PFAS exposure during pregnancy: GenX-induced latent health effects

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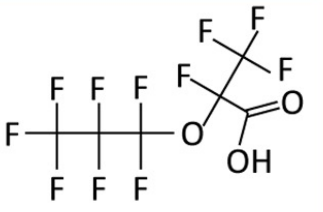
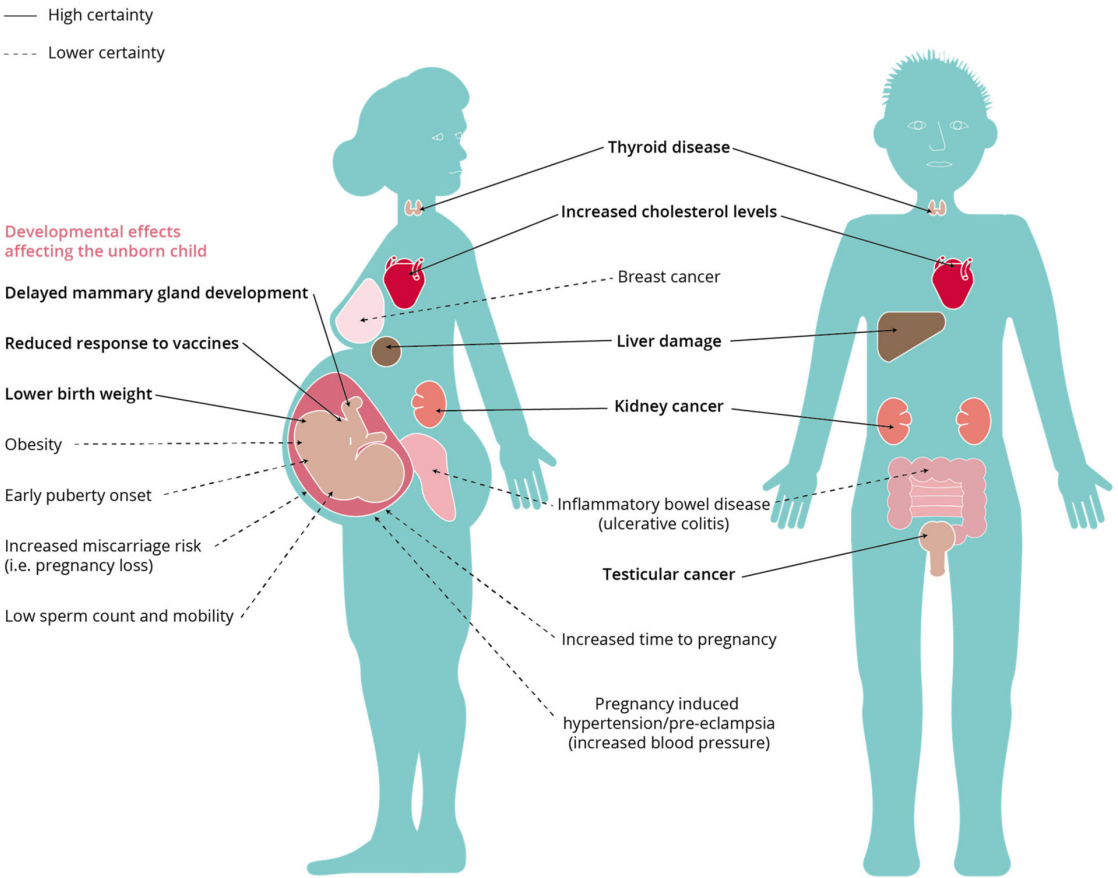


June 16, 2022

Effects of PFAS on human health



Highlighted:

Immune function

Thyroid function/disease

Liver disease/cancer

Metabolic Dysfunction

Kidney disease/cancer

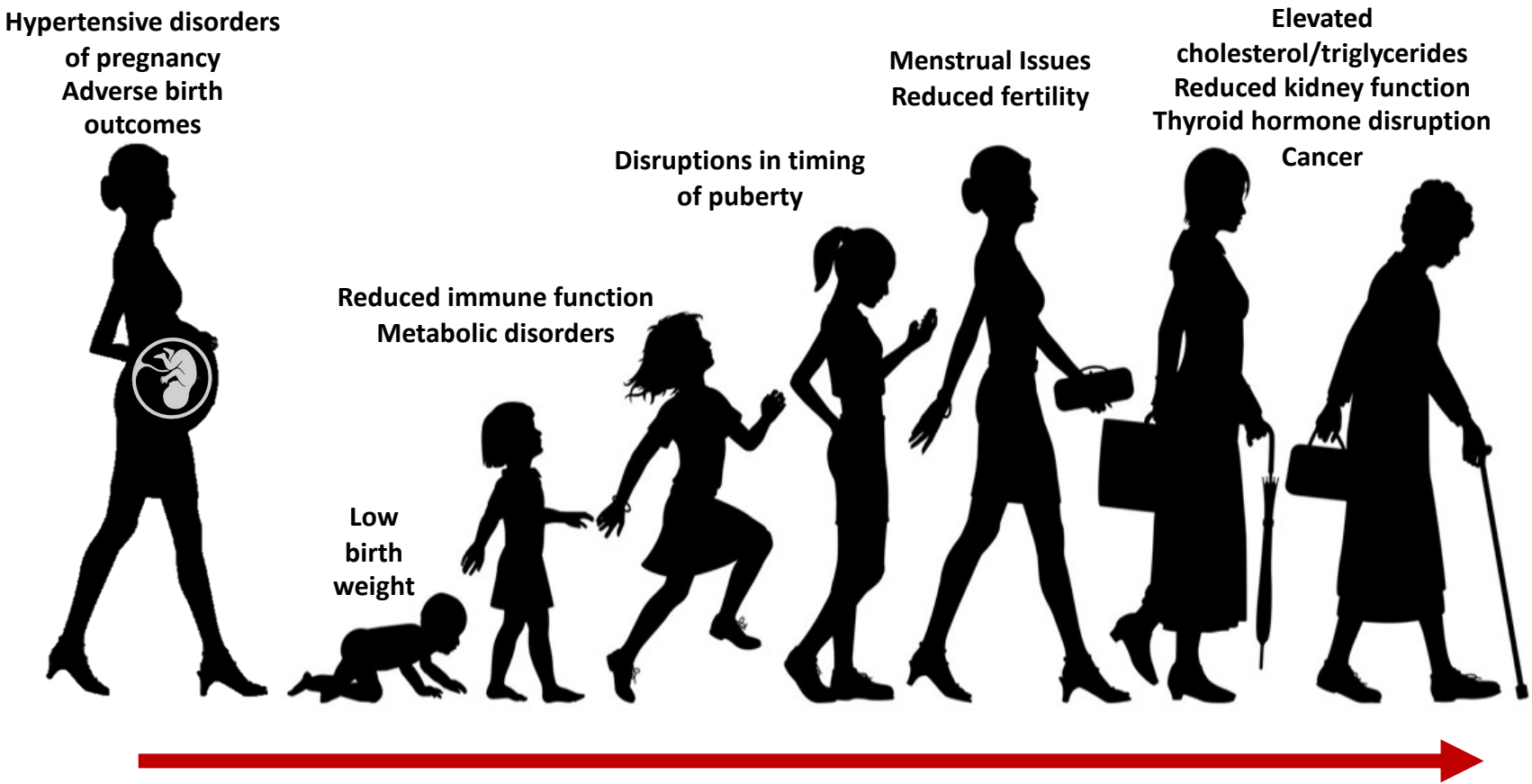
Repro & Developmental Outcomes

Used with permission from

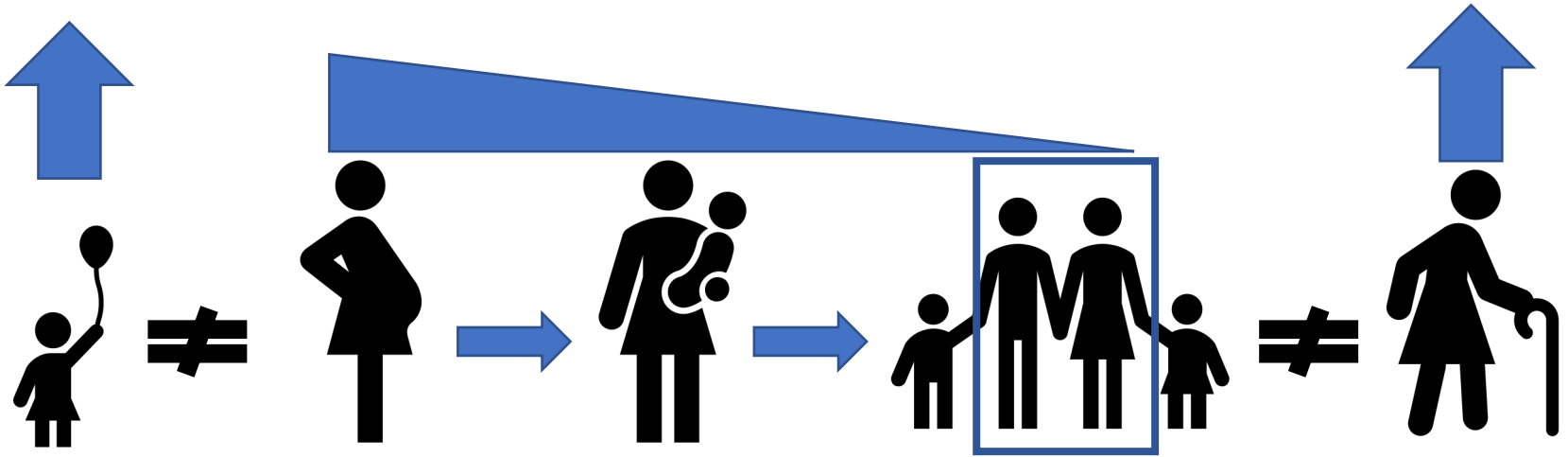
European Environment Agency (2019)

Fenton et al., ET&C 2021

In utero PFAS exposure may set the stage for a lifetime of increased disease susceptibility

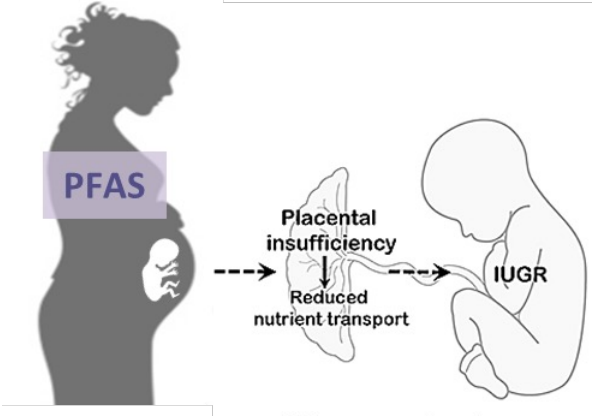


Challenges in studying PFAS - Toxicokinetics



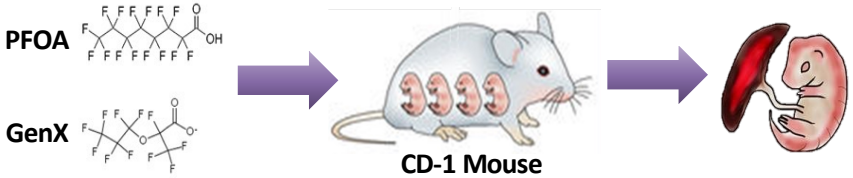
Rickard et al., 2021 *Toxicology*

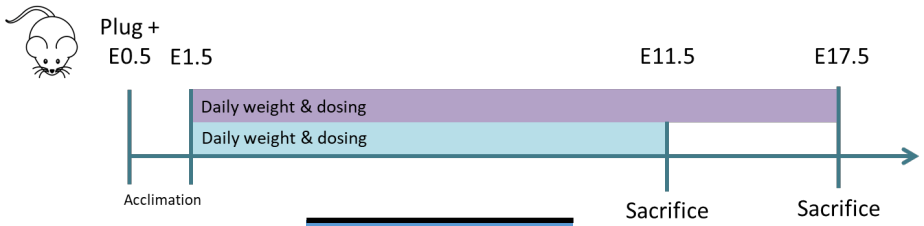
Compare PFOA and GenX Adverse Outcomes



Adapted from: Gaccioli & Lager Front Physiol 2016

- Pre-term birth and SGA
- Gestational diabetes
- Increased gestational weight gain
- Lowered infant birth weight
- Gestational hypertension





Treatment Groups N = 11-13 dams
Control (water)
1 mg/kg/day PFOA
5 mg/kg/day PFOA
2 mg/kg/day GenX
10 mg/kg/day GenX

Summary of Significant GenX vs PFOA Effects

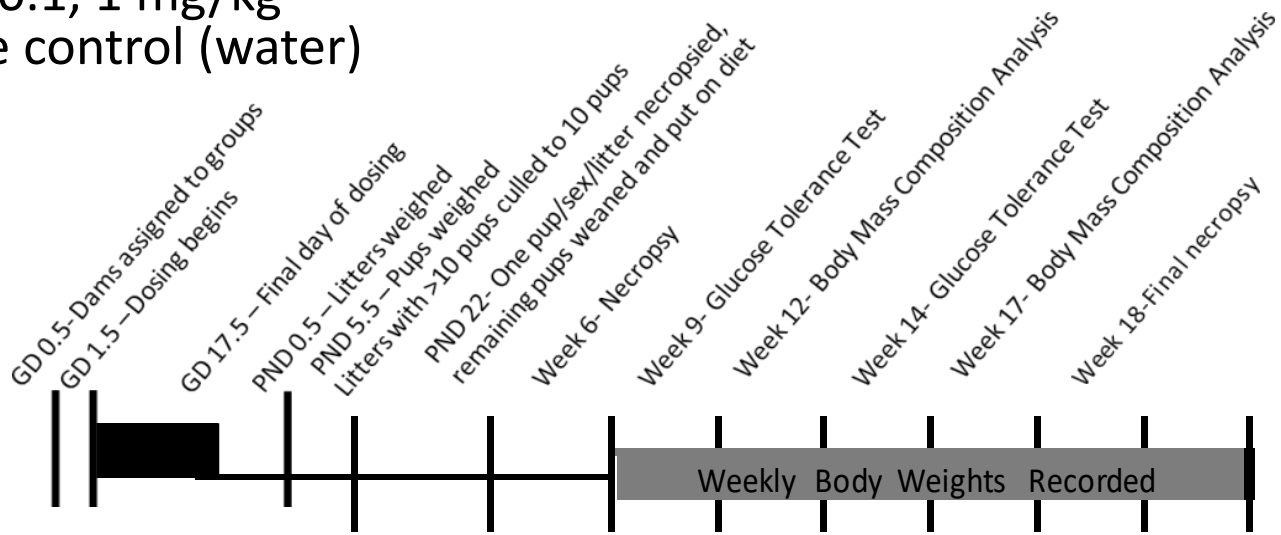
- No embryonic or fetal loss, fetal abnormalities, or difference in embryo number
- Similar disposition and measured levels in dam serum, amniotic fluid, or embryos (M or F) when comparing low or high doses of the two PFAS
- Both PFAS increased gestational weight gain (PFOA at high dose, GenX both doses)
- At high doses, both PFAS increased placental weight, decreased fetal:placental weight ratio
- 5 mg/kg PFOA decreased E17.5 fetal weight
- Increased dam liver lesions noted at all doses tested, with elevated relative liver weight
- Mitochondrial increase noted in TEM of liver for both compounds tested

- Two notable differences:
  1. placental pathology lesion patterns were unique for each PFAS
  2. GenX did not accumulate in the liver like PFOA (levels nearly 10X lower in GenX vs PFOA exposed livers). However, 100% of livers from dams exposed to PFAS showed some degree of cytoplasmic alteration

Reported in Blake *et al* 2020, *Environ Health Perspect*

Offspring Study Design: Dose Groups

- GenX: 0.2, 1, 2 mg/kg
- PFOA: 0.1, 1 mg/kg
- Vehicle control (water)



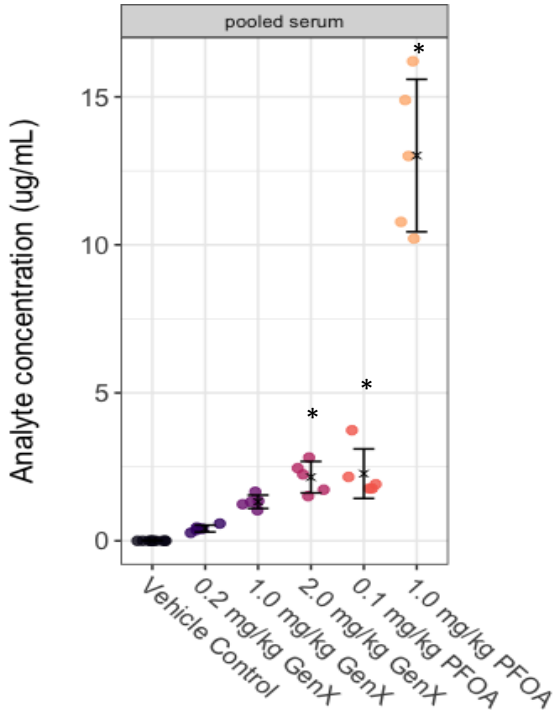
- **Divided into HIGH fat and NORMAL fat diets (calorically balanced)**
- **GTT = glucose tolerance testing**
- **BMC by Bruker body mass analyzer**
- **Blinded dosing, data collection and analyses**

What are the health effects in offspring over time?

PFAS serum half-life estimates in rat, mouse, monkey, and humans.

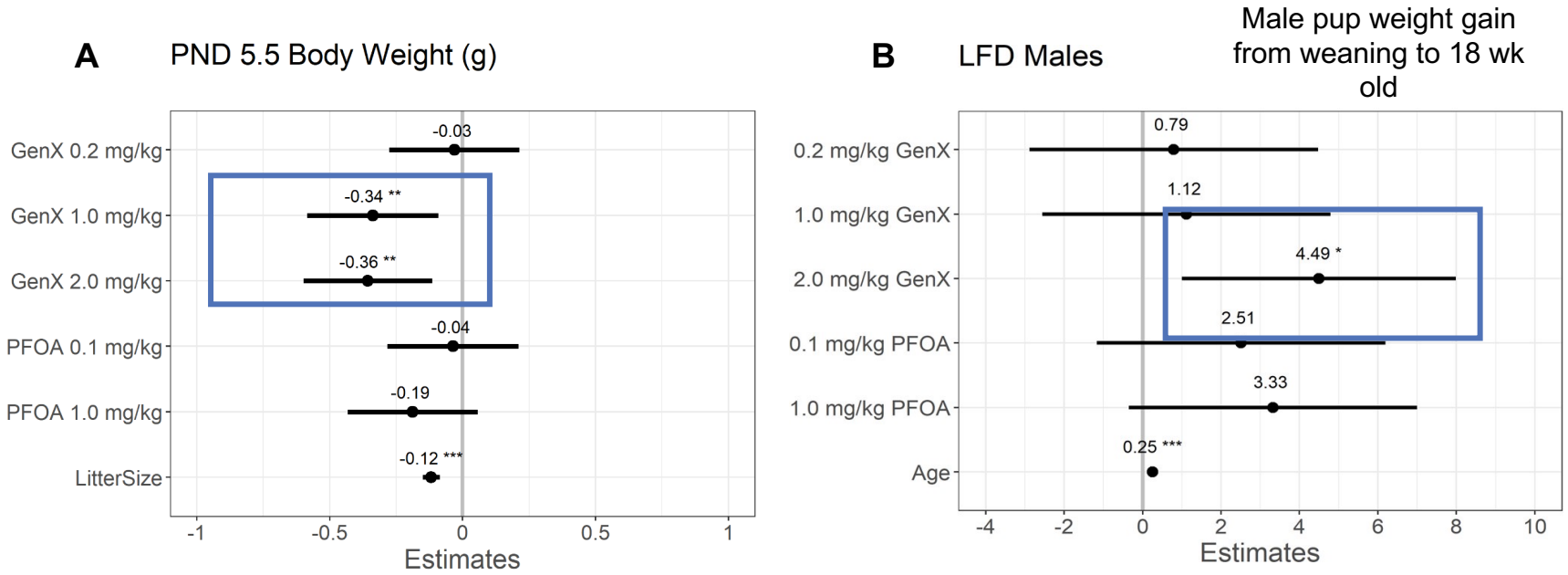
	PFOA (C8)		GenX	
	F	M	F	M
Rat	**2-4 hours**	**4-6 days**	**8 hours**	**3 hours**
Mouse	**16 days**	**22 days**	**18 hours**	**20 hours**
Monkey	**30 days**	**21 days**		
Humans	**2.1-3.8 years**		**81 h**	

PFOA and GenX in PND 5 pup serum



Accumulation and elimination of PFOA and GenX in the serum of developmentally exposed offspring at postnatal day (PND) 5. Both compounds were also present in urine. GenX was *undetectable* in serum at weaning, whereas PFOA was at contaminated human serum levels at weaning. From Cope et al. *Emerg Contam* 2021

GenX (HFPO-DA) decreases neonate weight, increases adult weight



Mixed model estimates of pup body weight at A) PND 5.5 (both male and female) and B) from PND22 to 18 weeks old (male). Horizontal bars represent 95% confidence intervals centered around the point estimate from the model. From Cope et al. *Emerg Contam* 2021

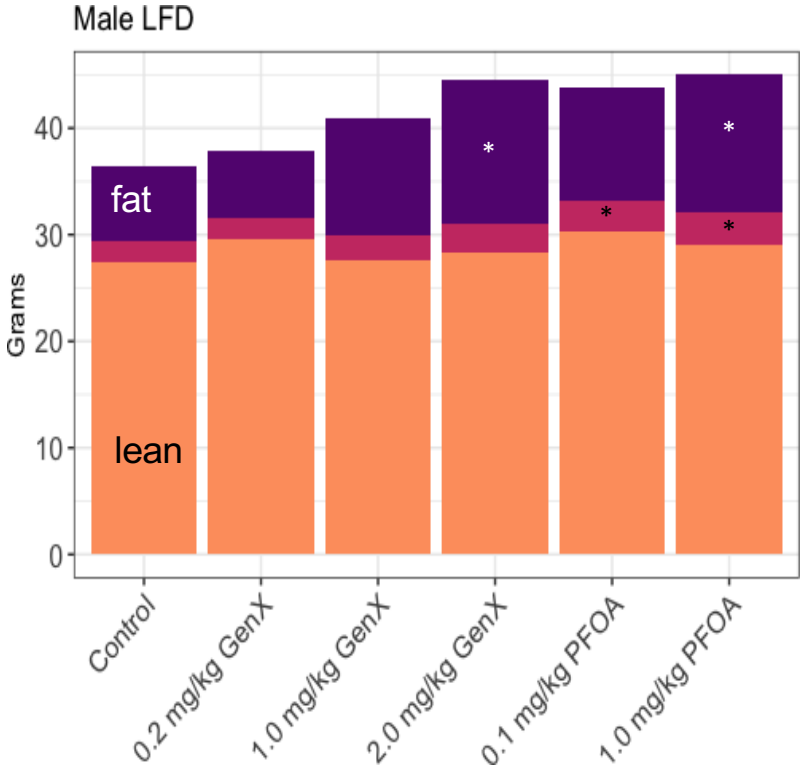
Metabolic Disease in Male Offspring

From Cope et al. *Emerg Contam* 2021

Offspring fasted glucose and insulin at Week 18 (mean ± SD, N=7-11)

	PFAS Dose	Glucose (mg/dL)	Insulin (pg/mL)	QUICKI
Male	Vehicle	179.7 ± 26.5	933.5 ± 791.3	0.802 ± 0.473
	GenX 0.2mg/kg	190.4± 32.3	1043.9 ± 515.6†	0.600 ± 0.094
	GenX 1.0mg/kg	192.4 ± 31.1	2506.5 ± 1588.8†	0.530 ± 0.187
	GenX 2.0mg/kg	181.0 ± 22.9	**6597.5 ± 8869.8*,†**	**0.463 ± 0.103***
	PFOA 0.1mg/kg	190.0 ± 29.3	2048.4 ± 1301.0†	0.587 ± 0.281
	PFOA 1.0mg/kg	250.2 ± 199.0	4271.2 ± 3391.1†	**0.456 ± 0.114***

Note – Triglycerides in males were significantly decreased at weaning by GenX (all doses) and 1 mg/kg PFOA. By 6 weeks of age, GenX (all doses) significantly increased cholesterol levels in males. By 18 weeks, cholesterol was still elevated compared to controls in male GenX treated pups (1 mg/kg –significant).

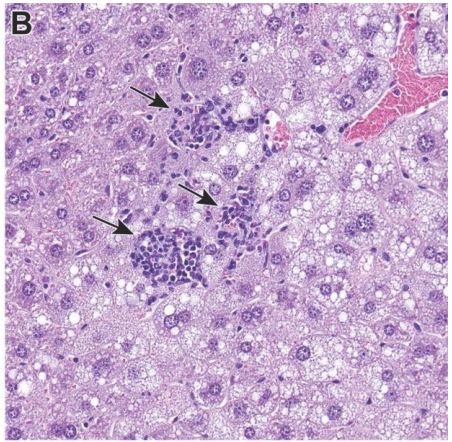


QUICKI = Quantitative insulin check index. Katz et al., *J Clin Endocrinol Metab*. 2000; doi:10.1210/jcem.85.7.6661

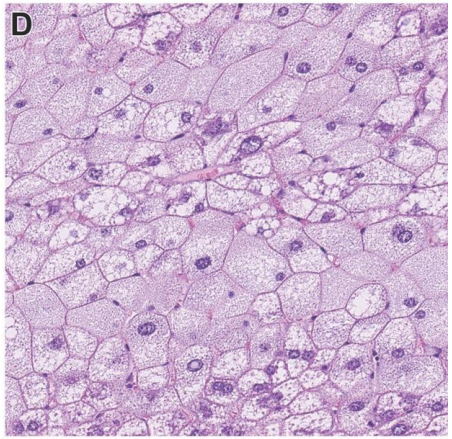
A “constellation of liver lesions” from PFOA and GenX

Sex-specific effects in liver and on metabolic disease phenotype

<u>Single cell necrosis</u>:
Increased in low and high fat diets
Evident in both males and females
Females more affected than males
Significant increase at 1 mg/kg PFOA and 1 mg/kg GenX

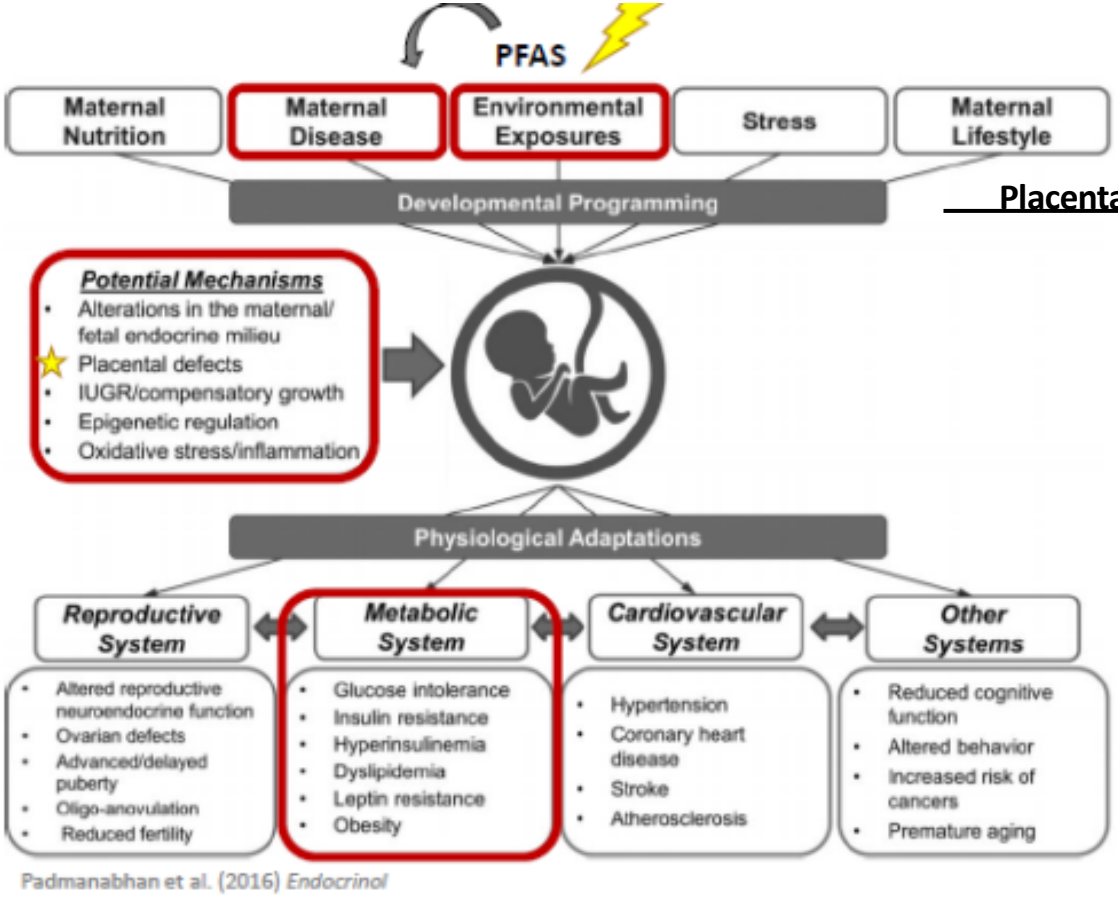


<u>Fatty change, microvesicular</u>:
Increased in males fed low fat diet @ 2 mg/kg GenX
Evident in both males and females
Males more affected than females
Strong effect of diet
Females had macrovesicular fatty change



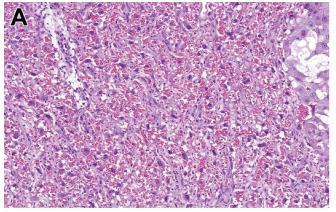
From Cope et al. *Emerg Contam* 2021

Developmental PFAS exposures affect numerous systems

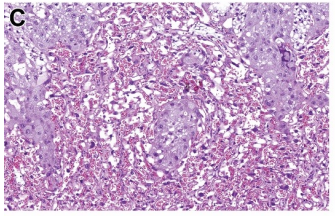


Padmanabhan et al. (2016) *Endocrinol*

Placenta

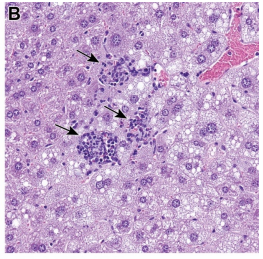


Control

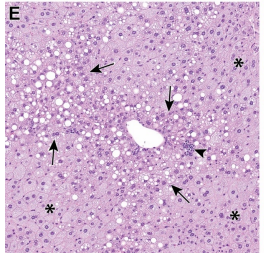


GenX-treated

Sex-specific Liver Outcomes



Male 1 mg/kg GenX

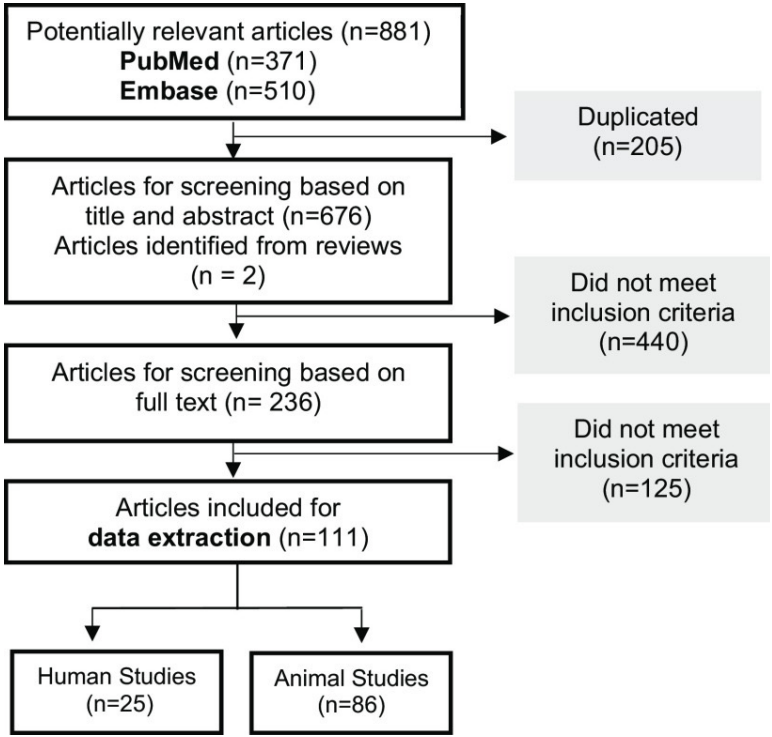


Female 0.2 mg/kg GenX

Results in Blake et al *EHP* 2020 and Cope et al *Emerg. Contam* 2021

Translatable to Human Health?

Evaluate the effects of PFAS exposure with a focus on the liver enzymes and related markers of liver injury commonly used in human epidemiological research



Published in Costello et al 2022, *Environ Health Perspect*

PFOA:

- Eight cross-sectional epidemiological studies assessed PFOA and ALT in participants ≥12 years of age. Weighted z-score of 6.20 ($p<0.001$) indicated a positive relationship between PFOA and ALT. A weighted z-score for PFOA and ALT of 5.12; $p<0.001$ was also calculated for 3 longitudinal studies
- 21/32 mouse studies reported significantly increased ALT, with 10/21 showing dose dependency – hepatocellular hypertrophy and necrosis reported in livers of mice and rats

GenX:

- No studies in humans
- 3 of 4 studies in mice reported steatosis or histopathological changes, but no changes in liver enzyme levels
- One study reported adverse liver histopathology and increased ALT with a PFAS mixture that included PFOA and GenX. Few reported on males and females.
- Our study – sex-dependent ALT changes (females on HFD)

Understanding the “E” in EHD:

1. **Cross-divisional Reproductive Health Disparities Workshop – April 2022** [Environmental Impacts on Women’s Health Disparities and Reproductive Health (nih.gov)]
2. **Incorporate unhealthy diets or test animals that have chronic disease or chronic chemical exposures (especially hypertension, obesity)**
3. **How to do a better job of evaluating effects of the environment that may differ due to food availability, stress, fear, poor living conditions or metabolic status?**
4. **Think more carefully about health outcome differences by race/sex**





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