Maternal and neonatal effects of maternal oral exposure to perfluoro-2-methoxyacetic acid (PFMOAA) during pregnancy and early lactation in the Sprague-Dawley rat

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Article

Maternal and Neonatal Effects of Maternal Oral Exposure to Perfluoro-2-methoxyacetic Acid (PFMOAA) during Pregnancy and Early Lactation in the Sprague–Dawley Rat

Justin M. Conley,* Christy S. Lambright, Nicola Evans, Jacqueline Bangma, Jermaine Ford, Donna Hill, Elizabeth Medlock-Kakaley, and L. Earl Gray, Jr.

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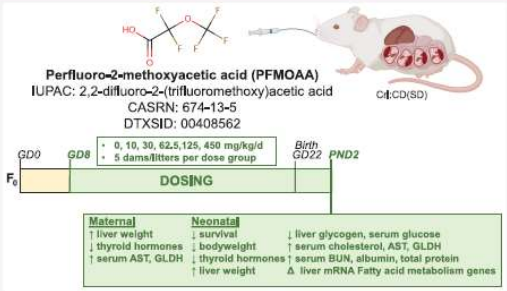
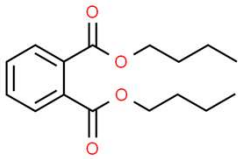
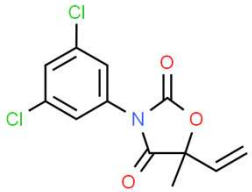
ABSTRACT: Perfluoro-2-methoxyacetic acid (PFMOAA) is a short-chain perfluoroalkyl ether carboxylic acid that has been detected at high concentrations (~10 μg/L) in drinking water in eastern North Carolina, USA, and in human serum and breastmilk in China. Despite documented human exposure there are almost no toxicity data available to inform risk assessment of PFMOAA. Here we exposed pregnant Sprague–Dawley rats to a range of PFMOAA doses (10–450 mg/kg/d) via oral gavage from gestation day (GD) 8 to postnatal day (PND) 2 and compared results to those we previously reported for perfluorooctanoic acid (PFOA) and hexafluoropropylene oxide–dimer acid (HFPO–DA or GenX). Newborn pups displayed reduced birthweight (≥30 mg/kg), depleted liver glycogen concentrations (all doses), hypoglycemia (≥125 mg/kg), and numerous significantly altered genes in the liver associated with fatty acid and glucose metabolism similar to gene changes produced by HFPO–DA. Pup survival was significantly reduced at ≥125 mg/kg, and at necropsy on PND2 both maternal and neonatal animals displayed increased liver weights, increased serum aspartate aminotransferase (AST), and reduced serum thyroid hormones at all doses (≥10 mg/kg). Pups also displayed highly elevated serum cholesterol at all doses. PFMOAA concentrations in serum and liver increased with maternal oral dose in both maternal and F1 animals and were similar to those we reported for PFOA but considerably higher than HFPO–DA. We calculated 10% effect levels (ED10 or EC10) and relative potency factors (RPF; PFOA = index chemical) among the three compounds based on maternal oral dose and maternal serum concentration (μM). Reduced pup liver glycogen, increased liver weights and reduced thyroid hormone levels (maternal and pup) were the most sensitive end points modeled. PFMOAA was ~3–7-fold less potent than PFOA for most end points based on maternal serum RPFs, but slightly more potent for increased maternal and pup liver weights. PFMOAA is a maternal and developmental toxicant in the rat producing a constellation of adverse effects similar to PFOA and HFPO–DA.

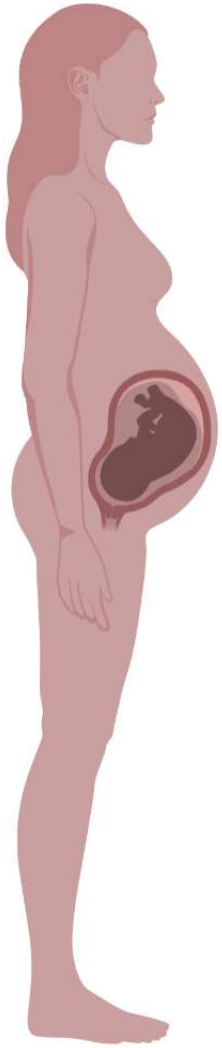


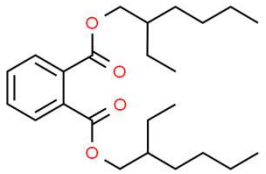
KEYWORDS: *PFAS, developmental toxicity, liver, birthweight, thyroid disruption, hepatic toxicity*

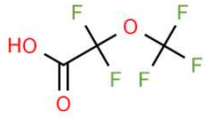
US EPA – Reproductive and Developmental Toxicology Branch

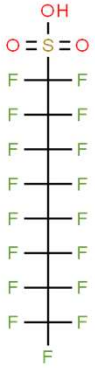


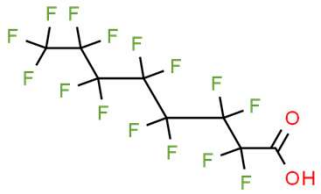


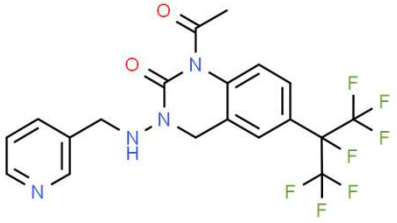


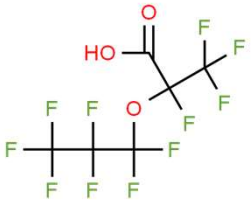


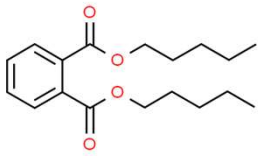


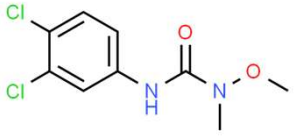


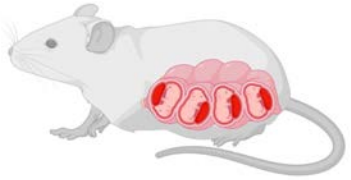






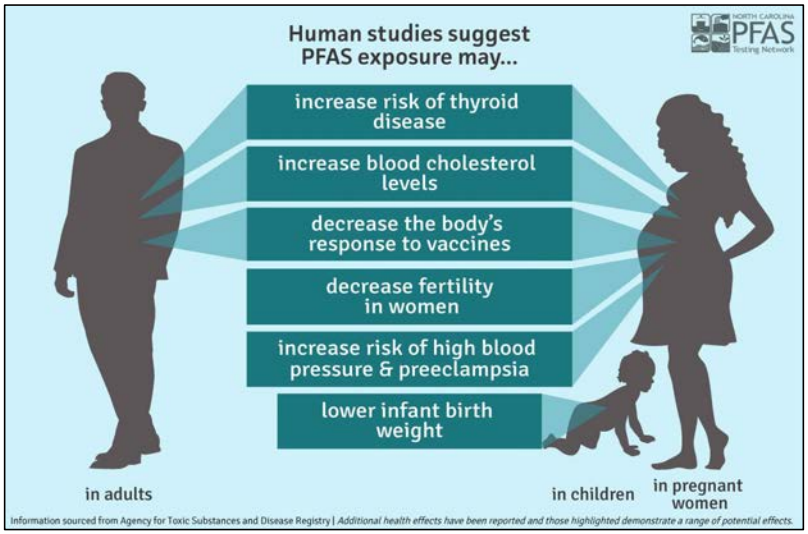


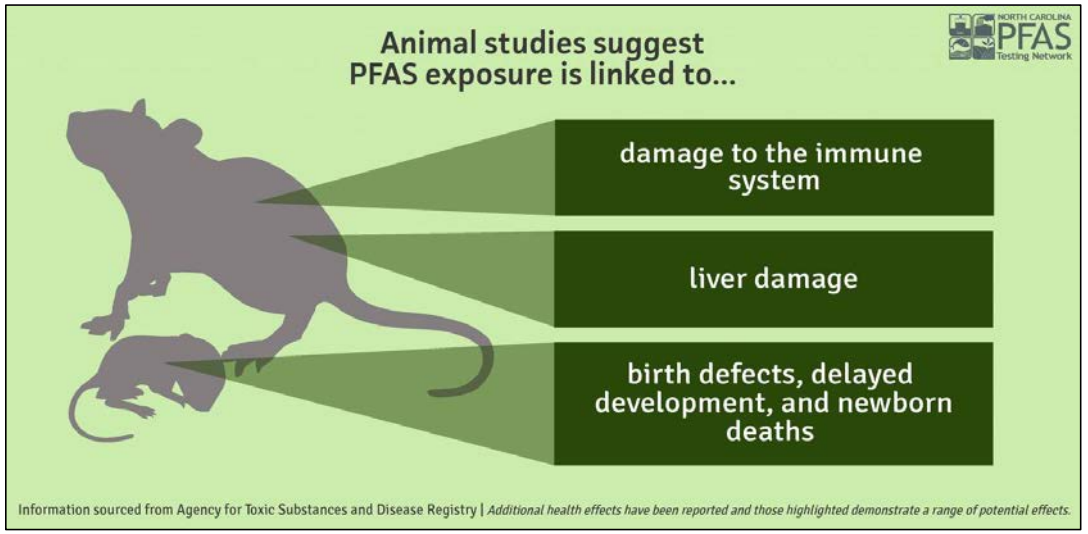




PFAS Developmental Toxicity

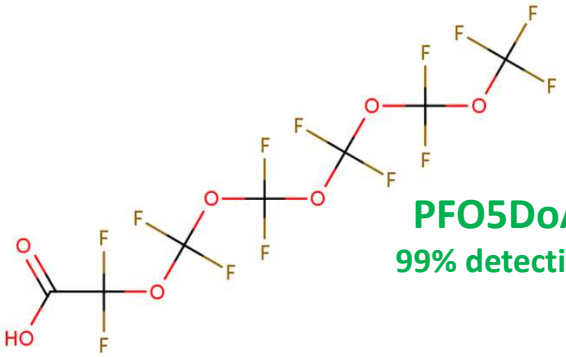
- Maternal and offspring effects reported from PFAS exposure during pregnancy in animal models and epidemiology studies
- Maternal and developmental effects are complex and remain incompletely characterized
- Most PFAS have not been evaluated in developmental toxicity studies



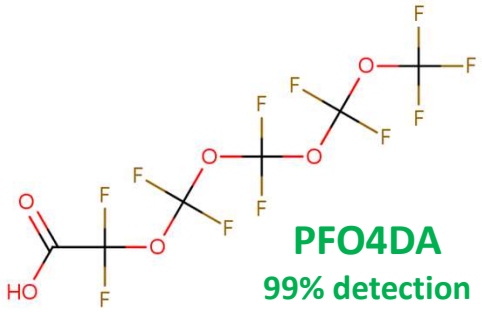


Emerging PFAS

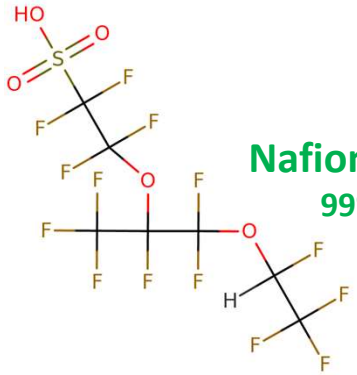
- Long-chain per- and polyfluoroalkylether compounds
  - Low drinking/surface water concentrations
  - High detection frequency in human samples



PFO5DoA
99% detection

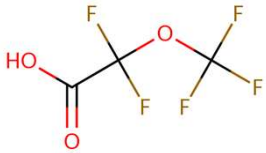


PFO4DA
99% detection

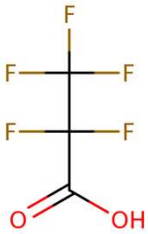


Nafion byproduct 2
99% detection

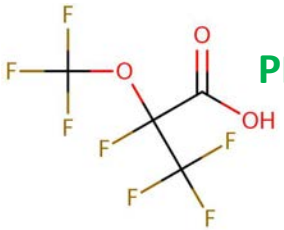
- Short-chain perfluoroalkyl and perfluoroalkylether compounds
  - High environmental concentrations
  - Little/no detection in human samples



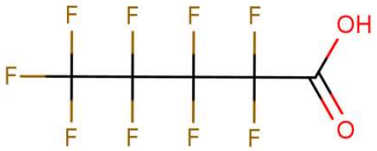
PFMOAA



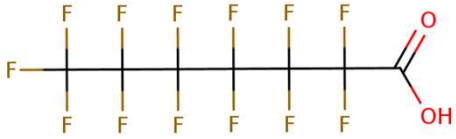
PFPrA



PMPA



PFPeA



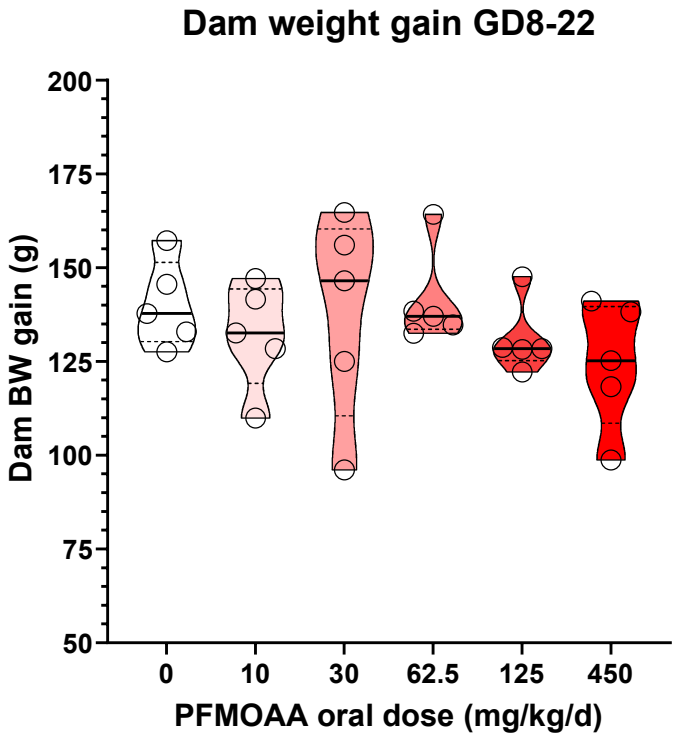
PFHpA

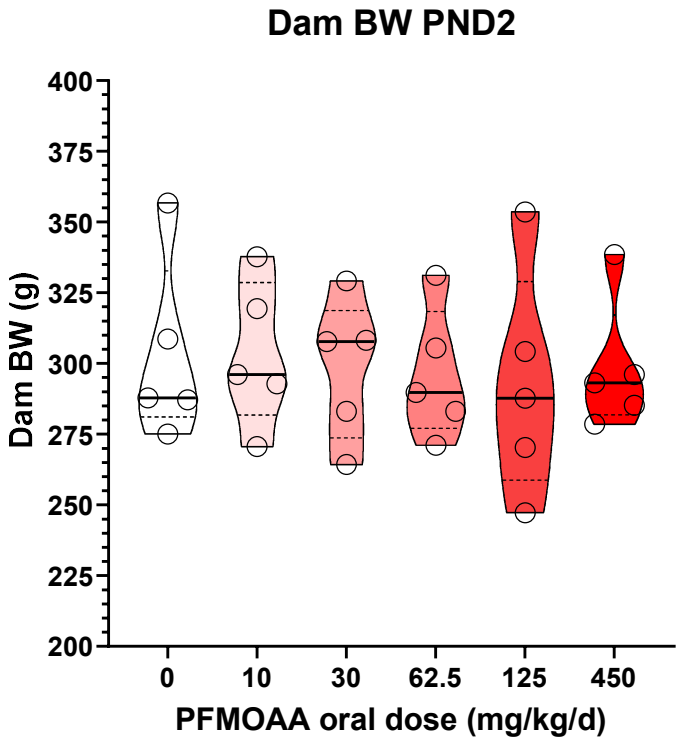
In vivo study design for PFMOAA

- 0, 10, 30, 62.5,125, 450 mg PFMOAA/kg/d
- 5 dams/litters per dose group

Conley et al. (2024) PMID 38163761

Results





No overt maternal toxicity

Results

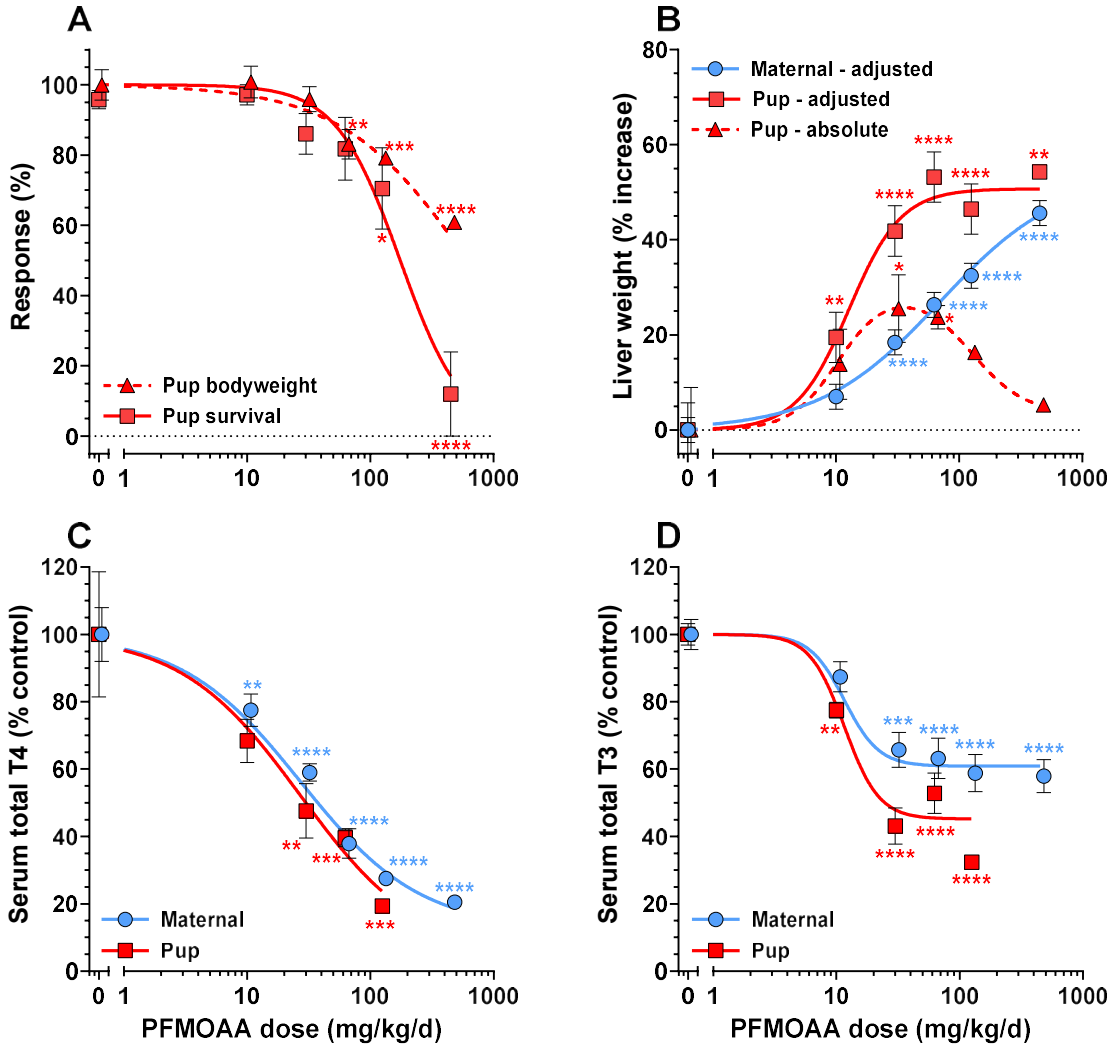


Figure 1.

Conley et al. (2024) PMID 38163761

Results

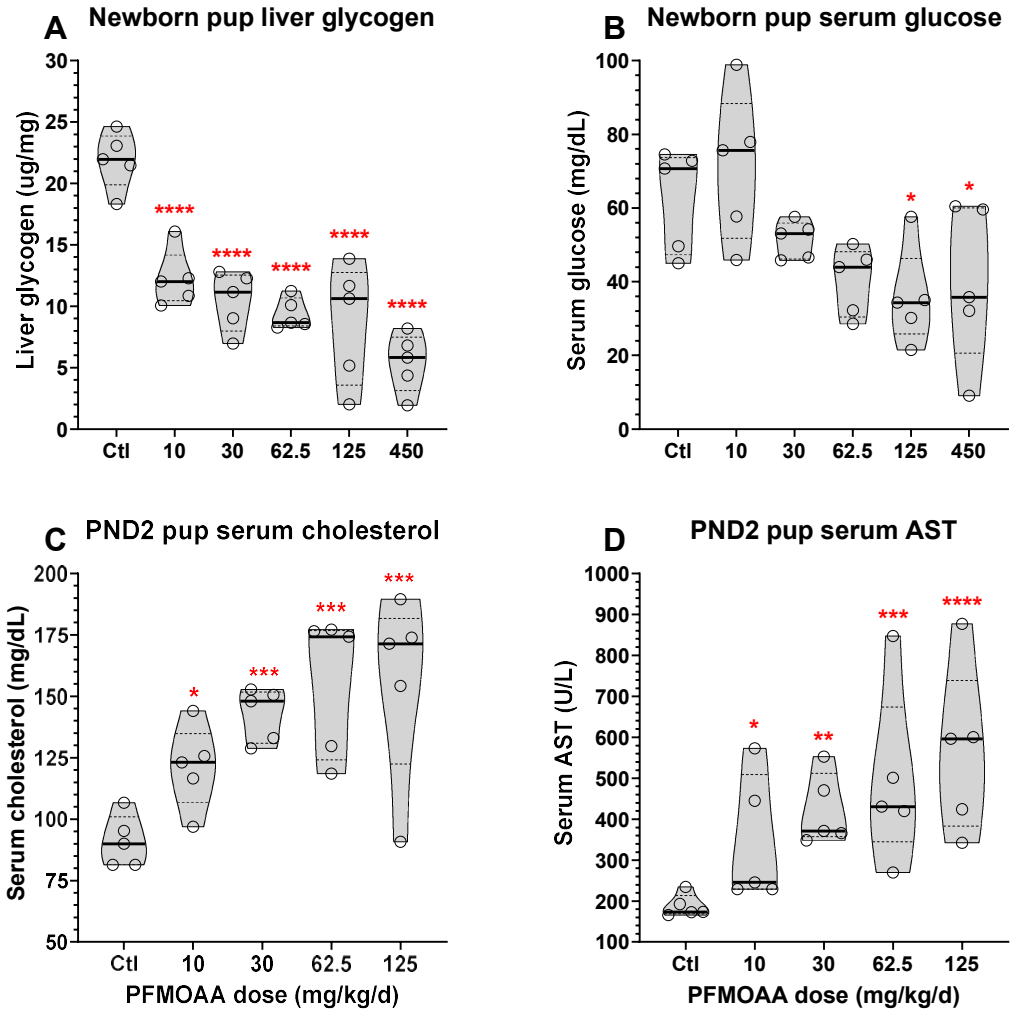


Figure 2.

Conley et al. (2024) PMID 38163761

Results

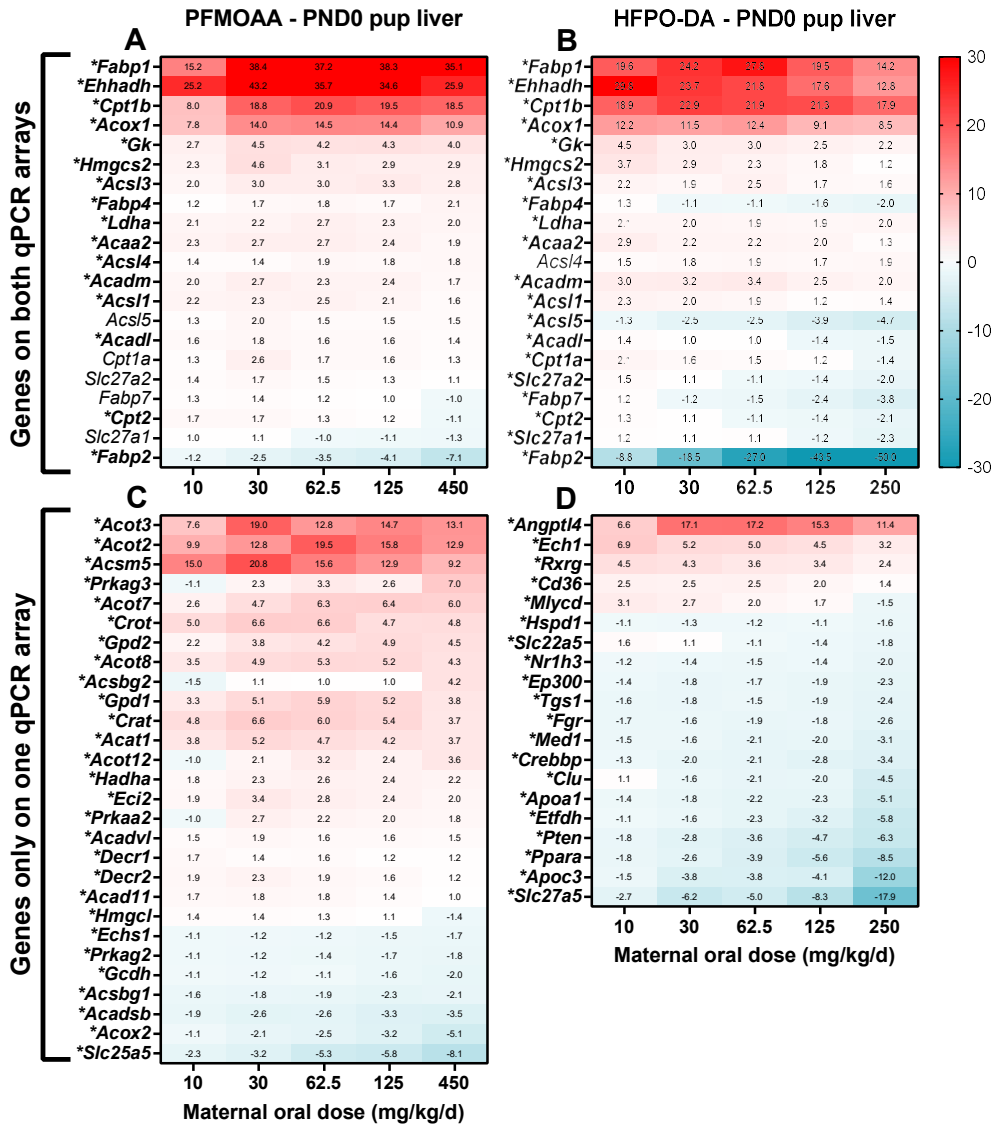


Figure 3.

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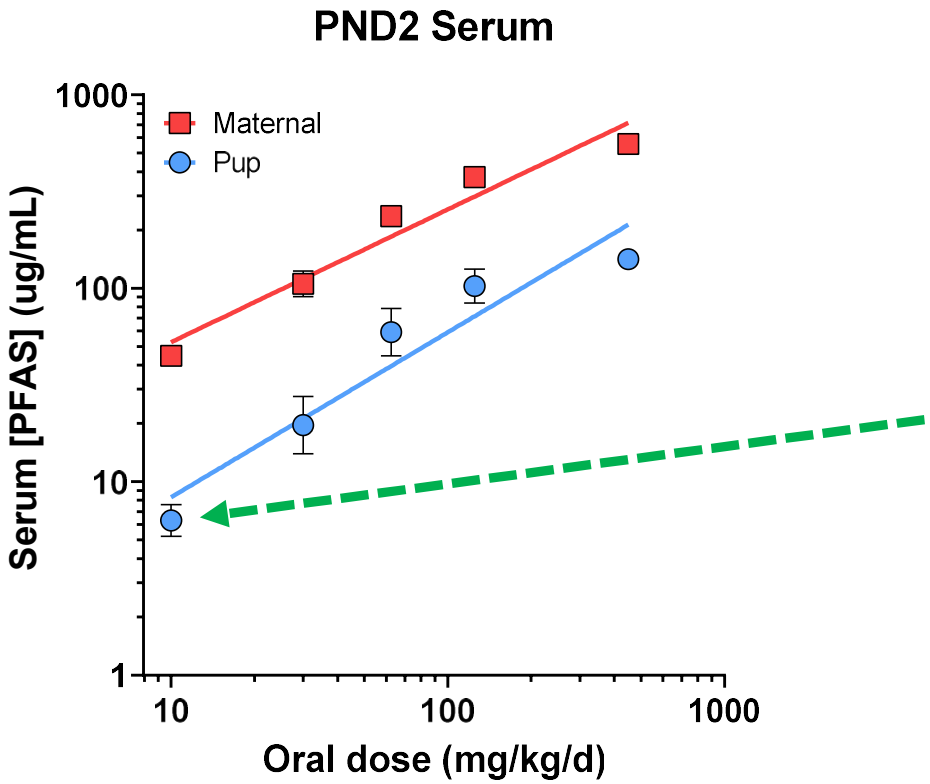
Results - dosimetry



- No data on human serum levels in NC
- Yao et al. (2023) – Shandong, China
  - Maximum serum = 0.158 µg/mL
- Mean pup serum at 10 mg/kg/d dose
  - 6.7 µg/mL
- ~42-fold margin of exposure
  - *not a NOAEL, adverse effects occurred at this exposure level

Figure S1.

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Results – dosimetry comparison with PFOA and HFPO-DA (GenX)

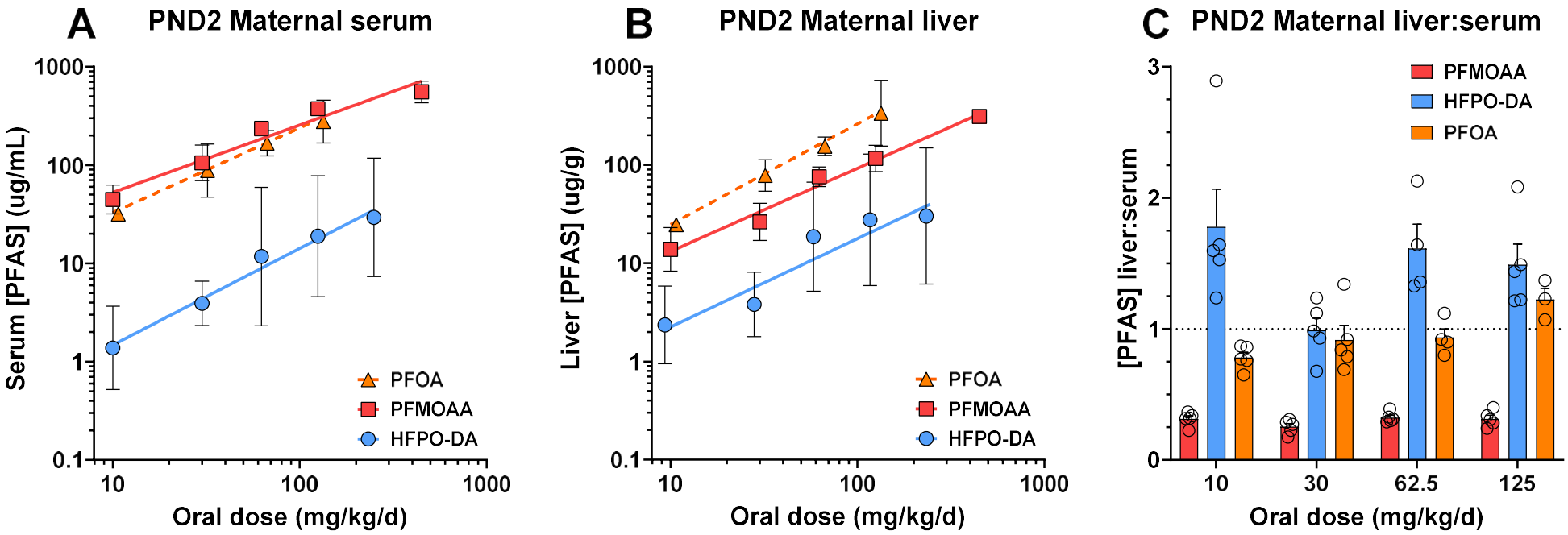

Figure 4.

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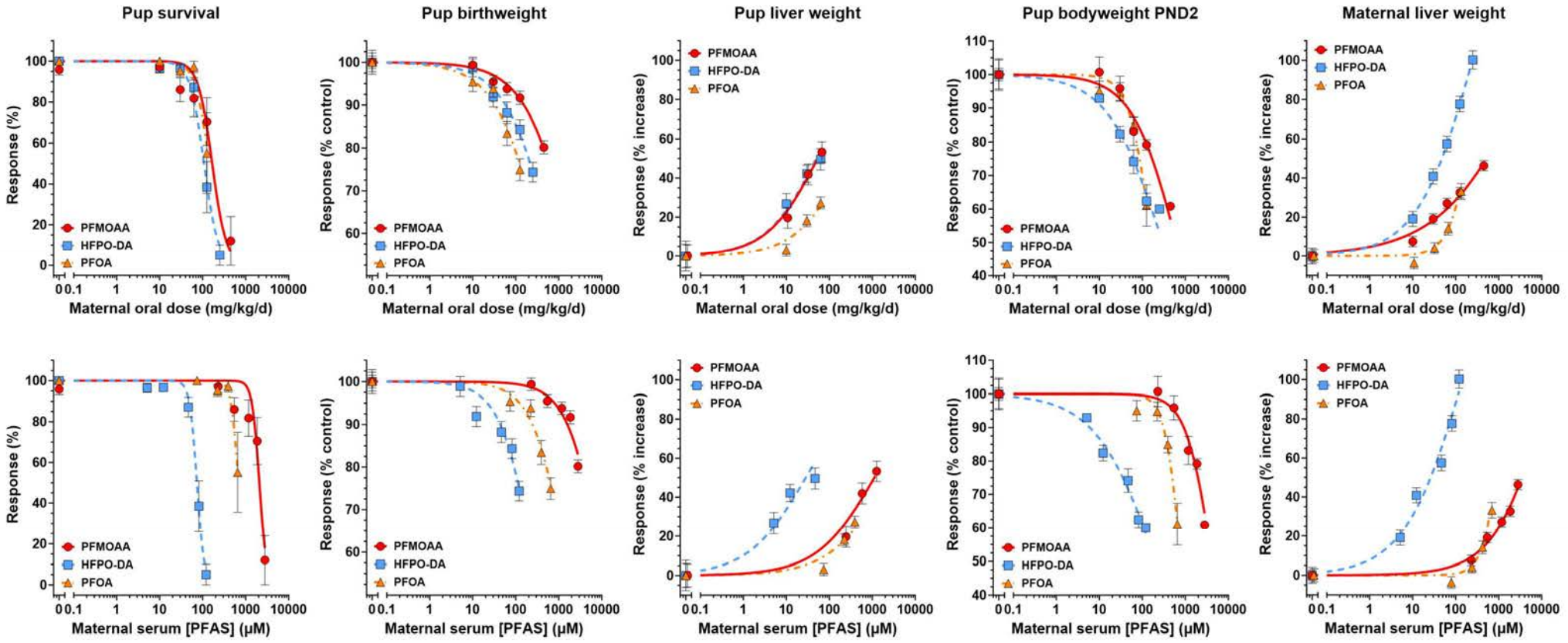
Results – dose response comparison with PFOA and HFPO-DA (GenX)



PFMOAA = 180 g/mol **HFPO-DA = 329 g/mol** **PFOA = 414 g/mol**

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Results – relative potency compared to PFOA and HFPO-DA (GenX)

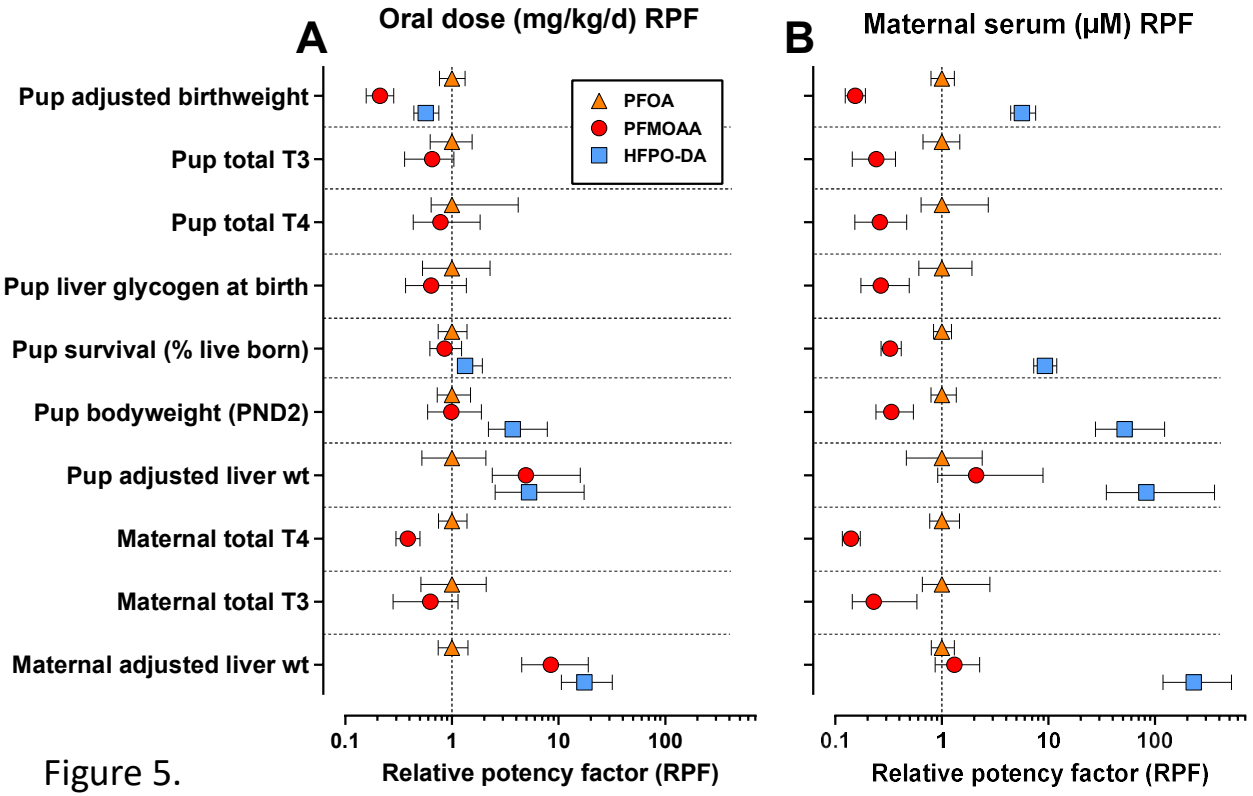

Figure 5.

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Exposure and toxic potency considerations

- Elimination rate is a major factor in evaluating PFAS risk and interpreting toxicity data

- PFMOAA elimination in female rat appears rapid, and likely rapid in humans due to chain length
  - PFBA half-life in female rat ~1-2 hours
  - PFBA half-life estimate in humans ~70-80 hours

- PFOA elimination in female rat is rapid, but very long in humans
  - PFOA half-life in female rat ~2-10 hours
  - PFOA half-life in humans is ~2-10 years

- Ability to achieve internal doses associated with toxicity is greater for compounds with longer half-life

- Rapid elimination does not necessarily mean “no risk”

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Main points

- Emerging/replacement PFAS have essentially same maternal/developmental effects as legacy compounds
  - Functional groups (carboxylate vs. sulfonate) are the primary drivers of toxic effects
  - Ether linkages breaking carbon chain do not appear to reduce hazard
  - Chain length largely dictates elimination/half-life and oral dose potency (species and sex differences)

- Short-chain compounds produce hazardous effects despite rapid clearance
  - Risk dependent on extent of exposure levels

- High need for compound-specific data for multiple emerging PFAS with known human exposure in NC and other US locations

- Important to remember that exposure to multiple PFAS is essentially ubiquitous and joint effects occur from combined exposure
  - Common effects have shown to be dose additive regardless of functional group

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EPA Research Team and Collaborators

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Overview of PFMOAA immunotoxicity studies

DeWitt Lab

PFAST Network & NC State Superfund

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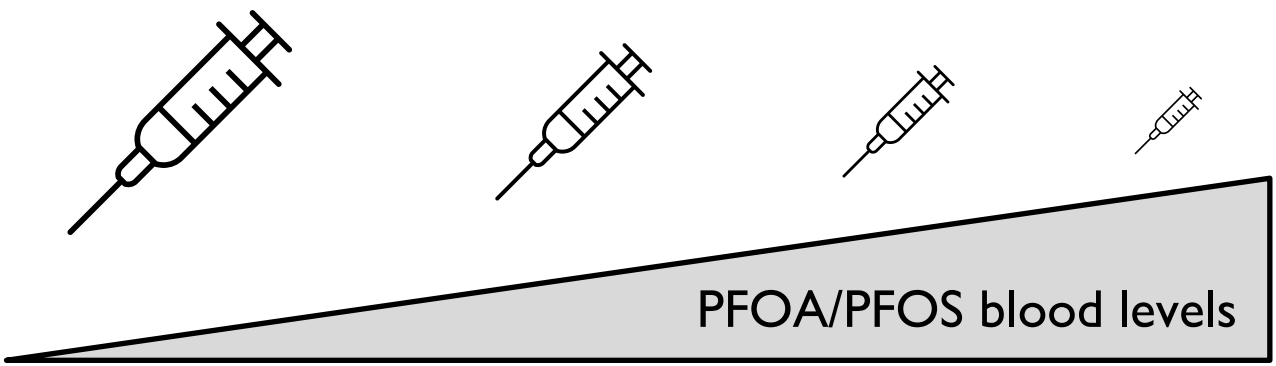
• *Presented for the NC SSAB 7 August 2024* •

Declarations

I currently am funded to study immune system effects of PFAS, from US EPA/Oregon State University (83948101) and NIEHS SRP/NC State University (P42 ES031009-01).

I serve/have served as a plaintiff's expert witness in PFAS cases.

Impetus for studies



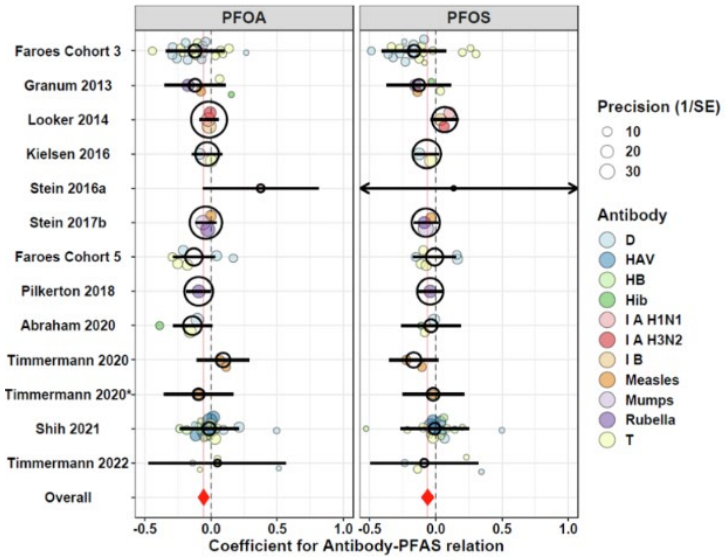
Decreased* responses to vaccines/antigens** in experimental animal models, children, and adults who have ***higher levels PFOA/PFOS in their blood is a critical effect linked to PFOA/PFOS exposure.

Impetus for studies

Systematic Review

Systematic review and meta-analysis of epidemiologic data on vaccine response in relation to exposure to five principal perfluoroalkyl substances

Lori Crawford [a,*], Scott A. Halperin [b,c,d], Michael W. Dzierlenga [e], Becky Skidmore [f], Matthew W. Linakis [g], Shinichi Nakagawa [h], Matthew P. Longnecker [g]



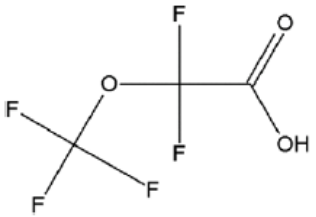
Key takeaways:

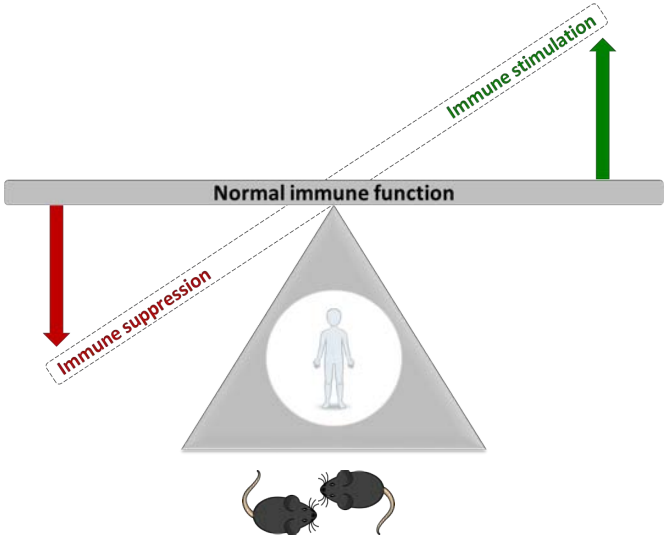
- Homogeneity of associations across antibody types for each PFAS.
- When Abs treated as one type, inverse associations for all PFAS.
- Confidence intervals excluded zero for PFOA, PFOS, and PFHxS.
- Children appear more sensitive than adults.

Basic experimental design

Main experimental endpoints:

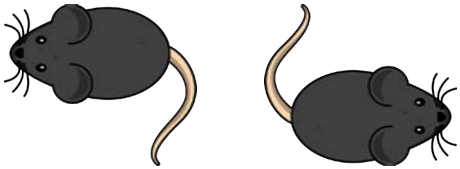
- *The T cell-dependent antibody response ("the TDAR")*
- *Liver peroxisomal enzyme activity*
- Selected lymphoid cell subsets from spleen & thymus
- Daily body weights and in-life observations
- Organ weights at terminus
- Urine and serum for PFAS concentrations



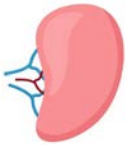


OPPTS 870.7800 as guideline protocol
30-day exposure period
Male and female C57BL/6 mice (N = 6-8/dose)
Oral exposures to include a dose close to the concentration of PFOA known to induce suppression of the TDAR (7.5 mg/kg) as mid-range dose.

Organ and body weights



No detectable effects on **body weights.**

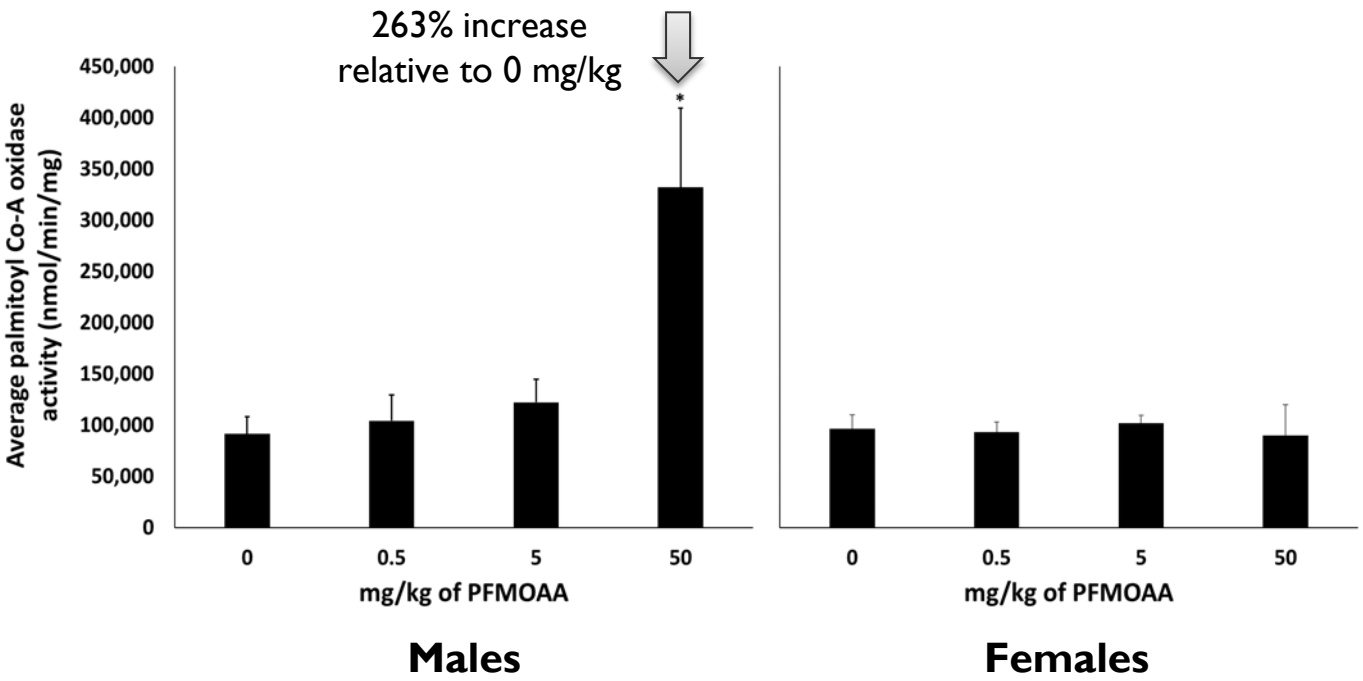


No detectable effects on **spleen weights** or **numbers of cells in the spleen** (cellularity).

50 mg/kg ↑ F liver weights by 44% (ns) and ↑ M liver weight by 153%

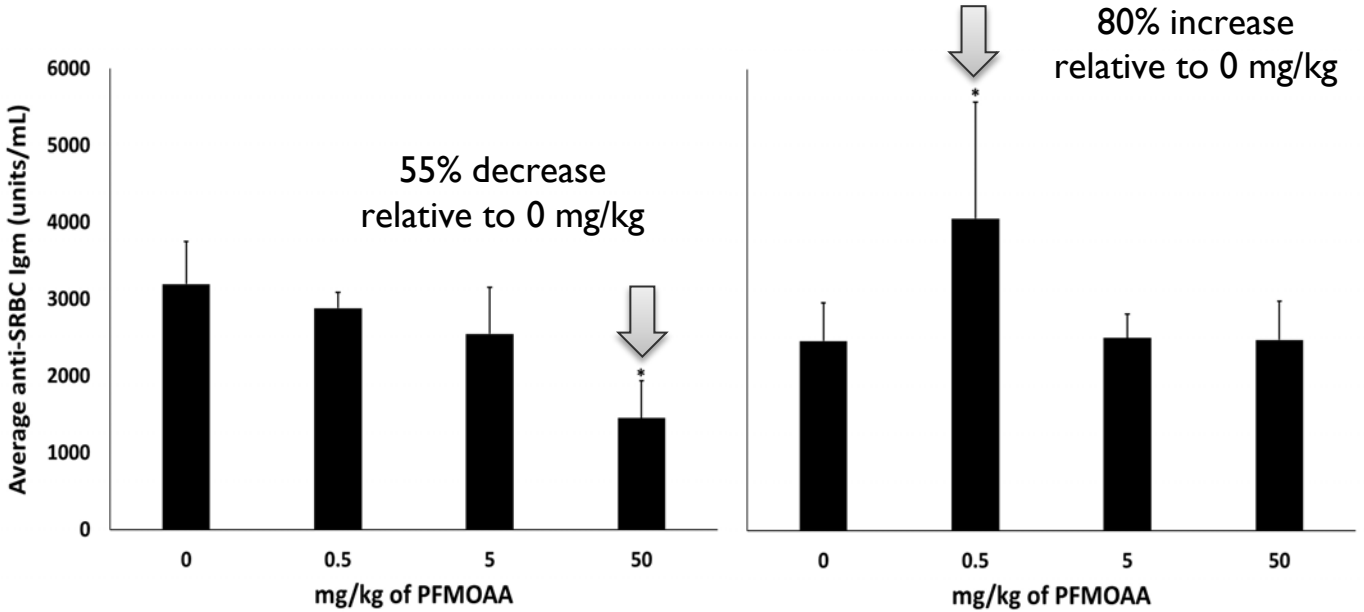
No detectable effects on **thymus weights** or **numbers of cells in the thymus** (cellularity).

Liver peroxisomal enzyme activity



Highest administered dose (50 mg/kg) given to males elevated liver peroxisomal enzyme activity.

The T cell-dependent antibody response (the TDAR)



The highest administered dose (50 mg/kg) given to males reduced the TDAR and the lowest administered dose (0.5 mg/kg) given to females increased the TDAR.