

Long-Term Health Effects: Immune System

Experimental animal data

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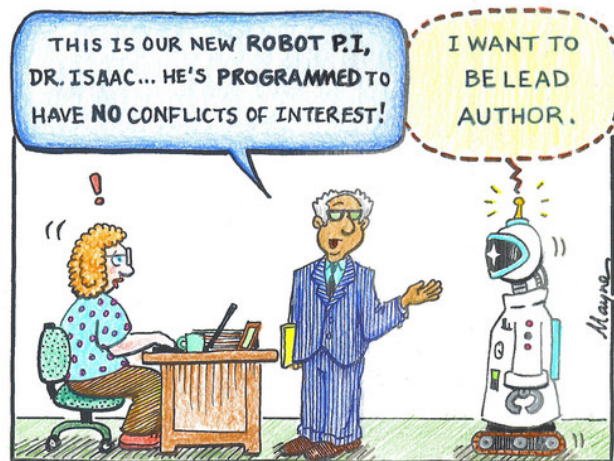
*3rd Annual PFAS Meeting
June 15-17, 2022 in Wilmington, NC*

Declarations

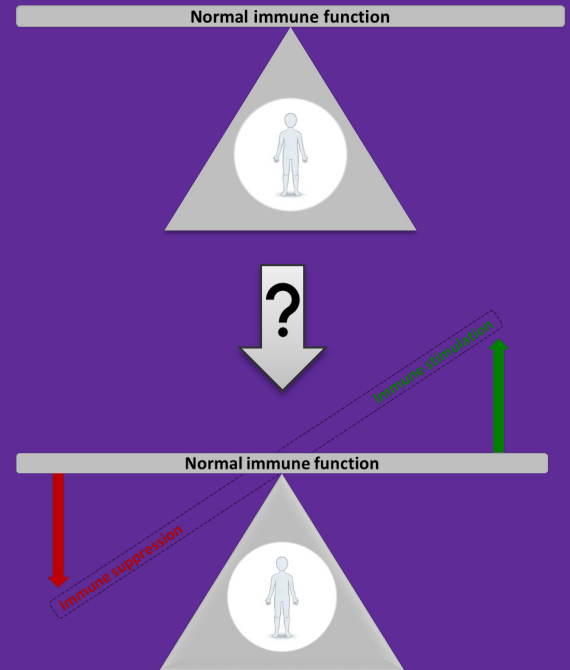
I currently am funded to study immune system effects of PFAS (sources of funding: North Carolina Policy Collaboratory/NC General Assembly, US EPA/Oregon State University (83948101), NIEHS SRP/NC State University (1 P42 ES031009-01).

I currently am a member of the U.S. EPA PFAS Science Advisory Board and have served as an external peer-reviewer for some of the documents used to support assertions in this slide set.

I often speak publicly about my understanding of PFAS toxicity, serve/have served as a plaintiff's expert witness, advocate for the need to protect the public from their exposures to PFAS, and am a proponent of the essential use concept and the class approach for PFAS management.



**What have we
learned about
effects of PFAS
exposure on the
immune system?**



PFAS immunotoxicity

Human studies suggest
PFAS exposure may...



Decreased responses to vaccines. This may decrease protection from the vaccine but also may indicate that other parts of the immune system are affected.



in adults

in children

in pregnant
women

PFAS immunotoxicity



Animal studies suggest
PFAS exposure is linked to...



damage to the immune
system

liver damage

birth defects, delayed
development, and newborn
deaths

Information sourced from Agency for Toxic Substances and Disease Registry

Weighing of the evidence

Table 7. PFOA Main Immune Effects Summary Table

Category of Immune Response	Immune Outcomes	Confidence Ratings in the Body of Evidence		Level of Evidence in the Body of Evidence		Hazard Conclusion
		Human	Animal	Human	Animal	
Immunosuppression	Antibody response	Moderate	High	Moderate	High	<u>Presumed</u> to be an Immune Hazard to Humans

Table 9. PFOS Main Immune Effects Summary Table

Category of Immune Response	Immune Outcomes	Confidence Ratings in the Body of Evidence		Level of Evidence in the Body of Evidence		Hazard Conclusion
		Human	Animal	Human	Animal	
Immunosuppression	Antibody response	Moderate	High	Moderate	High	<u>Presumed</u> to be an Immune Hazard to Humans



National Toxicology Program
U.S. Department of Health and Human Services

NTP MONOGRAPH ON IMMUNOTOXICITY ASSOCIATED WITH
EXPOSURE TO PERFLUOROOCTANOIC ACID (PFOA) OR
PERFLUOROOCTANE SULFONATE (PFOS)

Weighing of the evidence

Reference doses for recommended maximum contaminant level goals (MCLGs) by the U.S. EPA are based on risks of immunotoxicity as represented by impacts of PFAS exposure on vaccine responses in children.

The RfD selected for PFOA is 1.5×10^{-9} mg/kg-day based on the critical effect of decreased serum anti-tetanus antibody concentration in children.

The RfD selected for PFOS is 7.9×10^{-9} mg/kg-day based on the critical effect of decreased serum anti-diphtheria antibody concentration in children.



EXTERNAL PEER REVIEW DRAFT
Proposed Approaches to the Derivation of a
Draft Maximum Contaminant Level Goal for
Perfluorooctanoic Acid (PFOA)
(CASRN 335-67-1) in Drinking Water

EXTERNAL PEER REVIEW DRAFT
Proposed Approaches to the Derivation of a
Draft Maximum Contaminant Level Goal for
Perfluorooctane Sulfonic Acid (PFOS)
(CASRN 1763-23-1) in Drinking Water

Note that I am a member of the EPA PFAS Science Advisory Board that was charged with reviewing the processes used to derive these maximum contaminant level goals.

Weighing of the evidence



Statement on Potential Intersection between PFAS Exposure and COVID-19:

CDC/ATSDR understands that many of the communities we are engaged with are concerned about how PFAS exposure may affect their risk of COVID-19 infection. We agree that this is an important question.

CDC/ATSDR recognizes that exposure to high levels of PFAS may impact the immune system. There is evidence from human and animal studies that PFAS exposure may reduce antibody responses to vaccines (Grandjean et al., 2017, Looker et al., 2014), and may reduce infectious disease resistance (NTP, 2016). Because COVID-19 is a new public health concern, there is still much we don't know. More research is needed to understand how PFAS exposure may affect illness from COVID-19.

References:

1. Grandjean P, Heilmann C, Weihe P, et al. Estimated exposures to perfluorinated compounds in infancy predict attenuated vaccine antibody concentrations at age 5-years. *J Immunotoxicol.* 2017;14(1):188-195. doi:10.1080/1547691X.2017.1360968
2. Looker C, Luster MI, Calafat AM, et al. Influenza vaccine response in adults exposed to perfluorooctanoate and perfluorooctanesulfonate. *Toxicol Sci.* 2014;138(1):76-88. doi:10.1093/toxsci/kft269
3. NTP (National Toxicology Program). 2016. Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Research Triangle Park, NC: National Toxicology Program. https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf  



Toxicological Profile for Perfluoroalkyls

Released May 2021

Last Updated March 2020



U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS20W-171A



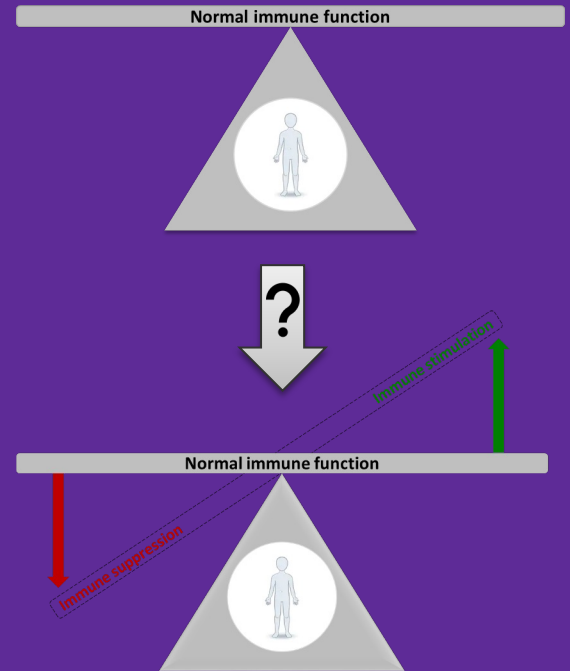
ATSDR
AGENCY FOR TOXIC SUBSTANCES
AND DISEASE REGISTRY

Immune suppression:

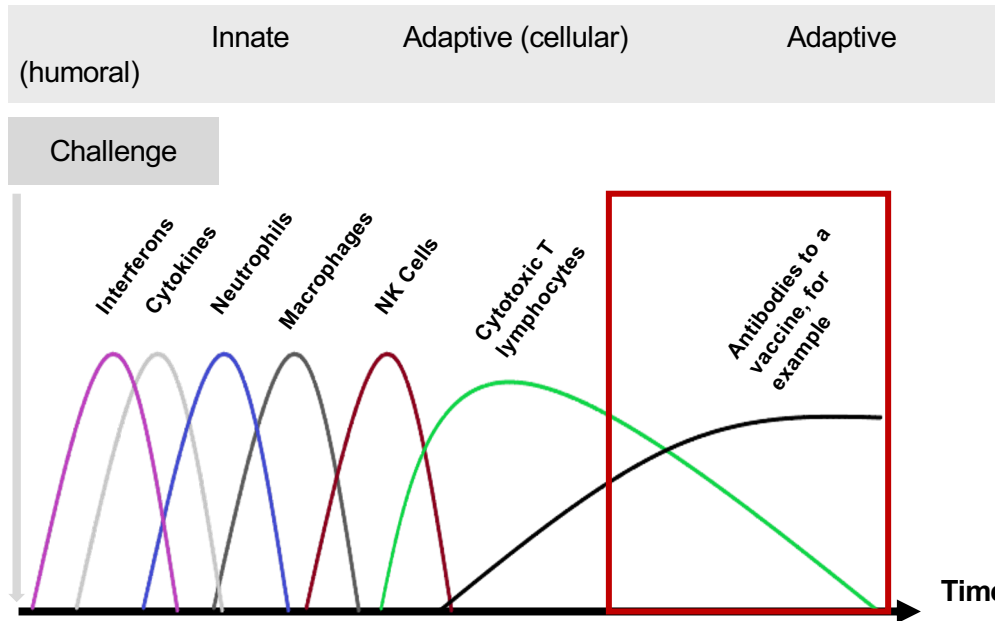
A reduced ability of the immune system to respond to a challenge from a level considered normal, regardless of whether clinical disease results (DeWitt et al., 2016). May also include inappropriate inflammatory responses.

Immune stimulation:

Inappropriate immune responses to common substances, i.e., allergic hypersensitivity, or responses to self-antigens, i.e., autoimmunity (DeWitt et al., 2016). May also include inappropriate inflammatory responses.

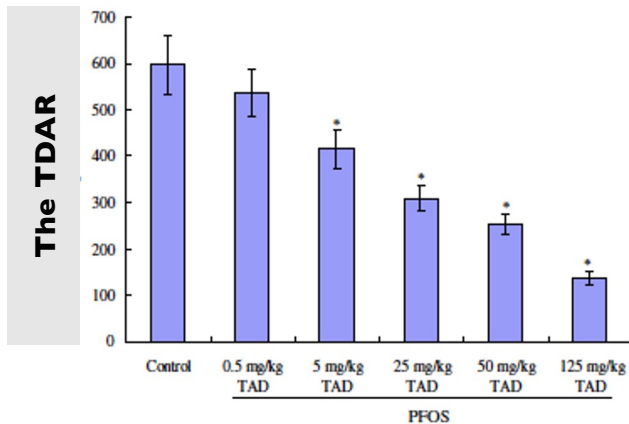


The “challenge” of a vaccine

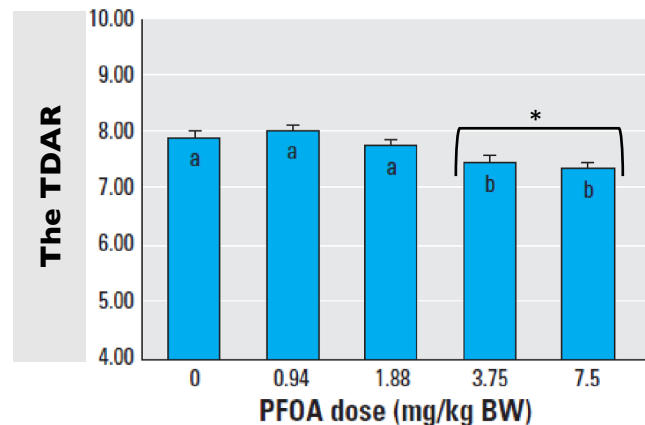


In a vaccination, the immune system is challenged and the response to that challenge is measured. It can be evaluated experimentally with “the T cell-dependent antibody response” or “the TDAR.”

Suppressed TDAR in experimental animal models

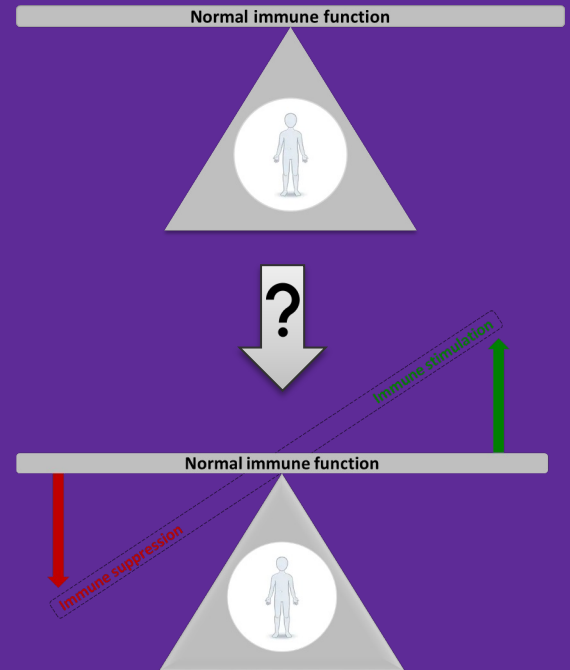


Oral PFOS exposure in male C57BL/6 mice (60d of exposure) and measurement of **the TDAR**.



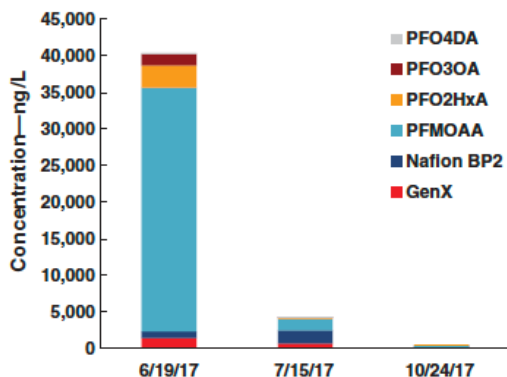
Oral PFOA exposure in female C57BL/6 mice (15d of exposure) and measurement of **the TDAR**.

Describing PFAS-induced immune suppression of understudied PFAS.

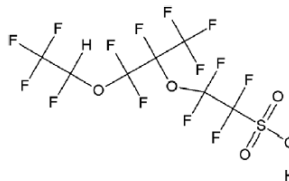
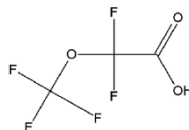


PFAS immunotoxicity

FIGURE 3 Evolution of PFEA concentrations in Cape Fear River water at a drinking water intake located approximately 90 mi downstream from a fluorochemical manufacturer



BP—byproduct, PFEA—perfluoroalkyl ether acid, PFMOAA—perfluoro-2-methoxyacetic acid, PFO2HxA—perfluoro-3,5-dioxahexanoic acid, PFO3OA—perfluoro-3,5,7-trioxaoctanoic acid, PFO4DA—perfluoro-3,5,7,9-tetraoxadecanoic acid



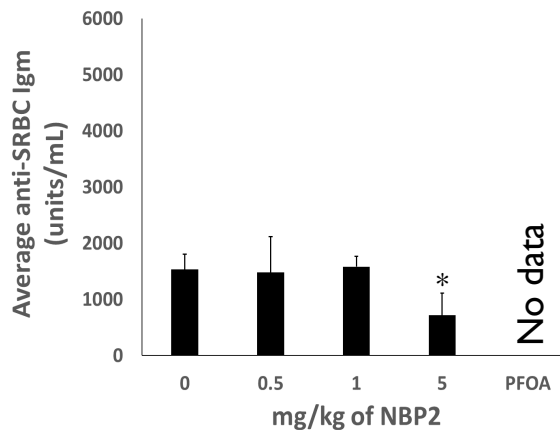
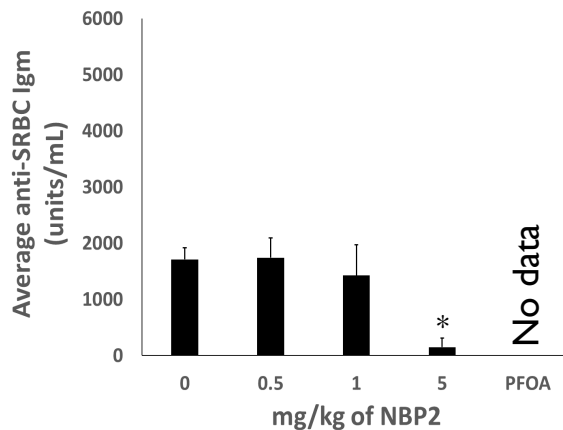
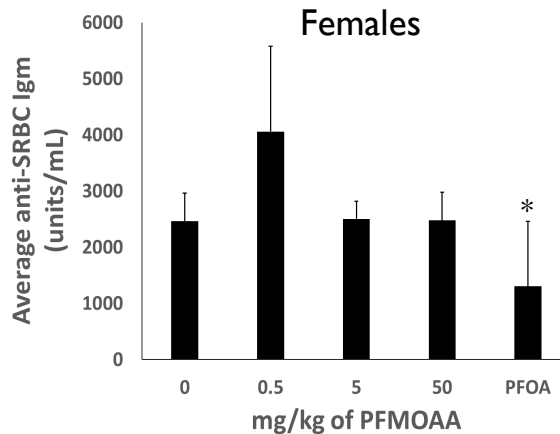
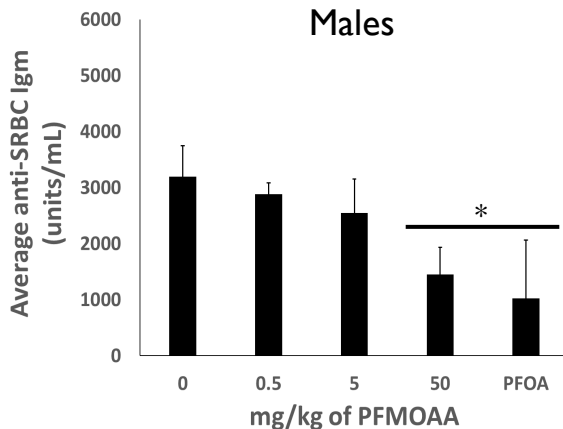
We are evaluating the TDAR

of PFAS detected in NC that are toxicologically understudied. These include the

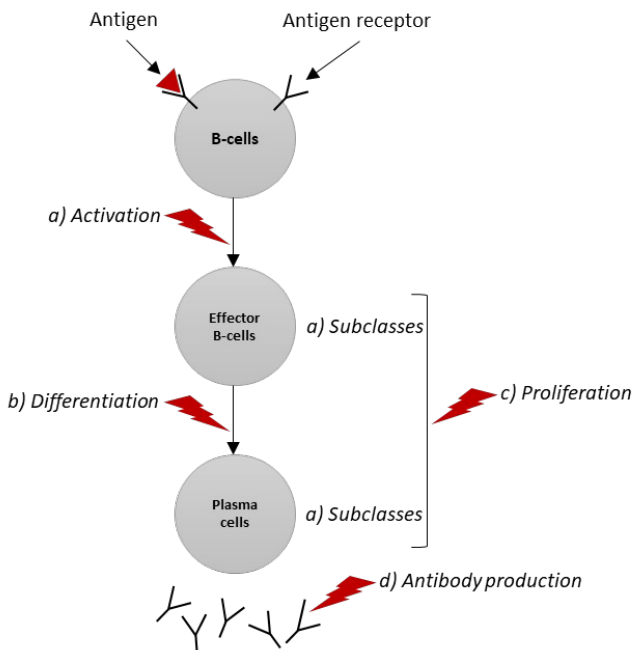
“perfluoroether acids” such as GenX, Nafion byproduct 2, PFMOAA, other individual PFEAs, and mixtures of these PFEAs. We often use PFOA as our positive control.

Descriptive immunotoxicological studies are important first steps for uncovering deficits in immune system function.

PFAS immunotoxicity



PFAS immunotoxicity

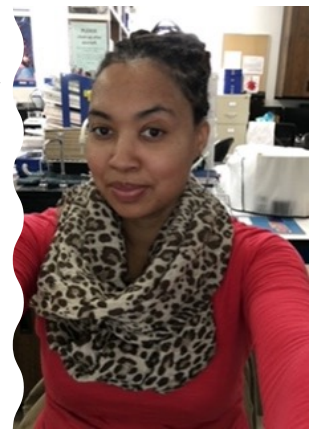


How does PFAS exposure affect the TDAR?

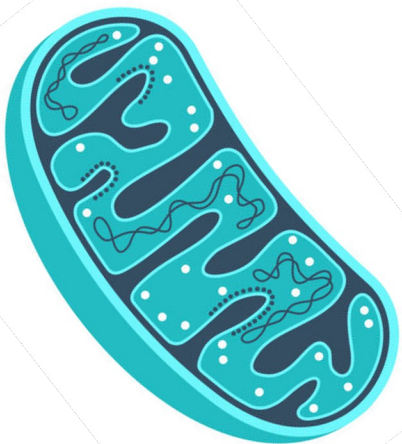
One focus of our lab is on B cells, the cells that eventually transform to become antibody-secreting plasma cells and memory B cells.

Future Dr. Krystal Taylor is asking about how PFAS exposure affects subsets of B cells.

Please visit her poster for more details!



PFAS immunotoxicity



How does PFAS exposure affect the TDAR?

One focus of our lab is on B cells, the cells that eventually transform to become antibody-secreting plasma cells and memory B cells.

Dr. Tracey Woodlief Research Instructor is asking about how PFAS exposure affects how B cells use energy at the level of the mitochondria.



Source of funding: NIEHS/NC State University (1 P42 ES031009-01:
NC State University Center for Environmental and Human Health Effects of PFAS).

PFAS immunotoxicity

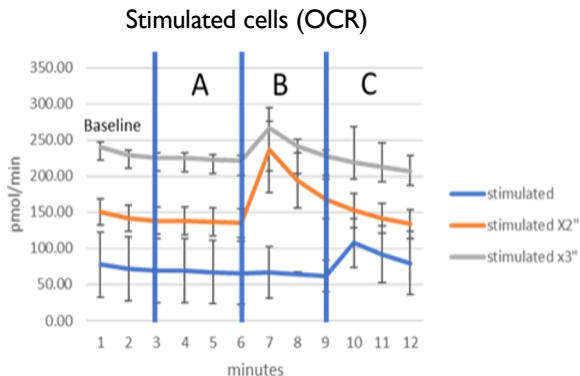
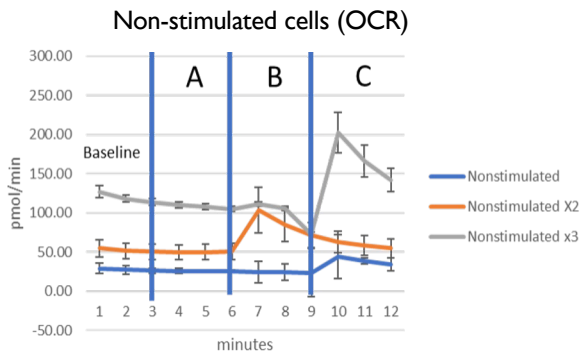
B cells are **unstimulated** in culture or **stimulated** with CD40 and IL4. Different lines = different B cell concentrations.

OCR: oxygen consumption rate in real time.

A, B, C panels = different concentrations of FCCP (disrupts ATP synthesis).

This tells us about how mitochondria in exposed B cells use energy!

We think PFAS shift energy use in B cells and weaken their ability to shift to antibody-secreting cells.



Source of (some) information: Post, 2020.