(Kannan, Perotta and Thomas 2006 ▸)
Bottlenose dolphin *Tursiops truncatus*	Significant positive associations between serum total PFAS concentrations and multiple immunological, hematopoietic, renal, and hepatic function endpoints	(Fair et al. 2013 ▸)
Wood mouse *Apodemus sylvaticus*	Significant positive relationship between liver PFOS concentration and hepatic endpoints (relative liver weight, microsomal lipid peroxidation level); significant negative association with serum alanine aminotransferase (ALT) activity	(Hoff 2004 ▸)
Wild pig *Sus scrofa*	No significant correlation between PFAS liver concentrations and multiple blood, hepatic, and immunological endpoints, whereas significant correlations were observed for other pollutants (for example, dioxin-like compounds, PCBs, organohaline pesticides)	(Watanabe et al. 2010 ▸)
Note: Refer to Table 7-3 in the separate Excel spreadsheet for toxicological endpoints and values.		

Interstate Technology Regulatory Council (ITRC) summary of available studies of toxicological outcomes in mammalian wildlife.

Table source: https://pfas-1.itrcweb.org/7-human-and-ecological-health-effects-of-select-pfas/

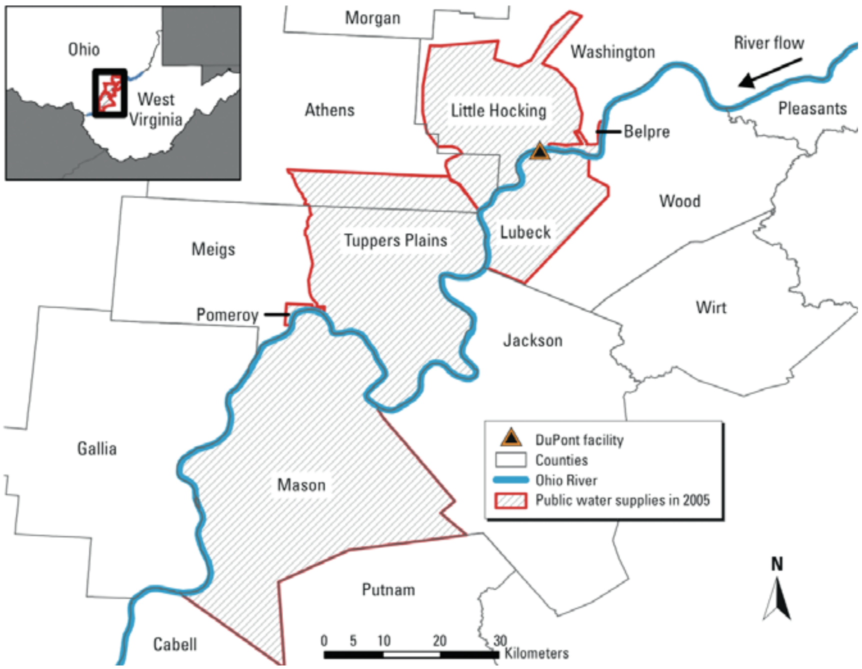
PFAS toxicity reported in wildlife – a recent example



Guillette et al. (2020) demonstrated increases in biomarkers for immunotoxicity and liver toxicity with increases in serum PFOS in striped bass from the Cape Fear River of North Carolina, US.

Image source: Guillette et al. 2020.

PFAS health effects from epidemiological studies



C8 Science Panel

http://www.c8sciencepanel.org

Probable links for <u>PFOA</u> in this community included:

Cancer - kidney and testicular

Diagnosed elevated cholesterol

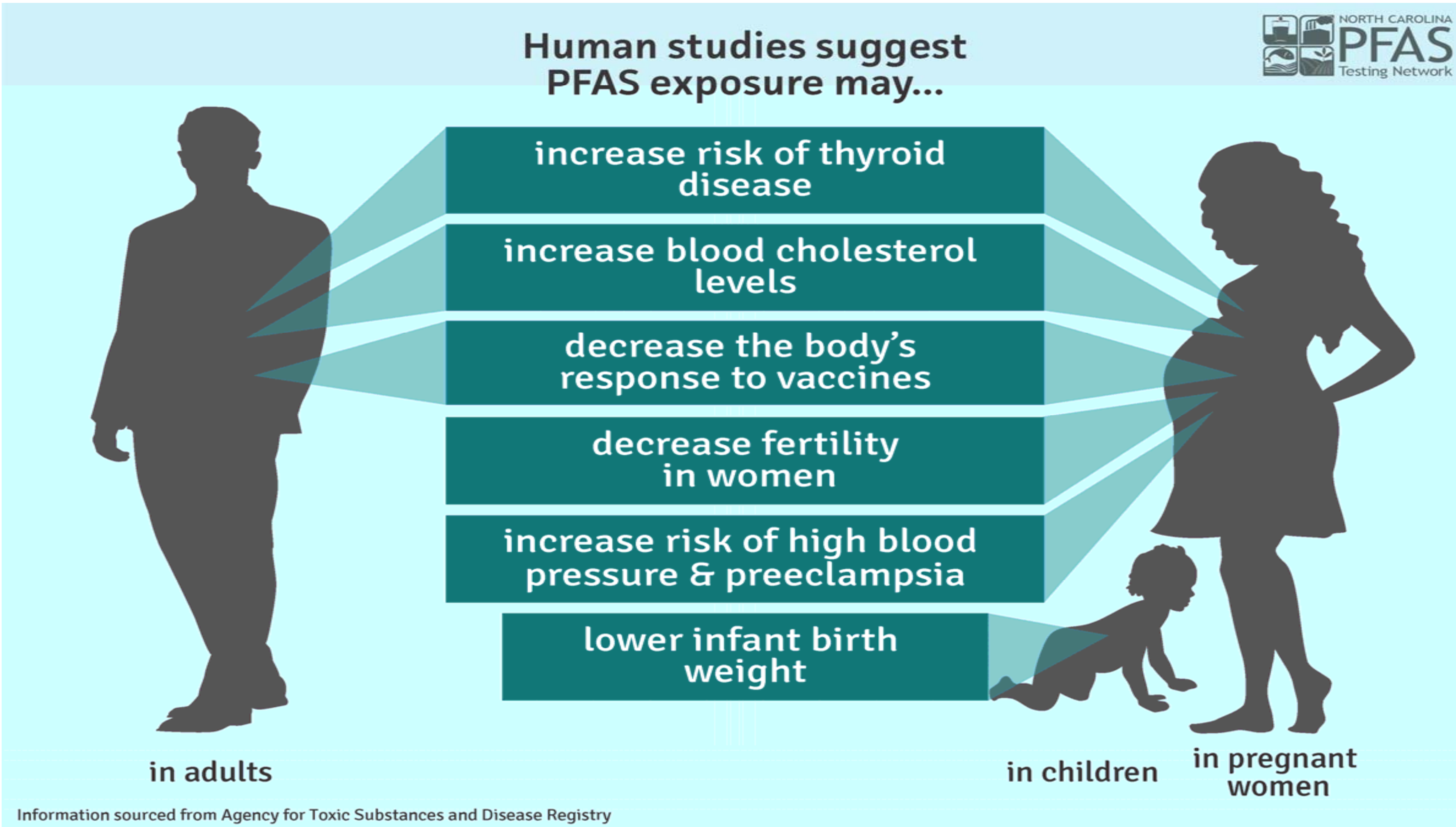
Pregnancy-induced hypertension and preeclampsia

Thyroid Disease

Ulcerative colitis

The C8 Science Panel was created by the class action lawsuit featured in the film "Dark Waters."

PFAS health effects from epidemiological studies



PFAS health effects from epidemiological studies

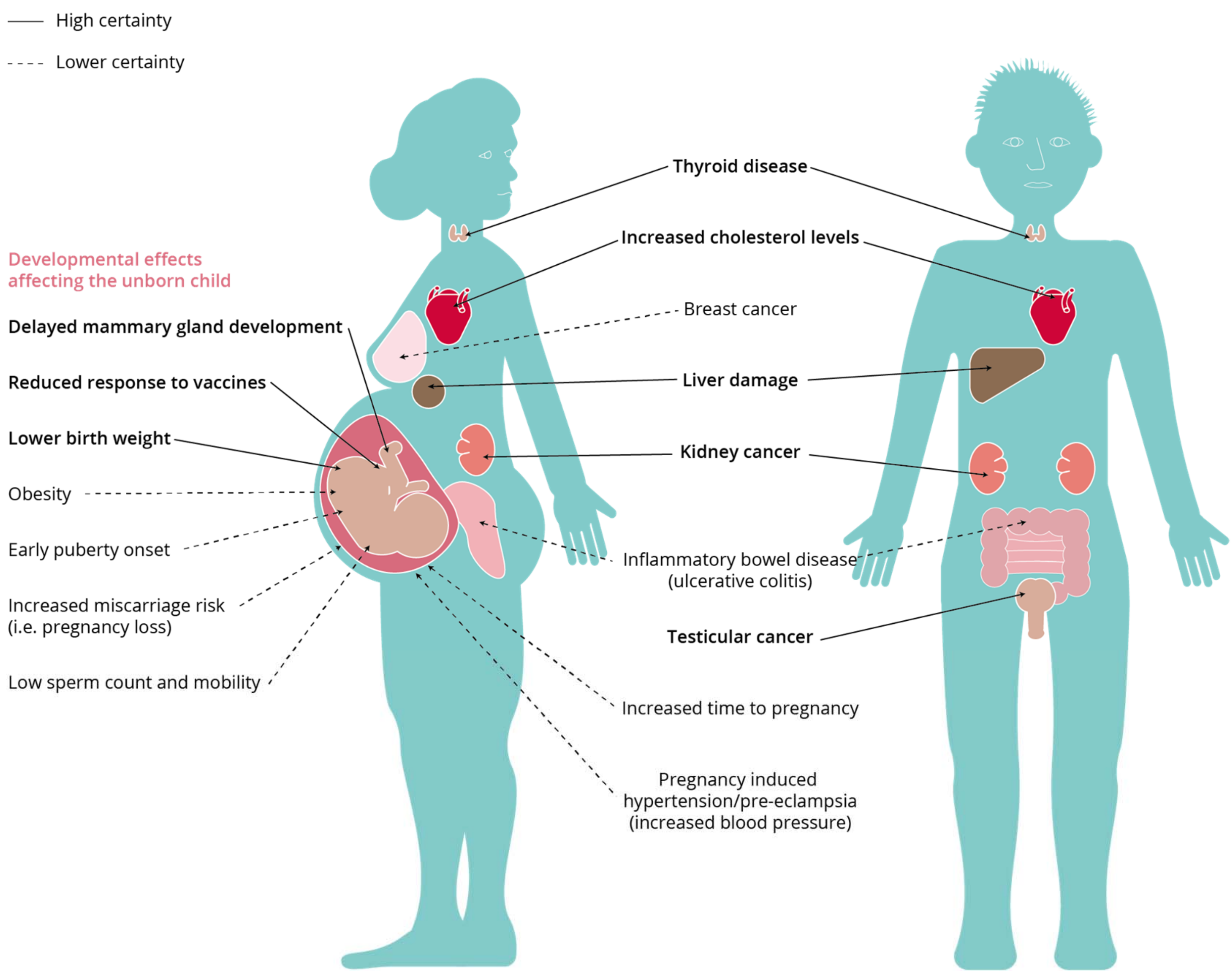
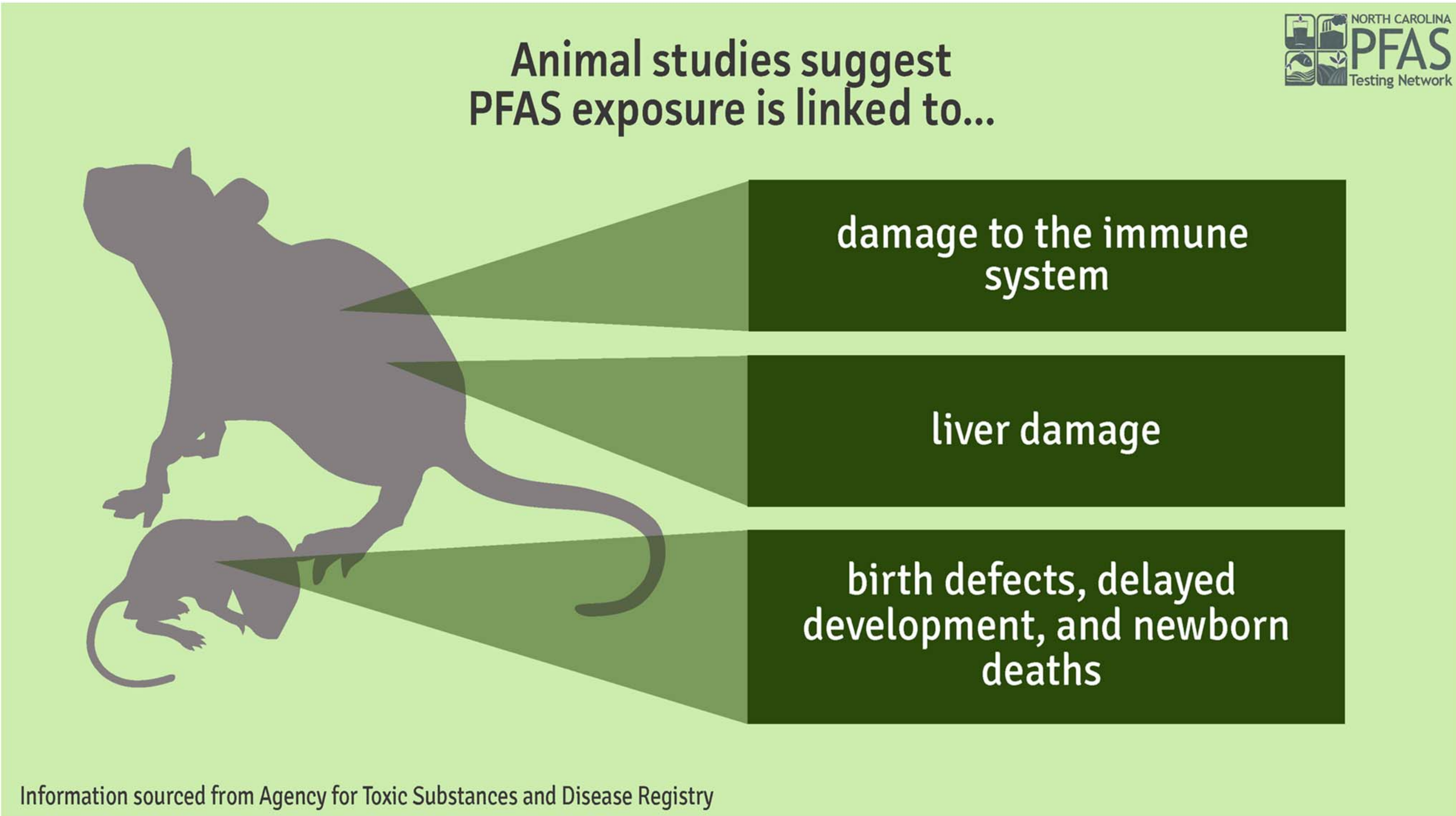
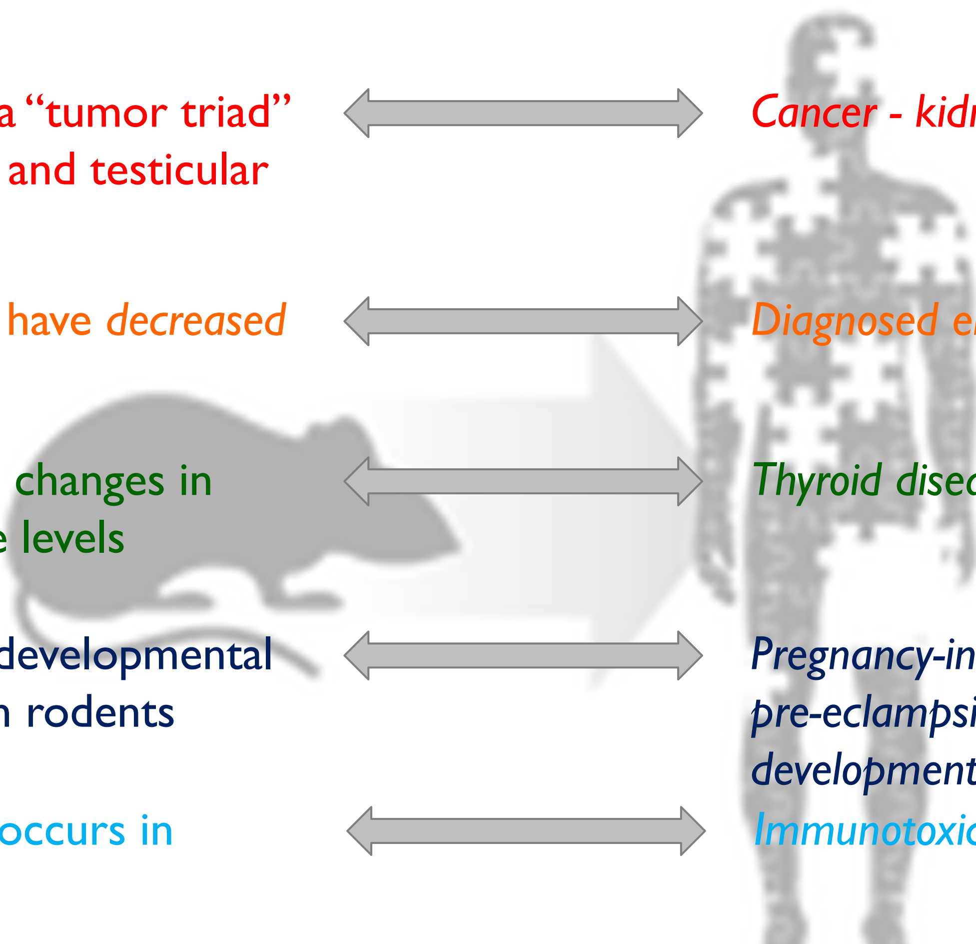


Image source: https://www.eea.europa.eu/themes/human/chemicals/emerging-chemical-risks-in-europe

Multiple lines of evidence for PFAS toxicity



Multiple lines of evidence for PFAS toxicity



Rodents exhibit a "tumor triad" (liver, pancreatic, and testicular tumors)	*Cancer - kidney and testicular*
Rodents tend to have *decreased* cholesterol	*Diagnosed elevated cholesterol*
Rodents develop changes in thyroid hormone levels	*Thyroid disease*
Reproductive & developmental toxicity occurs in rodents	*Pregnancy-induced hypertension & pre-eclampsia & other developmental effects*
Immunotoxicity occurs in rodents	*Immunotoxicity*
Autoimmune/inflammatory alterations occurs in rodents	*Ulcerative colitis*

Image source: http://www.mouse2man.org/

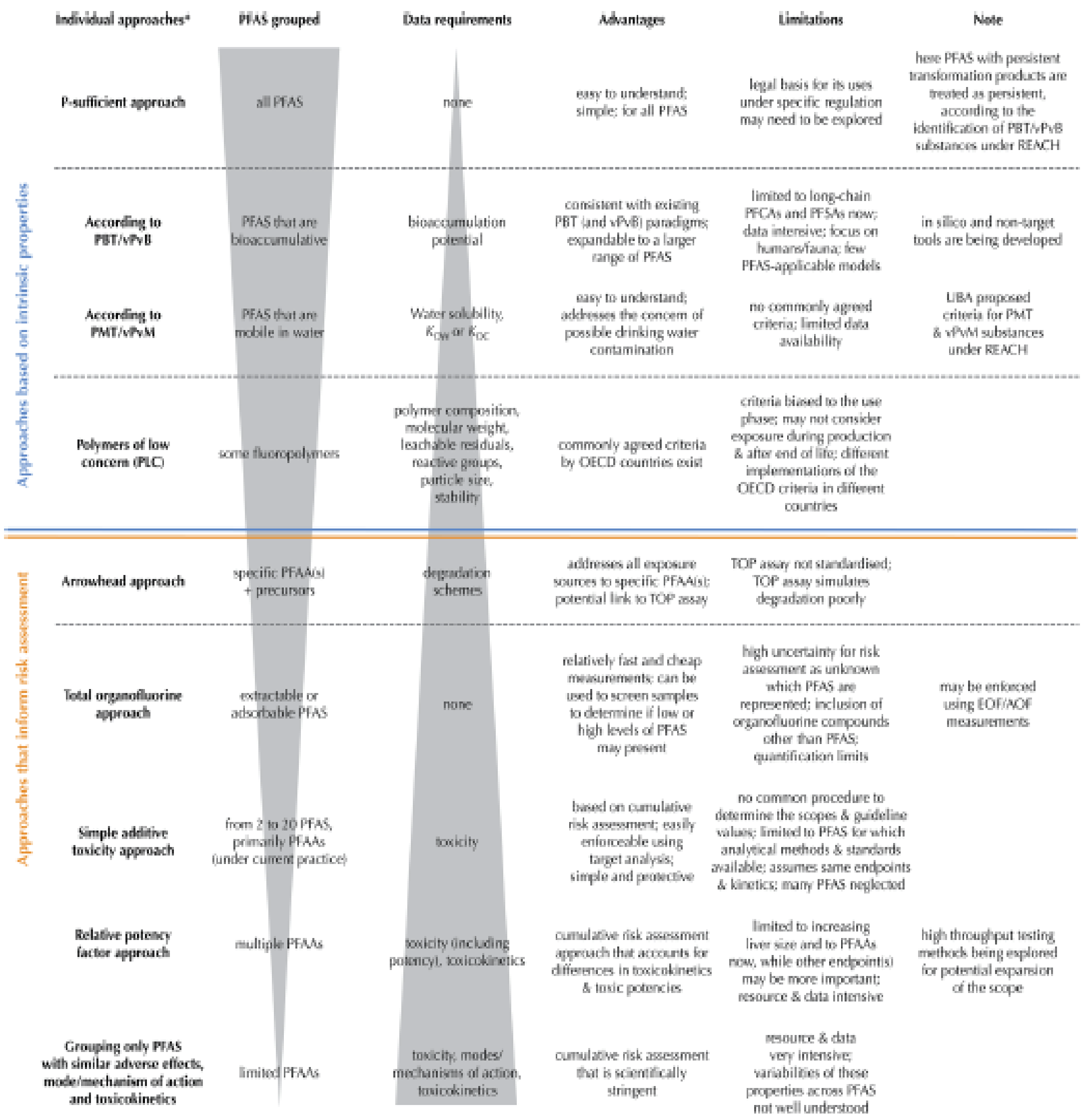
Approaches for public health protection

Cousins et al. (2020) evaluated strategies for grouping PFAS.

Main conclusions:

The P-sufficient approach, based on persistence alone, would be most precautionary.

An approach based on common toxicities, modes/mechanisms of action, and elimination kinetics, would be least precautionary.



	Individual approaches*	PFAS grouped	Data requirements	Advantages	Limitations	Note
Approaches based on intrinsic properties	P-sufficient approach	all PFAS	none	easy to understand; simple; for all PFAS	legal basis for its uses under specific regulation may need to be explored	here PFAS with persistent transformation products are treated as persistent, according to the identification of PBT/vPvB substances under REACH
	According to PBT/vPvB	PFAS that are bioaccumulative	bioaccumulation potential	consistent with existing PBT (and vPvB) paradigms; expandable to a larger range of PFAS	limited to long-chain PFCAs and PFSAs now; data intensive; focus on humans/fauna; few PFAS-applicable models	in silico and non-target tools are being developed
	According to PMT/vPvM	PFAS that are mobile in water	Water solubility, K_{OW} or K_{OC}	easy to understand; addresses the concern of possible drinking water contamination	no commonly agreed criteria; limited data availability	UBA proposed criteria for PMT & vPvM substances under REACH
	Polymers of low concern (PLC)	some fluoropolymers	polymer composition, molecular weight, leachable residuals, reactive groups, particle size, stability	commonly agreed criteria by OECD countries exist	criteria biased to the use phase; may not consider exposure during production & after end of life; different implementations of the OECD criteria in different countries	
Approaches that inform risk assessment	Arrowhead approach	specific PFAA(s) + precursors	degradation schemes	addresses all exposure sources to specific PFAA(s); potential link to TOP assay	TOP assay not standardised; TOP assay simulates degradation poorly	
	Total organofluorine approach	extractable or adsorbable PFAS	none	relatively fast and cheap measurements; can be used to screen samples to determine if low or high levels of PFAS may present	high uncertainty for risk assessment as unknown which PFAS are represented; inclusion of organofluorine compounds other than PFAS; quantification limits	may be enforced using EOF/AOF measurements
	Simple additive toxicity approach	from 2 to 20 PFAS, primarily PFAAs (under current practice)	toxicity	based on cumulative risk assessment; easily enforceable using target analysis; simple and protective	no common procedure to determine the scopes & guideline values; limited to PFAS for which analytical methods & standards available; assumes same endpoints & kinetics; many PFAS neglected	
	Relative potency factor approach	multiple PFAAs	toxicity (including potency), toxicokinetics	cumulative risk assessment approach that accounts for differences in toxicokinetics & toxic potencies	limited to increasing liver size and to PFAAs now, while other endpoint(s) may be more important; resource & data intensive	high throughput testing methods being explored for potential expansion of the scope
	Grouping only PFAS with similar adverse effects, mode/mechanism of action and toxicokinetics	limited PFAAs	toxicity, modes/mechanisms of action, toxicokinetics	cumulative risk assessment that is scientifically stringent	resource & data very intensive; variabilities of these properties across PFAS not well understood	

Image source: Cousins et al. 2020.

Approaches for public health protection

Cousins et al. (2020) evaluated strategies for grouping PFAS.

What has been done where grouping approaches were used?

The least precautionary approach.

Denmark

Groups 12 PFAS under assumption all are similarly toxic to PFOS

Sweden

Groups 11 PFAS under assumption all are similarly toxic to PFOS

Australia, Canada, US

Group 2 PFAS under assumption of similar toxicity or additive toxicity

Approaches for public health protection

But the least precautionary approach becomes less palatable as the number of PFAS grows.

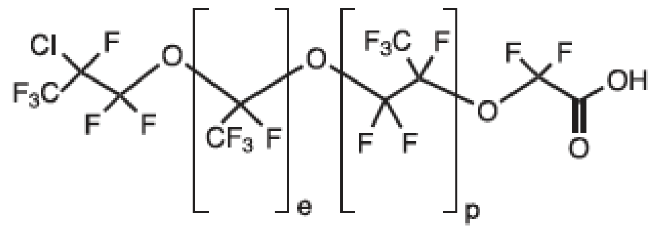


Fig. 1. A chloroperfluoropolyether carboxylate (ClPFPECA) identified by nontargeted MS analyses in soil samples from New Jersey. In the New Jersey samples, perfluoroethyl (e) plus perfluoropropyl (p) groups were observed to range in sum from one to four. The example congener depicted here would be designated (e,p) = 1,1. Isomers likely include an alternative terminal structure of $ClCF_2CF(CF_3)O–$ (*13*, *14*) as well as relative positions for the perflluoroethyl and perfluoropropyl groups.

Image source: Washington et al. 2020.

Approaches for public health protection

Kwiatkowski et al. (2020) recommended a scientific basis for managing PFAS as a class.

Main recommendation:

High persistence, accumulation potential, AND/OR hazards (known and potential) of PFAS studied to date is sufficient justification for treating ALL PFAS as a single class.

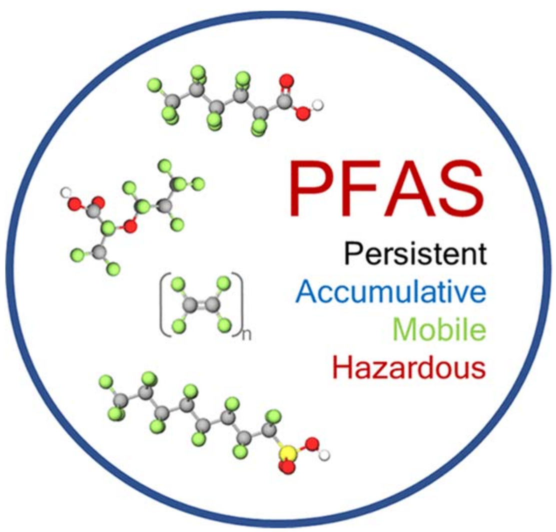


Image source: Kwiatkowski et al. 2020.

Approaches for public health protection

An essential use approach can support PFAS phase-outs:

An essential use is a use necessary for health or safety or for the functioning of society and an essential use is a use for which there are no available technically and economically feasible alternatives.

Environmental Science Processes & Impacts

ROYAL SOCIETY OF CHEMISTRY

CRITICAL REVIEW

View Article Online
View Journal

Check for updates

Cite this: DOI: 10.1039/c9em00163h

The concept of essential use for determining when uses of PFASs can be phased out

Ian T. Cousins,†*[a] Gretta Goldenman,[b] Dorte Herzke,[c] Rainer Lohmann,[d] Mark Miller,[e] Carla A. Ng,[f] Sharyle Patton,[g] Martin Scheringer,[h] Xenia Trier,[i] Lena Vierke,[j] Zhanyun Wang[k] and Jamie C. DeWitt[l]

Image source: Cousins et al. 2019.

Sources of laboratory funding for PFAS:

- North Carolina Policy Collaboratory & NC General Assembly
- US EPA/Oregon State University (83948101)
- NIEHS/NC State University (1 P42 ES031009-01)
- NC State University Center for Human Health and the Environment
- Brody Brothers Endowment

GLOBAL PFAS SCIENCE PANEL

International collaborators:
https://www.pfassciencepanel.org/

Thank you image from shutterstock.com.

References used in presentation:

Cousins et al. 2020. Strategies for grouping per- and polyfluoroalkyl substances (PFAS) to protect human and environmental health. Environmental Science Processes & Impacts. DOI: 10.1039/d0em00147c.

Cousins et al. 2019. The concept of essential use for determining when uses of PFASs can be phased out. Environmental Science Processes & Impacts. 21:1803-1815.

DeWitt et al. 2012. Immunotoxicity of perfluorinated compounds: Recent developments. Toxicologic Pathology. 40:300-311.

Emerging chemical risks in Europe – 'PFAS.' https://www.eea.europa.eu/themes/human/chemicals/emerging-chemical-risks-in-Europe.

FluoroCouncil. 2019. Fluorotechnology makes important products for vital industries possible. https://fluorocouncil.com/wp-content/uploads/2017/02/Fluoro-IG-compressed.pdf.

Galloway et al. 2020. Evidence of air dispersion: HPFO-DA and PFOA in Ohio and West Virginia surface water and soil near a fluoropolymer production facility. Environmental Science & Technology. 54:7175-7184.

Guillette et al. 2020. Elevated levels of per- and polyfluoroalkyl substances in Cape Fear River striped bass (*Morone saxatilis*) are associated with biomarkers of altered immune and liver function. Environment International. 136:105358.

Hopkins et al., 2018. Recently detected drinking water contaminants: GenX and other per- and polyfluoroalkyl substances. Journal AWWA. 110:13-28.

Interstate Technology Regulatory Council. PFAS technical and regulatory document. https://pfas-1.itrcweb.org/.

Kwiatkowski et al. 2020. Scientific basis for managing PFAS as a chemical class. Environmental Science & Technology Letters. 7:532-543.

Public Information Brief: PFAS. https://www.oaklodgewaterservices.org/surface-water/page/public-information-brief-pfas.

Sunderland et al. 2018. A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects. Journal of Exposure Science and Environmental Epidemiology. 29:131-147.

Washington et al. 2020. Nontargeted mass-spectral detection of chloroperfluoropolyether carboxylates in New Jersey soils. Science. 368:1103-1107.