PFOA-Induced Health Effects

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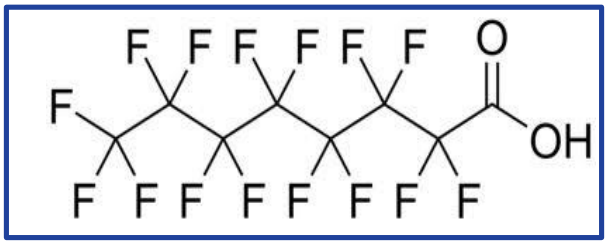
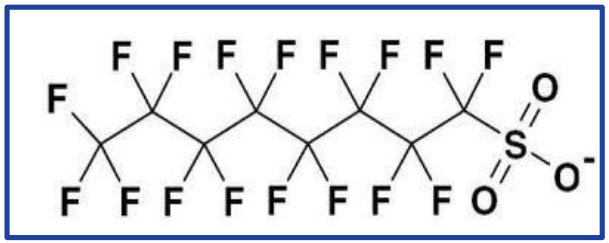
Per- and Poly-Fluoroalkyl Substances (PFAS)

- Non-stick, water/grease/friction repellant, stain resistance
  - Over 5,000 compounds; structurally diverse
  - PFOA (C8) was used as a polymer processing aid in preparation of Teflon and in textile coating processes; an emission and degradation product
  - *PFOS* (C8) - Scotchgard and Gore-Tex
- PFOS historical presence in MIL SPEC Aqueous film forming foam (AFFF); wide distribution across the U.S. military installations, airports, fire fighting training sites
- Hundreds of other applications, e.g. cosmetics, dental floss, wiring, waxes, polishes, paints, food contact surfaces, etc.
- PFAS known for age, sex, species, and strain-specific ADME
- PFOA and PFOS - "*Suggestive Evidence of Carcinogenic Potential" based on US EPA (2005 & 2016) and* International Agency for Research on Cancer (IARC V110 PFOA; *2016)*

PFOA





PFOS

Use of the Developing Mouse Model

Dawes et al. 2001

- Clearance rates of PFAS vary between chain lengths, species, and genders:
  - ✓ Half-lives of long chain lengths >> those of short chain lengths (w/exception)
  - ✓ Half-lives of humans >> monkeys >> rodents
  - ✓ Half-lives of long-chained PFAS in male rats >> those of females (gender differences are smaller in other species)
- Internal dose measurements necessary

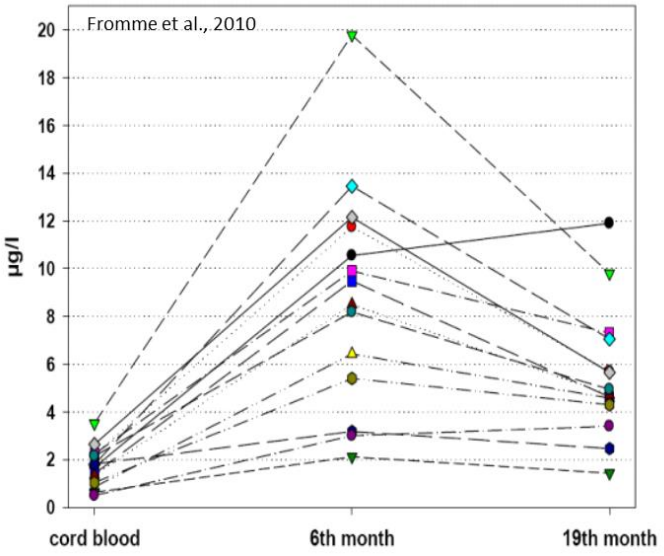
	PFBS (C4)		PFHxS (C6)		PFOS (C8)		PFBA (C4)		PFHxA (C6)		PFHpA (C7)		PFOA (C8)	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Rat	4.0 hours	4.5 hours	1.8 days	6.8 days	62-71 days	38-41 days	1.0-1.8 hours	6-9 hours	0.4-0.6 hours	1.0-1.6 hours	2.4 hours	1.2 hours	2-4 hours	4-6 days
Mouse	2.1 hours	3.3 hours	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
Monkey	3.5 days	4.0 days	87 days	141 days	110 days	132 days	1.7 days		2.4 hours	5.3 hours			30 days	21 days
Humans	28 days		8.5 years		4.3-5.0 years		3 days		32 days		1.2 years		2.1-3.8 years	

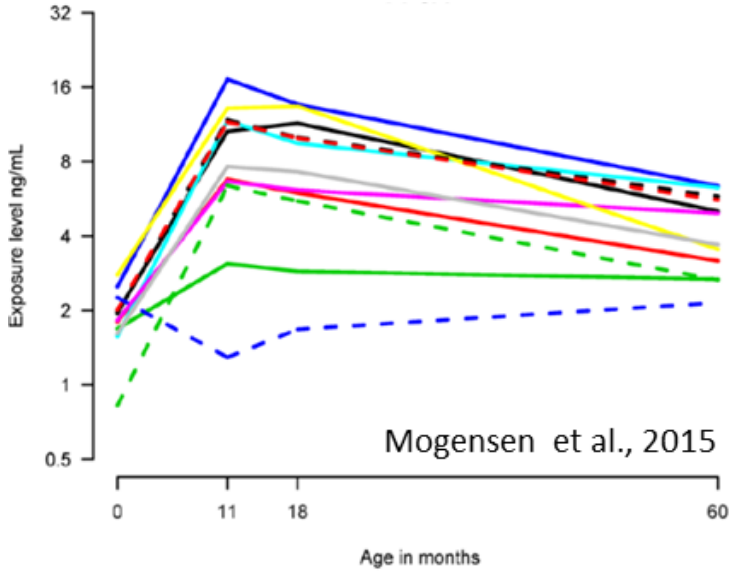
Table courtesy of Dr. Chris Lau, U.S. EPA

Absorption, distribution, metabolism, and excretion are all modified in fetus & pregnant female compared to adult male

PFOA Exposure Increases with Breastfeeding

- Infants have higher exposures from breast milk or formula:
  - PFOA levels in breast milk similar or higher than in maternal drinking water
  - Ingest much more fluid per body weight than older individuals
- PFOA transfers in mouse milk (Fenton et al. 2009; Reiner et al. 2009)
- Sensitive subpopulation for developmental and other short-term effects



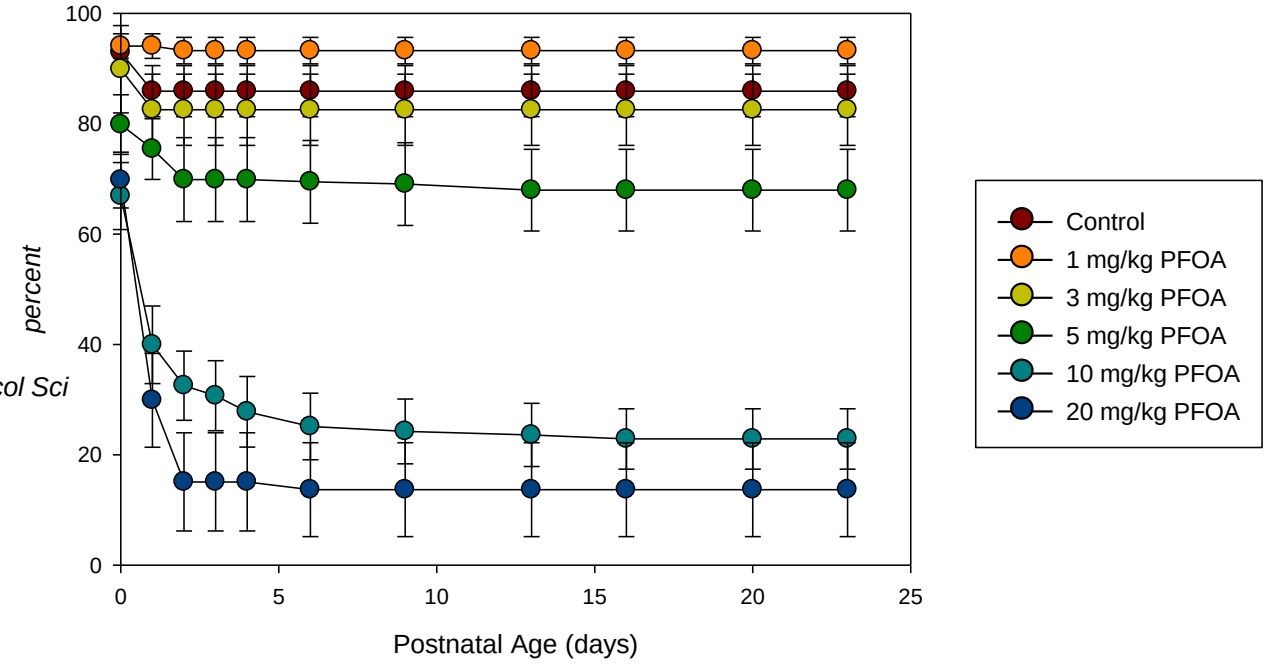


Fromme et al. 2010, Verner et al. 2016, and Mogensen et al. 2015

PFOA Alters Mammary Function & Offspring Outcomes

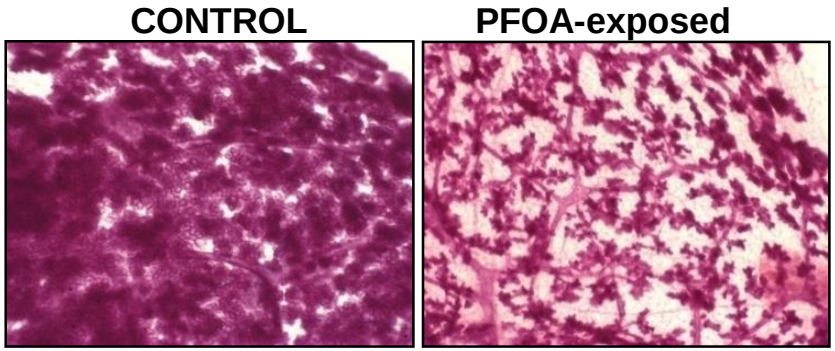
Significant increase in mouse pup mortality at 5 mg PFOA/kg BW

taken from Lau et al., 2006 *Toxicol Sci*



Impaired lactation in mice exposed to 5 mg PFOA/kg BW

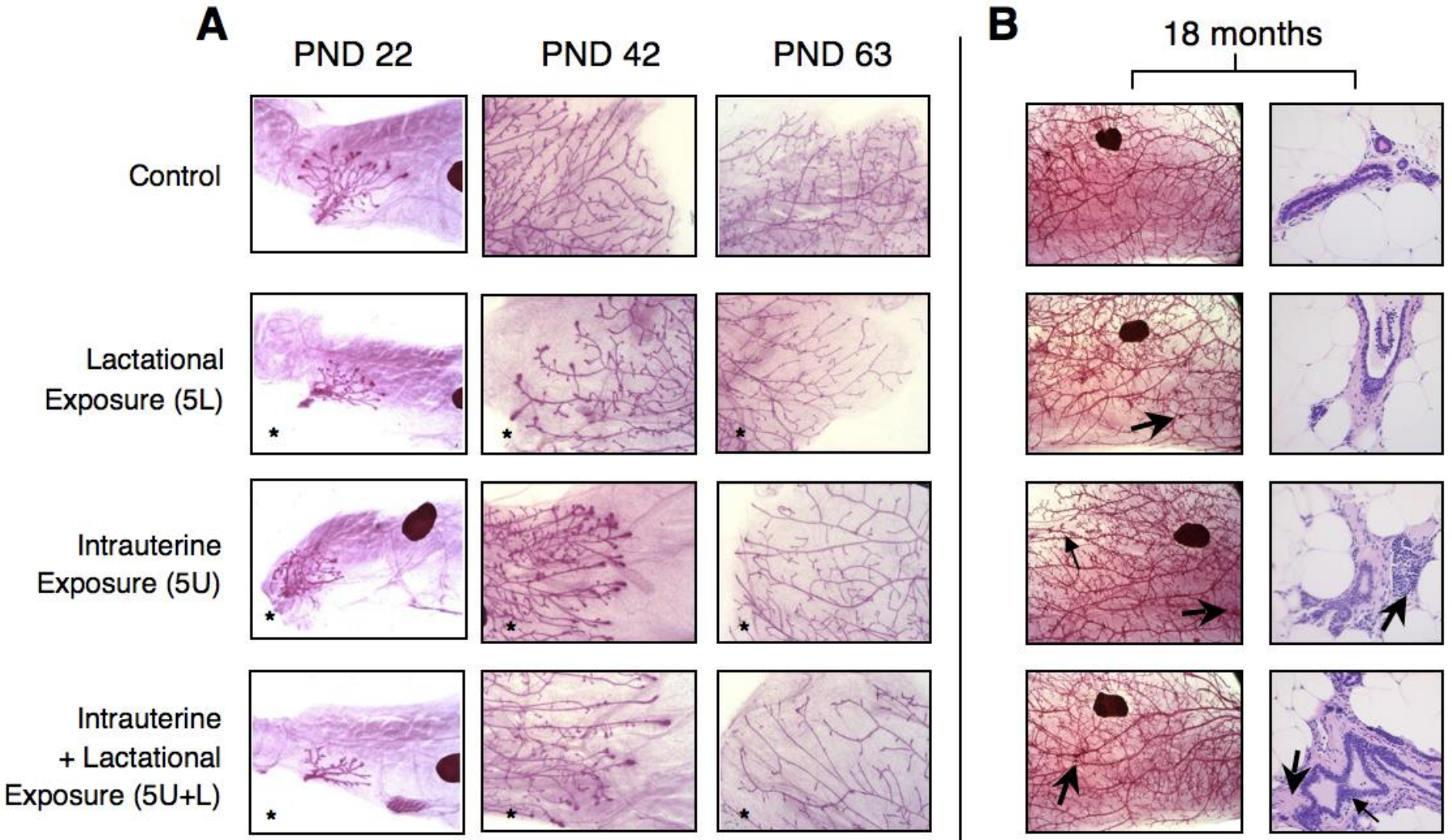
White et al., 2007 *EHP*



Significant decrease in mouse pup birth weight at 5 mg PFOA/kg BW

(reviewed in Navigation Guide Systematic Review – Koustas et al. 2014 *EHP*)

Prenatal & Postnatal Exposure Effects in Mice



5U + 5L = mice exposed to 5 mg PFOA/kg/d

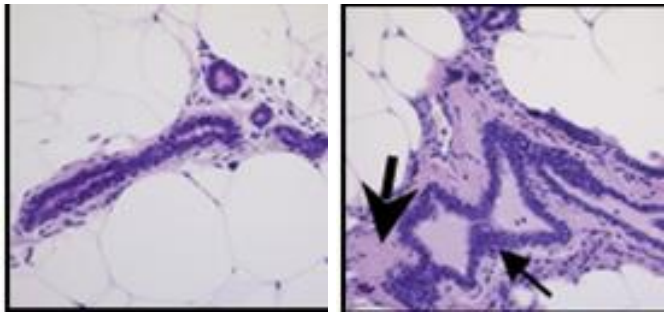
5L = PFOA transfer via milk after in utero exposure ended

from White et al. 2009, *Reprod Toxicol*

Persistence of Mammary Gland Effects

CD-1 mice, GD 1-17 exposure, @ 18 mon

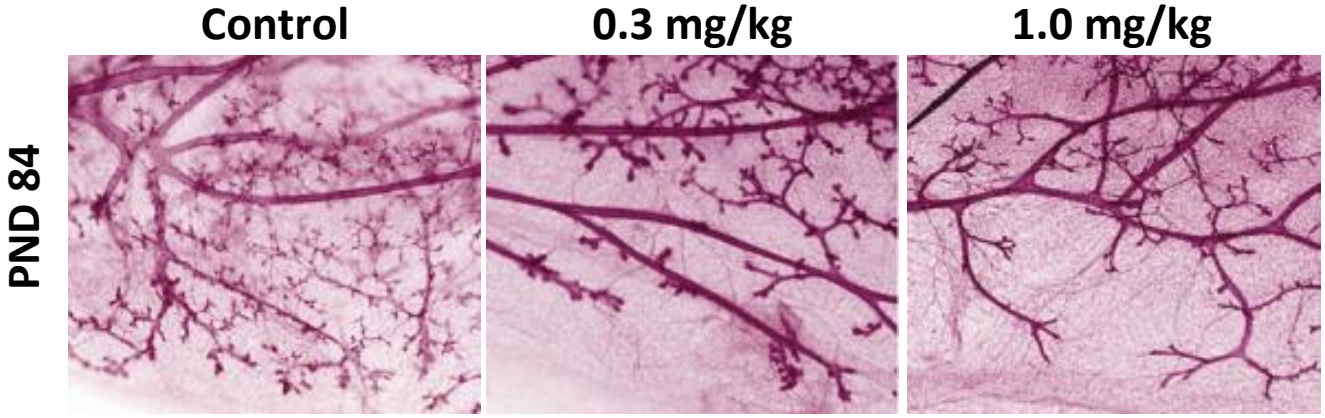
Control



5 mg/kg

White et al. 2009, *Reprod Toxicol*

Adult CD-1 mice, GD 1-17 exposure



Macon et al. 2011, *Toxicol Sci*

Mouse Serum PFOA Concentrations (ng/ml)

Days after PFOA ended	Control	0.01 mg/kg	0.1 mg/kg	1.0 mg/kg
7	6.7 ± 1.1 (5)	149.5 ± 11.7 (4)*	1113.5 ± 57.2 (4)*	9163.5 ± 629.7 (3)*
14	4.9 ± 1.2 (4)	95.0 ± 13.3 (3)*	747.7 ± 38.2 (4)*	6448.8 ± 328.3 (5)*
21	< 5, LOQ (5)	29.3 ± 12.5 (4)*	201.0 ± 27.1 (5)*	2250.0 ± 170.8 (5)*
28	< 5, LOQ (5)	8.0 ± 1.0 (5)*	64.0 ± 12.8 (5)*	1249.4 ± 227.6 (5)*
56	< 5, LOQ (5)	< 10, LOQ (5)*	13.1 ± 1.9 (5)*	57.9 ± 18.6 (5)*

Data are presented as mean ± SEM. Significant effects compared to controls by Dunnetts, *p<0.05

Ohio River Valley children's serum PFOA concentrations:

- ≤600 ng/ml (Ages 2-5; Emmett et al. 2006)
- 77.6 ng/ml (Ages <12; Frisbee et al. 2009)
- 59.9 ng/ml (Ages 12-19)

http://www.c8sciencepanel.org/

* Significant mammary effects present at these doses (Macon et al. 2011, *Tox Sci*)

Similar mammary effects reported in C57Bl/6J mice exposed in utero, but at higher PFOA exposures (0.3 mg/kg LOAEL) – Tucker et al. 2015, *Reprod Toxicol*

Abnormal Mouse Mammary Gland Development

- **Sensitive target** – Occurs in mouse offspring at doses/serum levels below those that increase offspring liver weight
  - *To date,* sensitive mouse developmental effects such as delayed mammary gland development and others have been taken into consideration in *7 states, resulting in use or proposed use of database uncertainty factors of 3 or 10: Cordner et al 2019 JESEE PMID:* 30622333

- **Well established** – 9 mouse studies; from gestational and/or lactational exposure
  - *Only one negative study; used different exposure scenario/strain*
  - *Differing mouse strain susceptibility consistent with toxicokinetic differences*

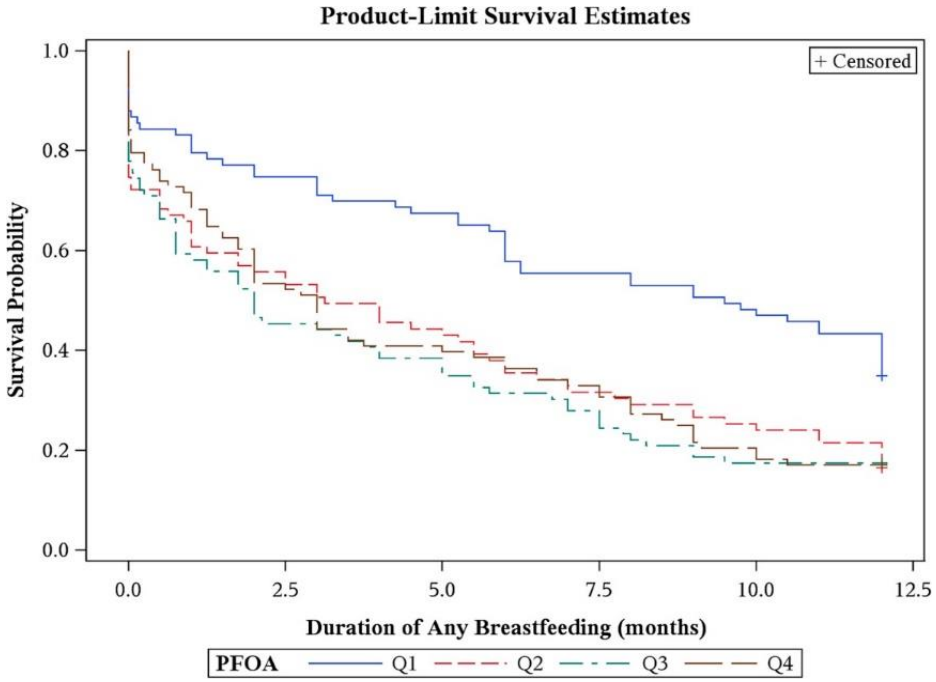
- **Adverse** – Structural changes persist until adulthood; effect on lactation

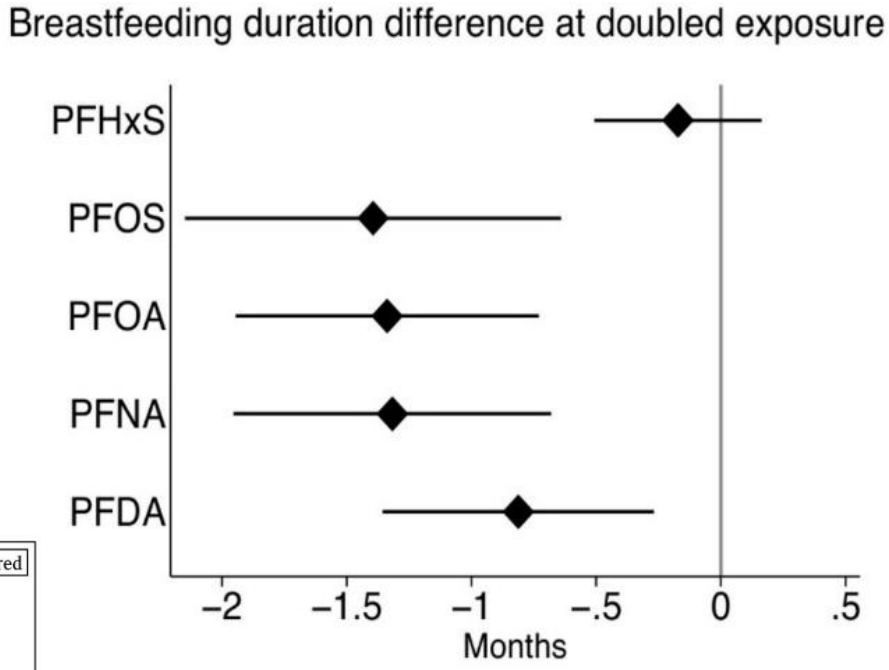
- **Human relevance** – Mice and humans have similar mode of action

- Accumulating data on effects on lactational function/duration in women
  - *Breast development evaluated in only one study of adolescents*
  - *Several human studies associate PFOA with ↓ duration of breastfeeding*

PFAS Affect Breastfeeding Duration in Women

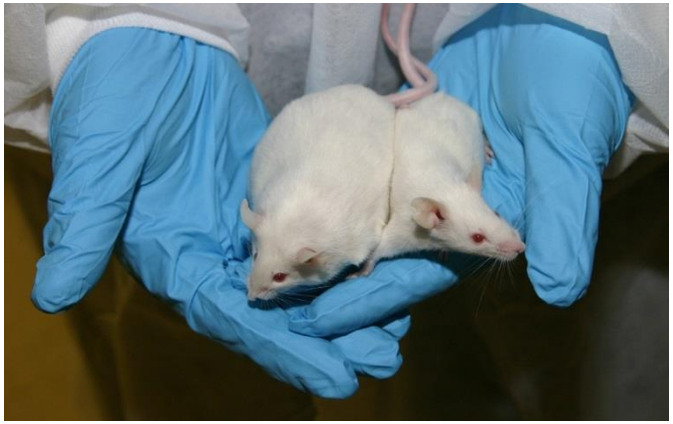
From Romano et al. 2016, *Environ Res*





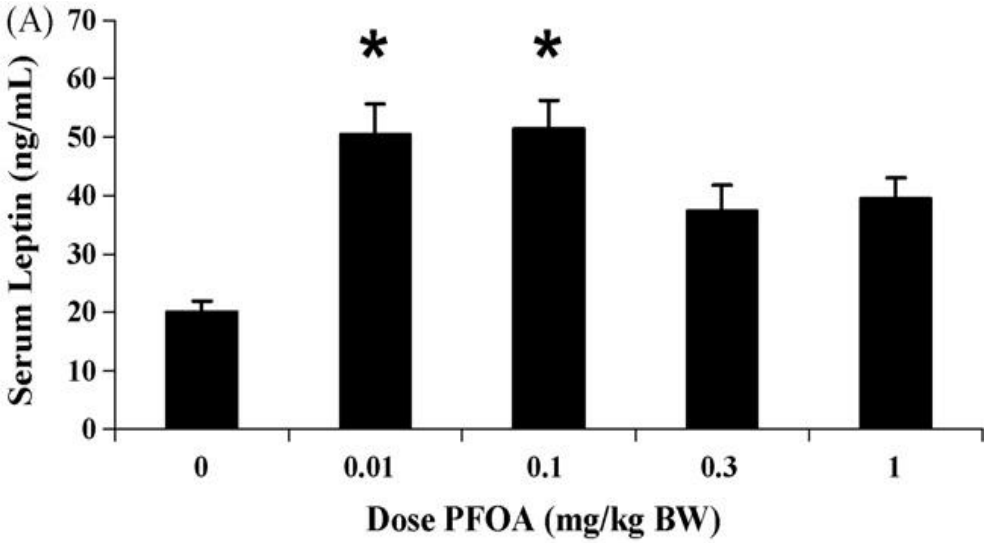
From Timmermann et al. 2017, *Reprod Toxicol*

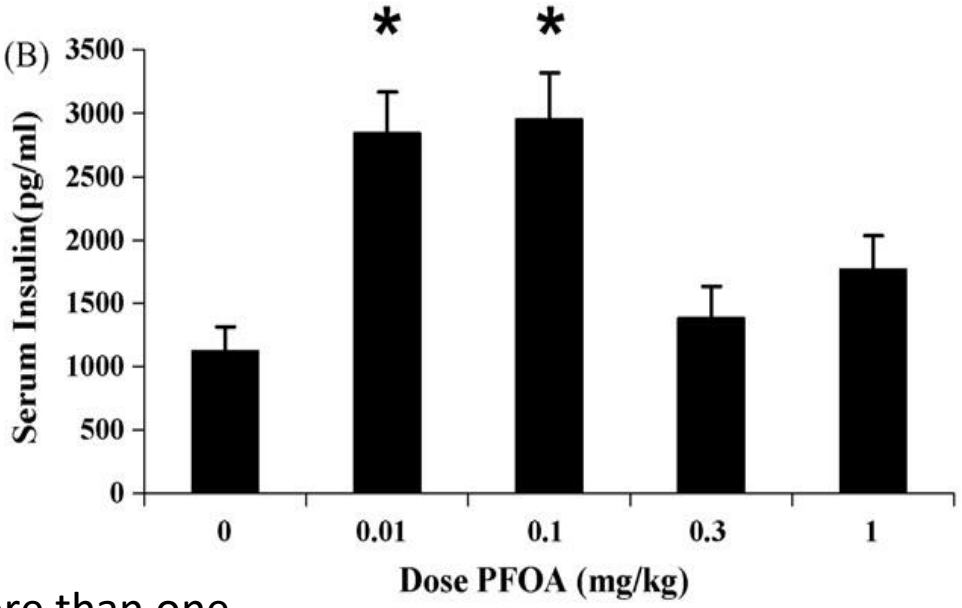
Prenatal PFOA & Early Adult Obesity in Mice



Highlighted in Holtcamp 2012 *Environ Health Perspect* PMID: 22296745

Data in Hines et al, 2009 *Mol. Cell Endocrinol. 304: 97-105*





Supported in epidemiological studies:

1. Increased gestational weight gain
Int J Environ Res Public Health 2016
2. Overweight in 20 yr old Danish daughters exposed in utero.
Environ Health Perspect 2012

Mechanisms are not understood – Likely more than one

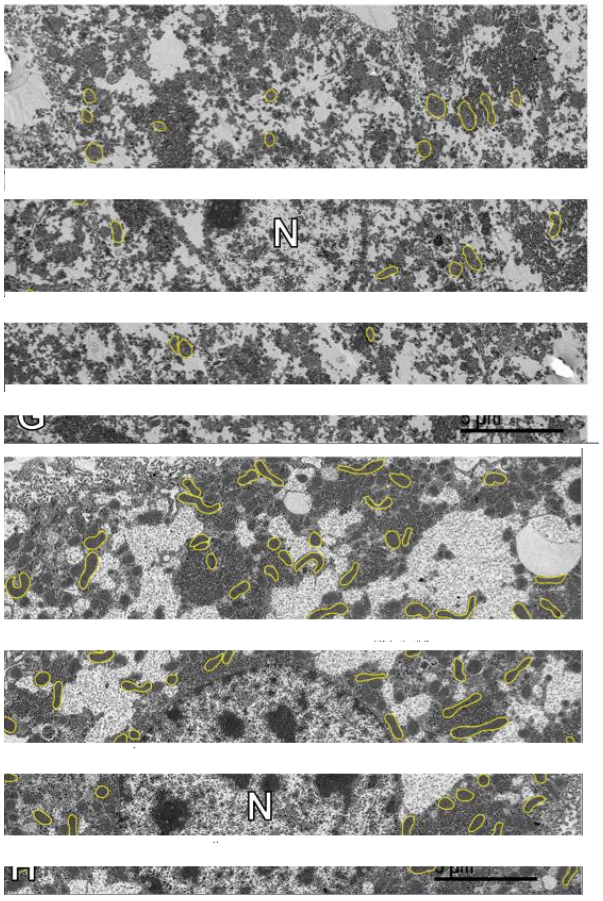
PFOA Induces Liver Tumors in CD-1 & PPAR-α KO Mice

In Filgo et al. 2015, *Toxicol Pathol*

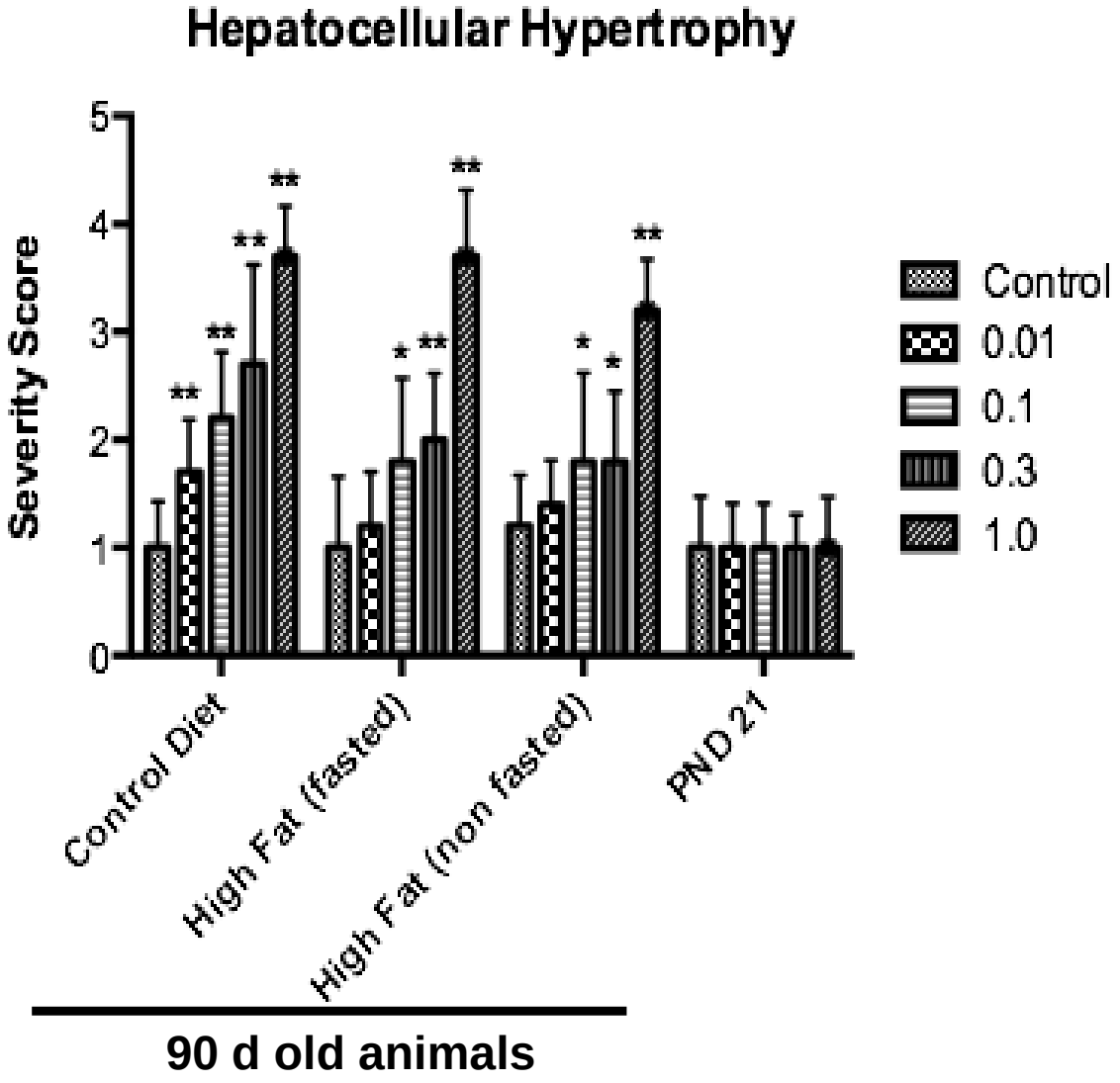
- Three strains of mice compared for effects of prenatal PFOA exposure on liver at 18 months of age
- Centrilobular hepatocyte hypertrophy significantly increased in incidence with PFOA dose in CD-1 and 129/Sv PPARα-KO mice, and increased in severity in the 129/Sv WT mice.
- Hepatocellular adenomas (HA) were significantly increased in CD-1 mice (0.3 mg/kg), but no significant dose-response. HA were also evident in over 13% of PFOA-exposed PPARα-KO mice; these lesions are stimulated by prenatal PFOA exposure, a process which may be independent of PPARα activation.
- A dose dependent trend in hemangiosarcomas was evident in CD-1 mice
- Hepatocellular adenomas were not found in historical CD-1 control female mice (485 mice examined; Giknis and Clifford, 2010).
- Bile duct hyperplasia and hematopoietic cell proliferation were two liver lesions that were only significantly increased with increasing dose of PFOA in the PPARα-KO mice

Hepatocellular Hypertrophy in CD-1 Mice

Control liver TEM



1 mg PFOA/kg/d liver TEM

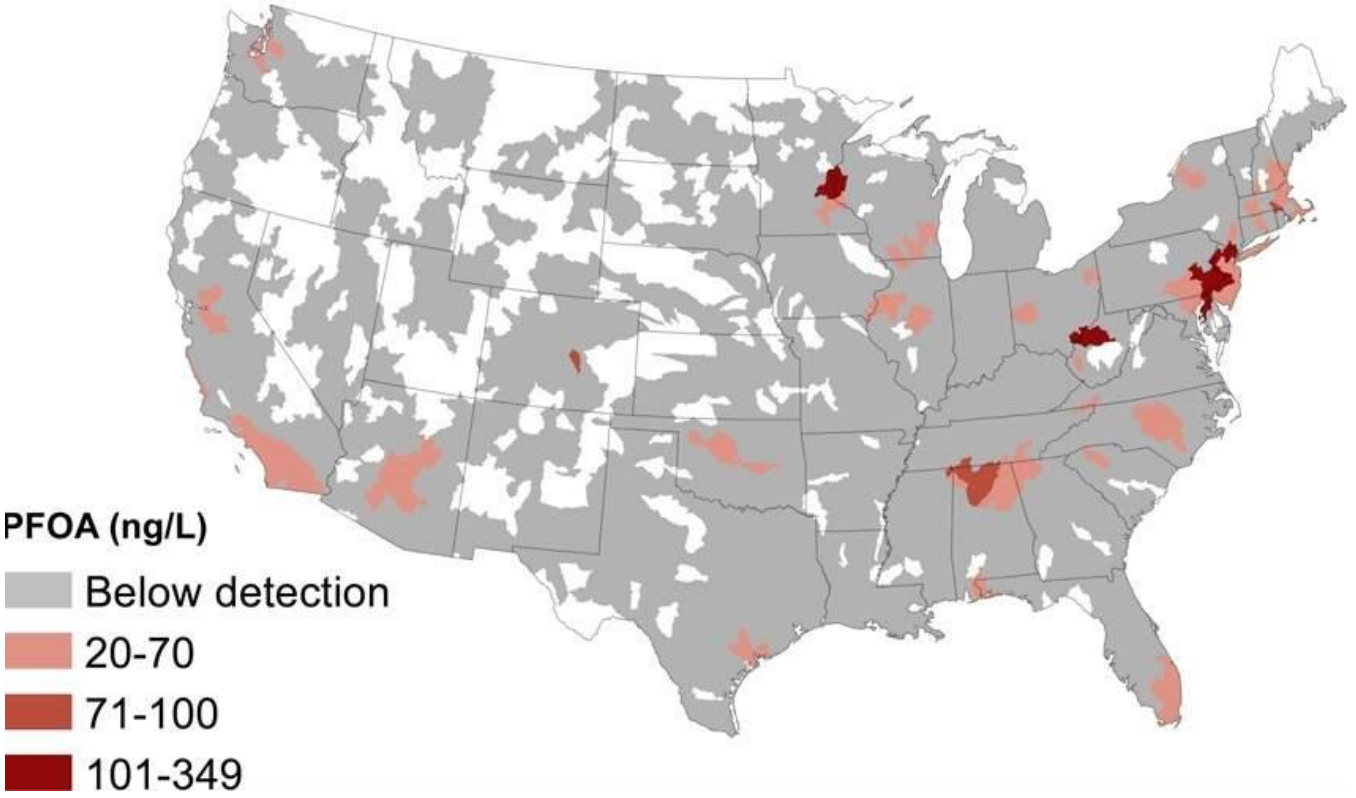


TEM=transmission electron microscopy

From Quist et al. 2015, *Toxicol Pathol*

A Lingering National Problem

PFOA isn't being produced or used in U.S. manufacturing anymore



Hu et al. 2016, ES&T Letters 81% associated with manufacturing site

- Many areas have not been sampled – well and small community water sources
- Other sensitive end points – immune system and placenta

Thanks for your attention!

Questions?

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