



Sources, Transport, Exposure & Effects of PFASs
UNIVERSITY OF RHODE ISLAND SUPERFUND RESEARCH PROGRAM

Lab tools to study emerging PFASs: what we can learn from human hepatocytes

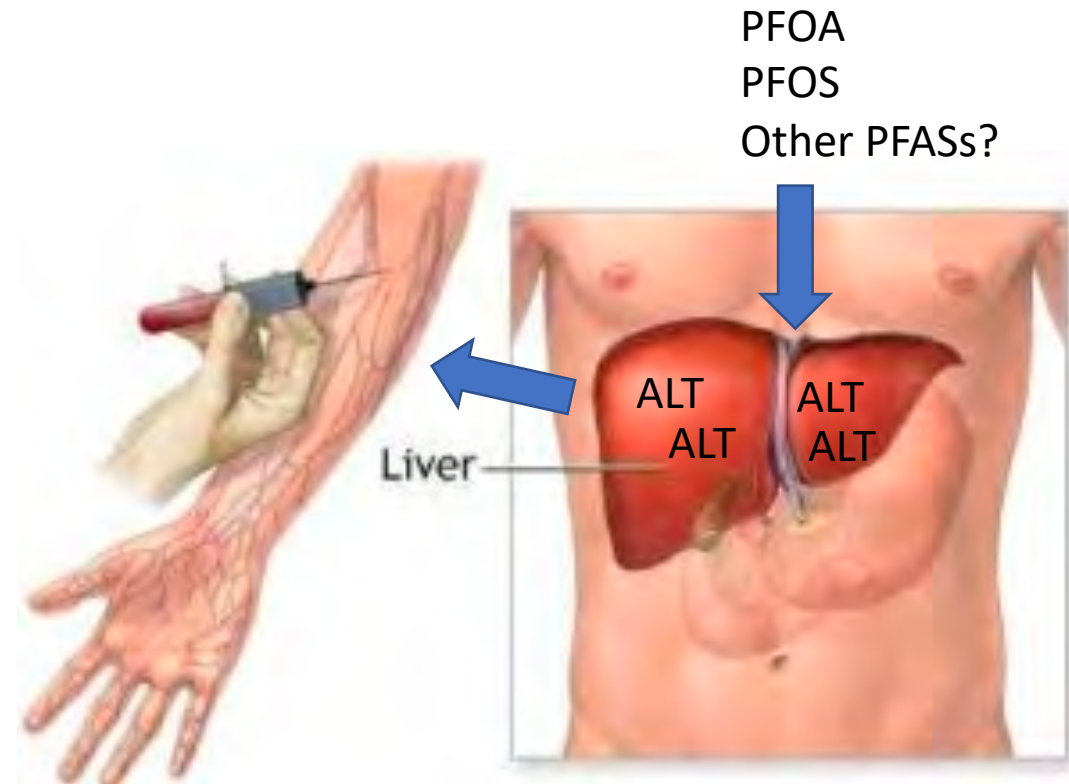
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PFAS Effects in Liver

- Liver is the tissue that often is for distribution and accumulation. Relatively high concentrations, likely due to enriched transporters.
- Associations with slight elevation in serum liver enzymes (multiple studies – human and rodent).
- Rodents demonstrate hepatomegaly (liver enlargement and cancer). This endpoint is widely debated about relevance to humans because of species differences in sensitivity to a signaling pathway in the cell called “PPAR-alpha”.
- Hall criteria – hepatomegaly + cytotoxicity is increased risk for cancer
- Some rodent and cell studies suggest that some PFASs might be associated with fatty liver disease (ongoing)



PFAS Health Effects

Adverse Health Effects

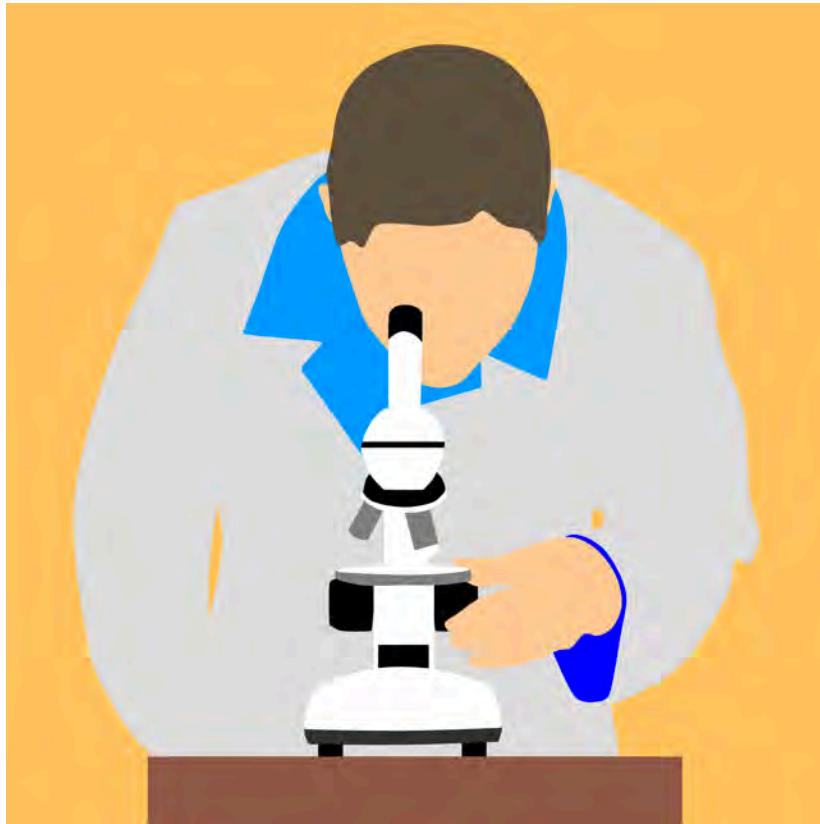
- ***Increased serum cholesterol***
- Immune effect
- ***Increased markers of liver damage (ALT)***
- ***Increased markers of liver damage (ALT) with Hepatomegaly (rodents)***^{\$}
- Developmental toxicity*
- Thyroid disease[#]
- Renal effects [#]

^{\$}Endpoint used to derive Rfd for EPA GenX Draft Toxicity Assessment

*Endpoint used to derive Rfd for EPA PFOA and PFOS Health Advisories

[#] Endpoint used to derive Rfd for EPA PFBS Draft Toxicity Assessment

How does our STEEP project relate to human health?



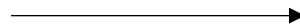
- We can use cell-based tools in the lab to understand the ways in which PFASs perturb cells and change the way that they behave
- We can use these tools to predict whether newer “replacement PFASs” behave in a similar way as legacy PFASs

What are we doing at URI?

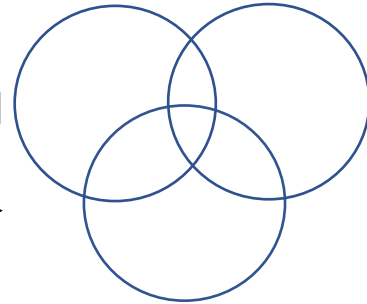
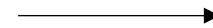
❖ Different PFASs

- ❖ Some we know a lot about (PFOA, PFOS)
- ❖ Some we know something about (PFHxS)
- ❖ Some we know very little about (GenX)

Treat cells in lab



Assess cell response

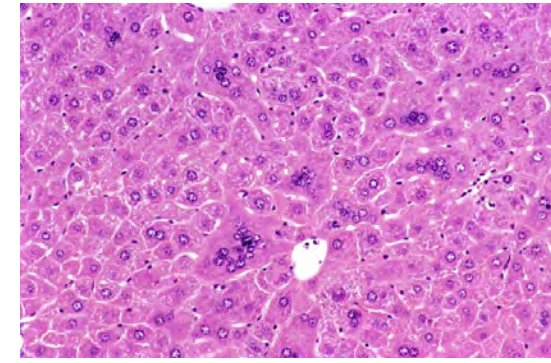


Understand similarities and differences



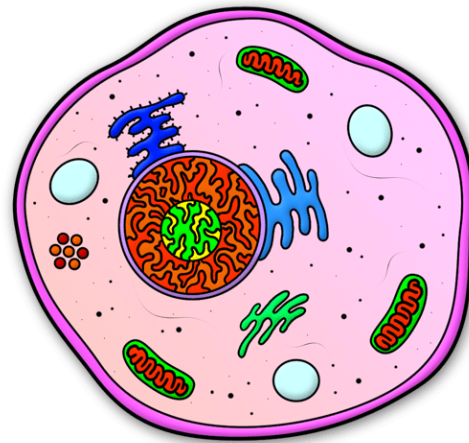
We plan to: Understand whether there is a relationship between the physiochemical properties of PFASs, especially those found in the waters of Cape Cod AND effects in liver cells from human donors cultured in the lab

Aim and Hypothesis



- **To screen critical members of the PFAS family for gene expression changes and liver lipid accumulation in cryopreserved human hepatocytes**
- **Do they behave similarly or differently to PFOS and PFOA?**

Treat cells with
PFASs

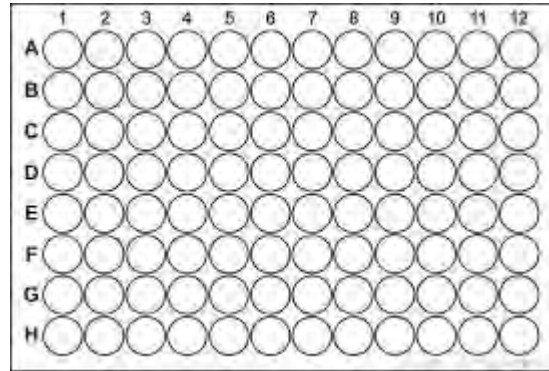


Measure cell
response

Approach



Cryostax 5-donor hepatocytes from XenoTech (thawed and cultured following protocols)



24h

Treatment with:
DMSO (vehicle), various PFASs and mixtures of PFASs at concentrations of 0.25 μ M to 25 μ M with daily media changes of treatments.

48h

Cell Response

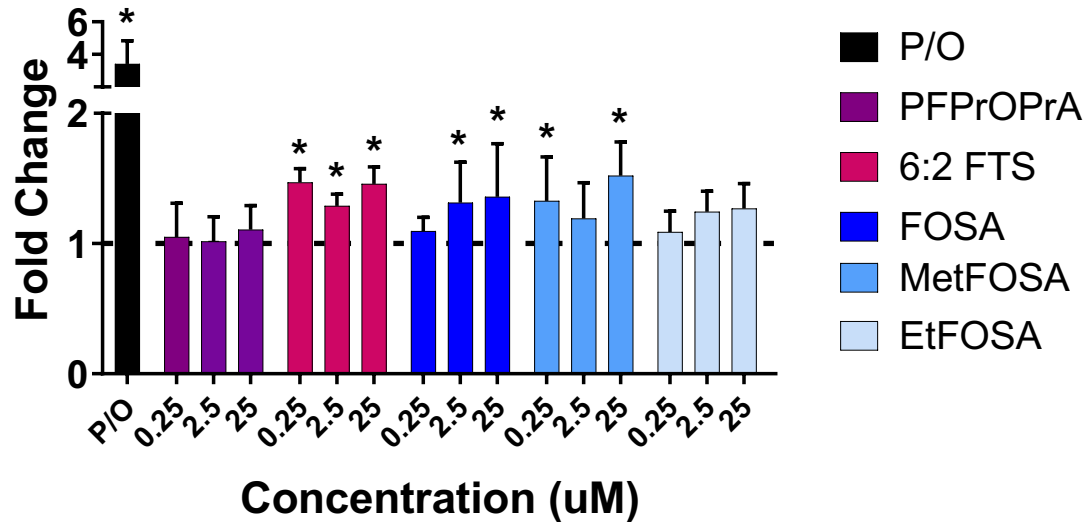
Does the cell alter the genes it turns on and off?
(Gene Expression)

72h

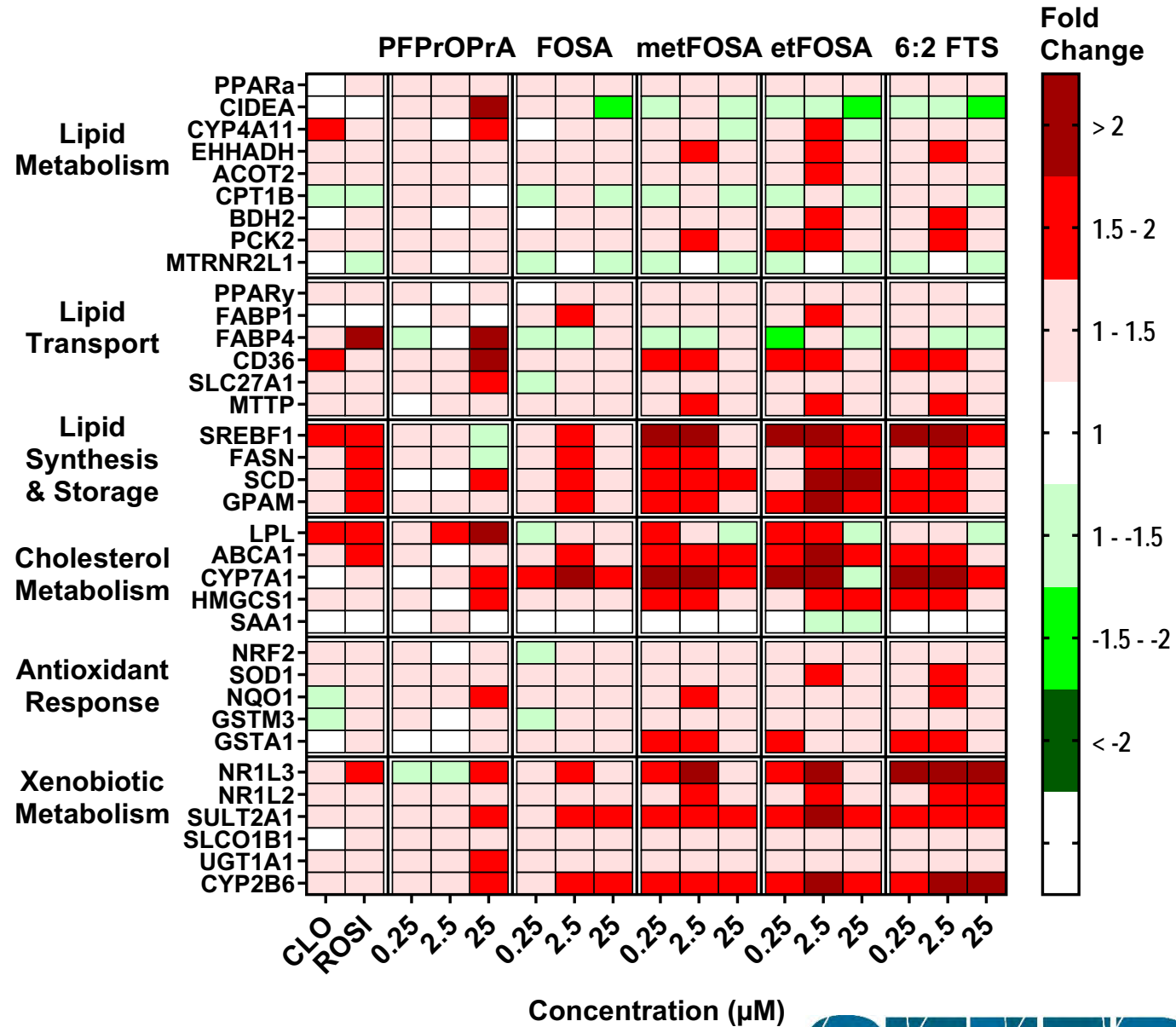
Cell Phenotype

Does the cell change its appearance?
(Does it accumulate fats?)

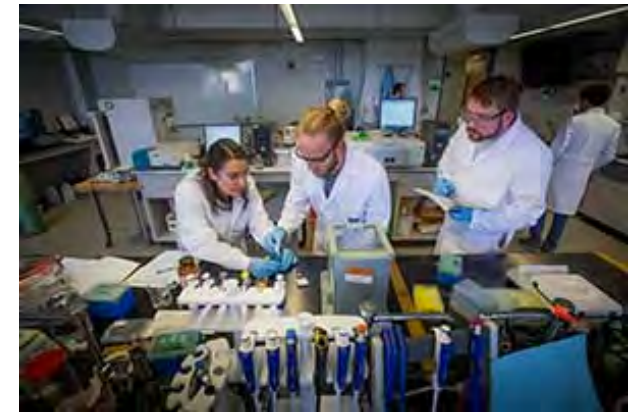
C. Alternative PFAS



- Alternative PFASs have similar gene expression changes to short chain PFAAs
- 6:2 FTS, FOSA, and MetFOSA induced lipid accumulation



Summary



- PFAS replacements induced activity in human liver cells
- Some of the PFAS replacements were more potent than PFOA and PFOS
- PFAS alternatives were also active in the hepatocyte assays
- The replacements generally showed similar signatures as PFOA and PFOS

<https://www.epa.gov/pfas>

Rotander *et al.*, 2015