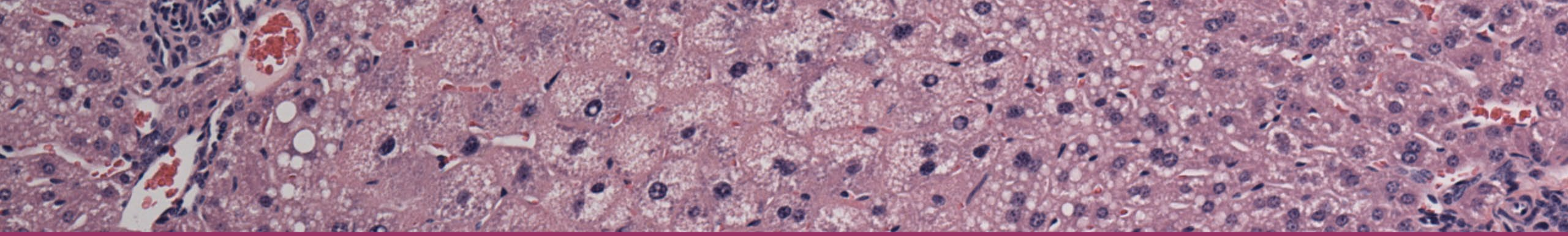


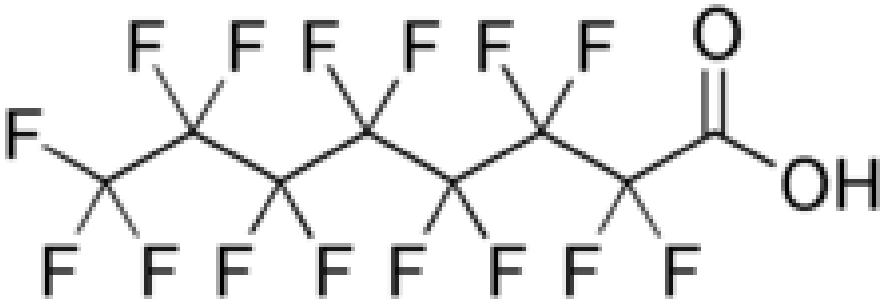
PFOA Induces Liver and Serum Dyslipidemia in a Humanized PPARα Mouse Model Fed an American Diet

Jennifer Schlezinger, Greylin Nielsen, Eric Reed, Wendy Heiger-Bernays, Thomas Webster

Boston University School of Public Health, Department of Environmental Health

Funding: NIEHS P42ES007381 and R01ES027813

PFAS are a human health hazard



- Increased cholesterol levels
- Changes in liver enzymes
- Small decreases in infant birth weights
- Decreased vaccine response in children
- Increased risk of high blood pressure or pre-eclampsia in pregnant women
- Increased risk of kidney or testicular cancer

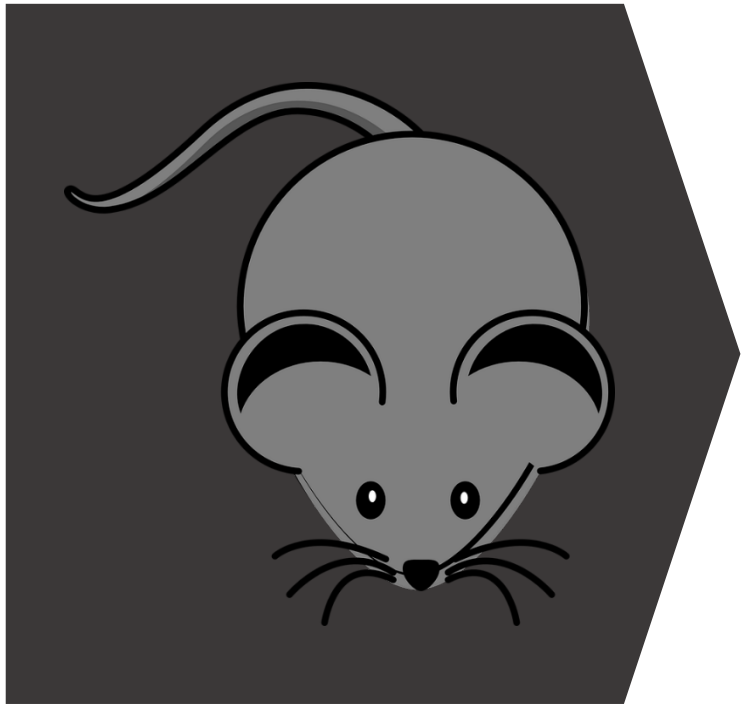
https://www.atsdr.cdc.gov/pfas/health-effects/index.html

Human PFAS exposure is strongly associated with increased serum cholesterol

Atherogenic dyslipidemia (elevated triglycerides, decreased HDL) and increased blood LDL are major contributors to cardiovascular disease, the leading cause of mortality in the US.

Global Burden of Cardiovascular Diseases, C. *et al.* 2018. PMID: 29641820

HDL = high density lipoprotein cholesterol particles
LDL = low density lipoprotein cholesterol particles



Do inconsistencies in results from rodent studies imply that the epidemiology is incorrect?

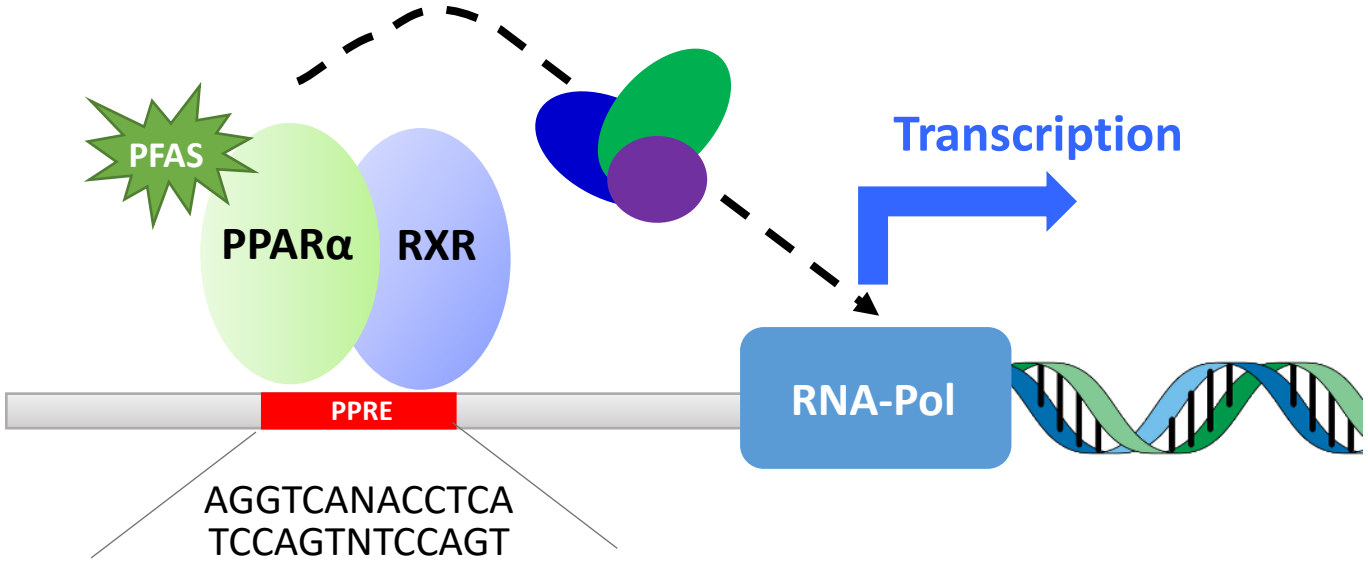
<u>Some considerations:</u>

- **Strain differences**
- **Diet (standard rodent chow is low in fats/cholesterol)**
- **Dose (and serum levels) in mice vs humans**
- **Sex (few studies conducted in females)**

Genes in the liver regulate serum lipid homeostasis

Lipid Handling

Genes involved in lipid uptake, synthesis, transport, storage, oxidation, and excretion



What is the BIG STINK about PPARα?

1. **PPARα is not highly expressed in human liver.**
   NOT TRUE.
2. **PPARα activation induces hepatocellular carcinoma in mice but not humans.**
   TRUE but not relevant.
3. **PPARα is a therapeutic target of lipid-lowering drugs.**
   TRUE but unclear relevance.
4. **Mouse PPARα is more efficaciously activated than human PPARα.**
   TRUE and highly relevant.

PPARα is relevant to humans. Therefore, using human relevant models is crucial to:
1) Understanding effect PFAS on serum lipids
2) Identifying the mechanism(s) of action

Kersten and Stienstra. 2017. PMID: 28077274; Morimura et al., 2006. PMID: 16377806;
Watts et al., 1999. PMID: 10680050. Vanden Heuvel et al., 2006. PMID: 16731579

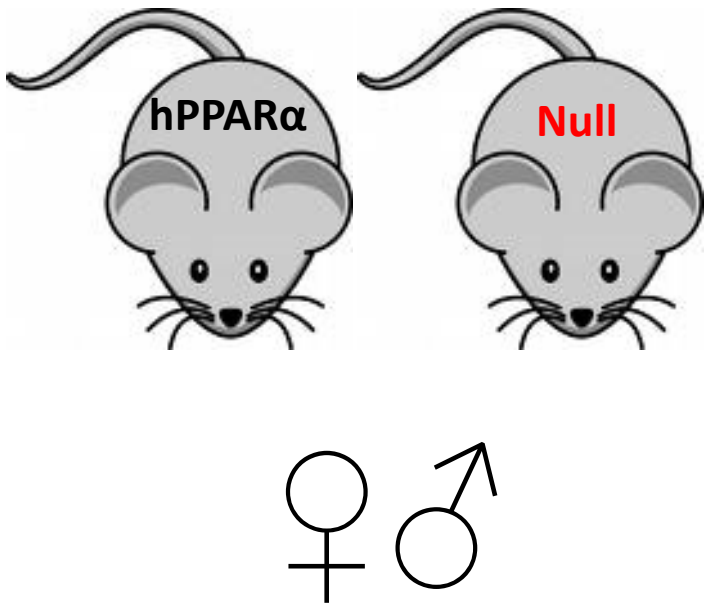
Hypothesis:

PFAS induce dyslipidemia* through human PPARα activation.

*Increased serum triglycerides (vLDL) and LDL, major contributors to CVD

In Vivo Experimental design

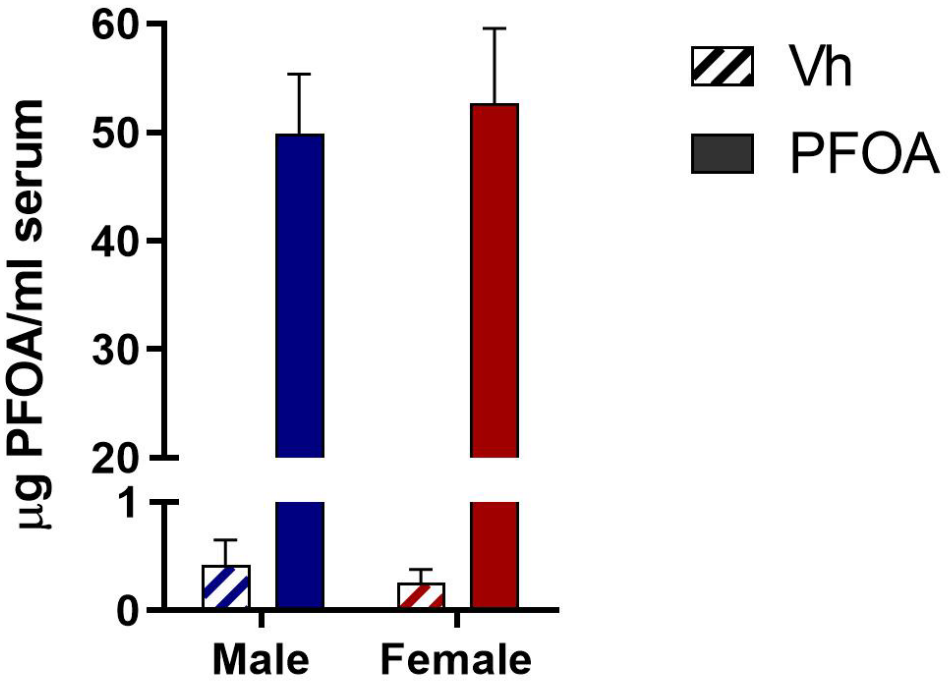
Humanized PPARα
PPARα null
SV129 strain



“What we eat in America” diet
NHANES 2013/14
2-19 year olds

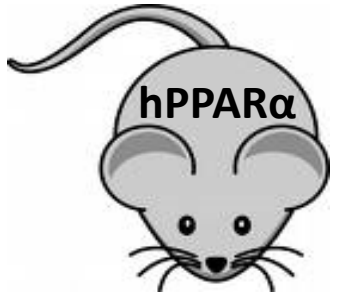
Control Water
PFOA Water

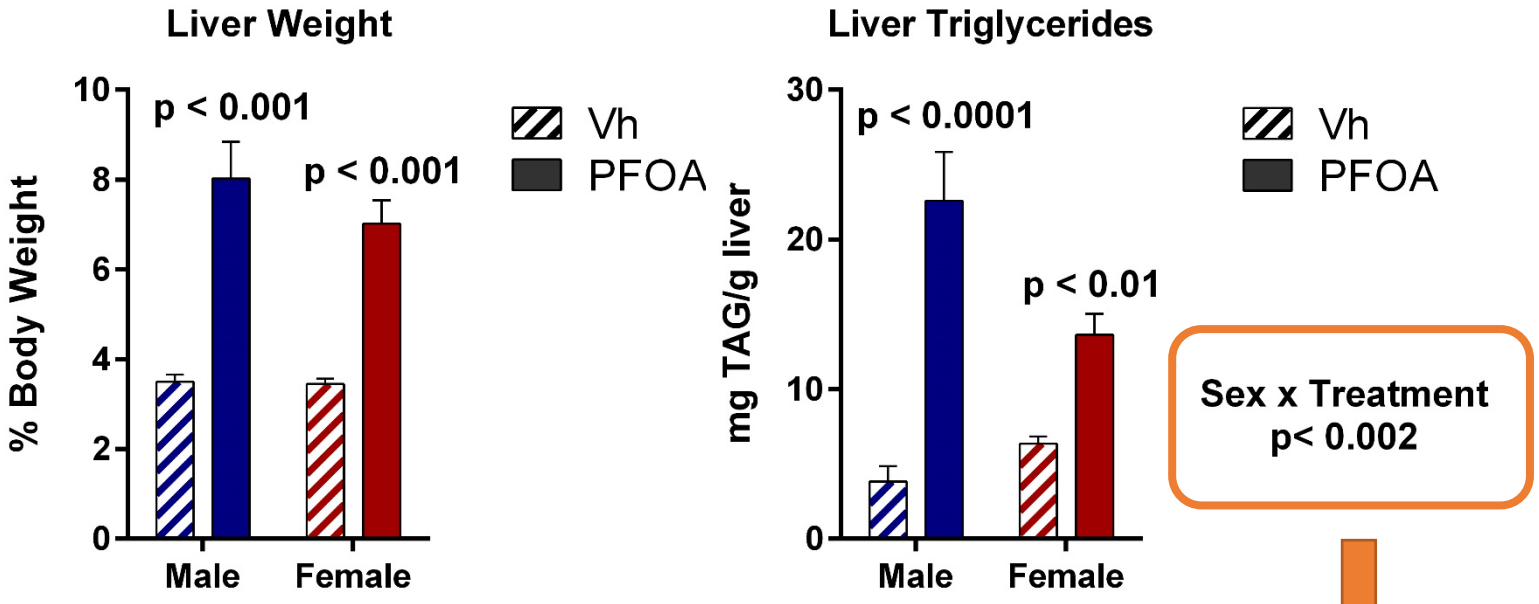
Treated 3-9 weeks of age



Schlezinger et al., 2020. PMID: 32822737
Steenland, et al., 2010. PMID: 20423814

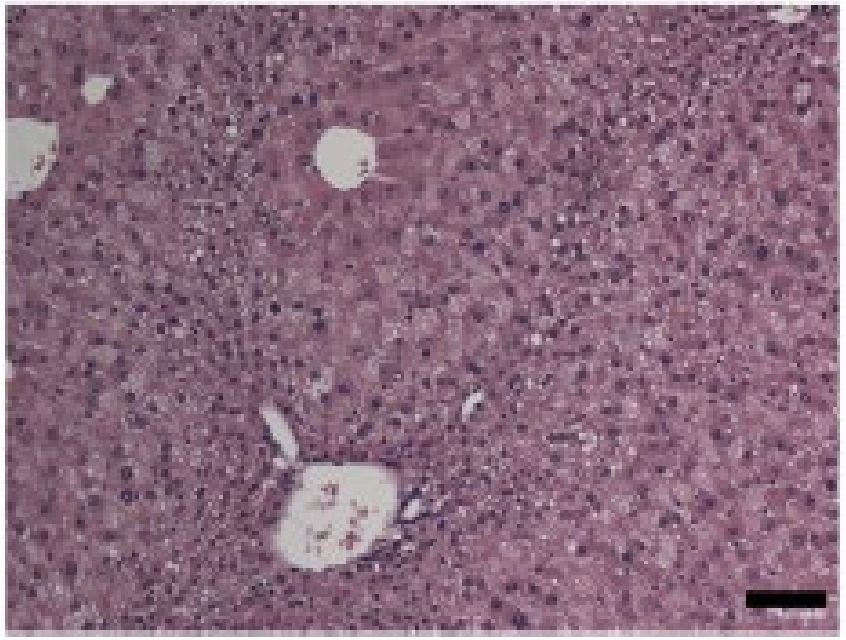
PFOA induces hepatomegaly and increases in liver triglycerides, in a sex-dependent manner.





Sex x Treatment
p< 0.002

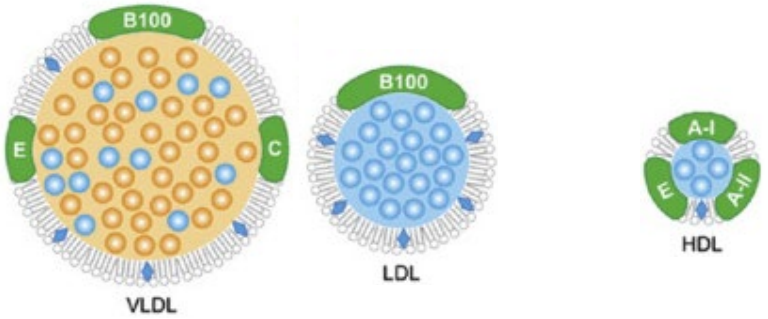
Male
hPPARa
PFOA

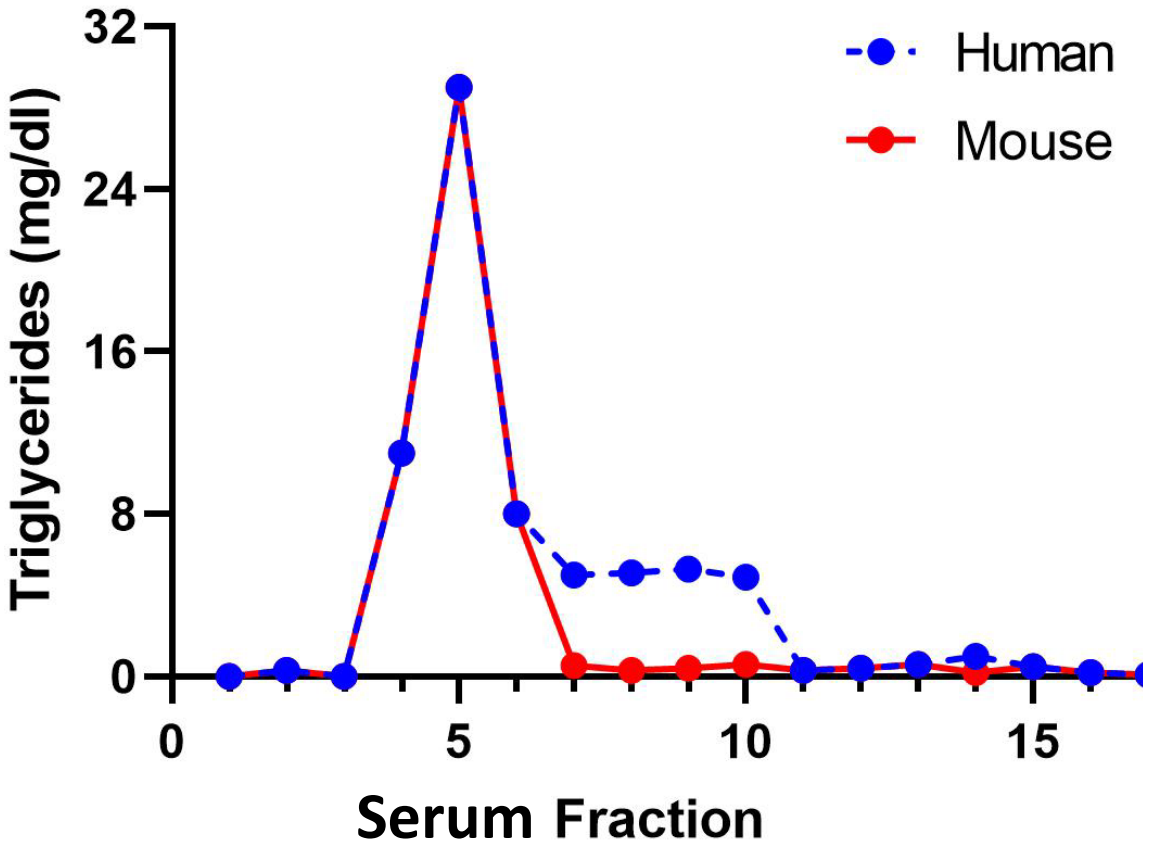


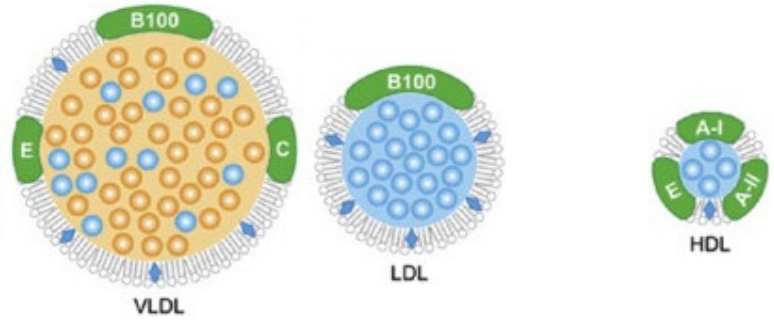
Effect is more strongly dependent on PPARα in females than males

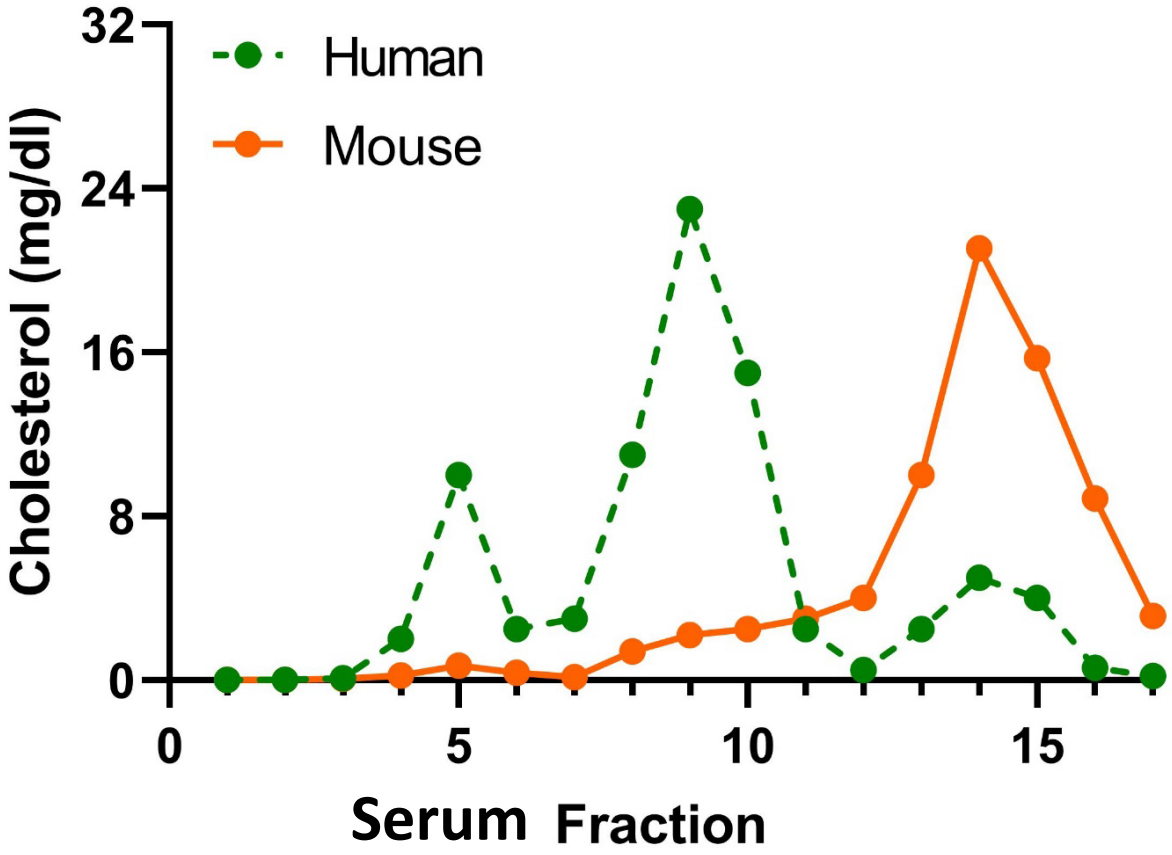
Schlezinger et al., 2020. PMID: 32822737

Cholesterol is packaged in particles with triglycerides.

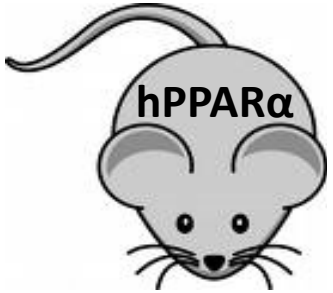


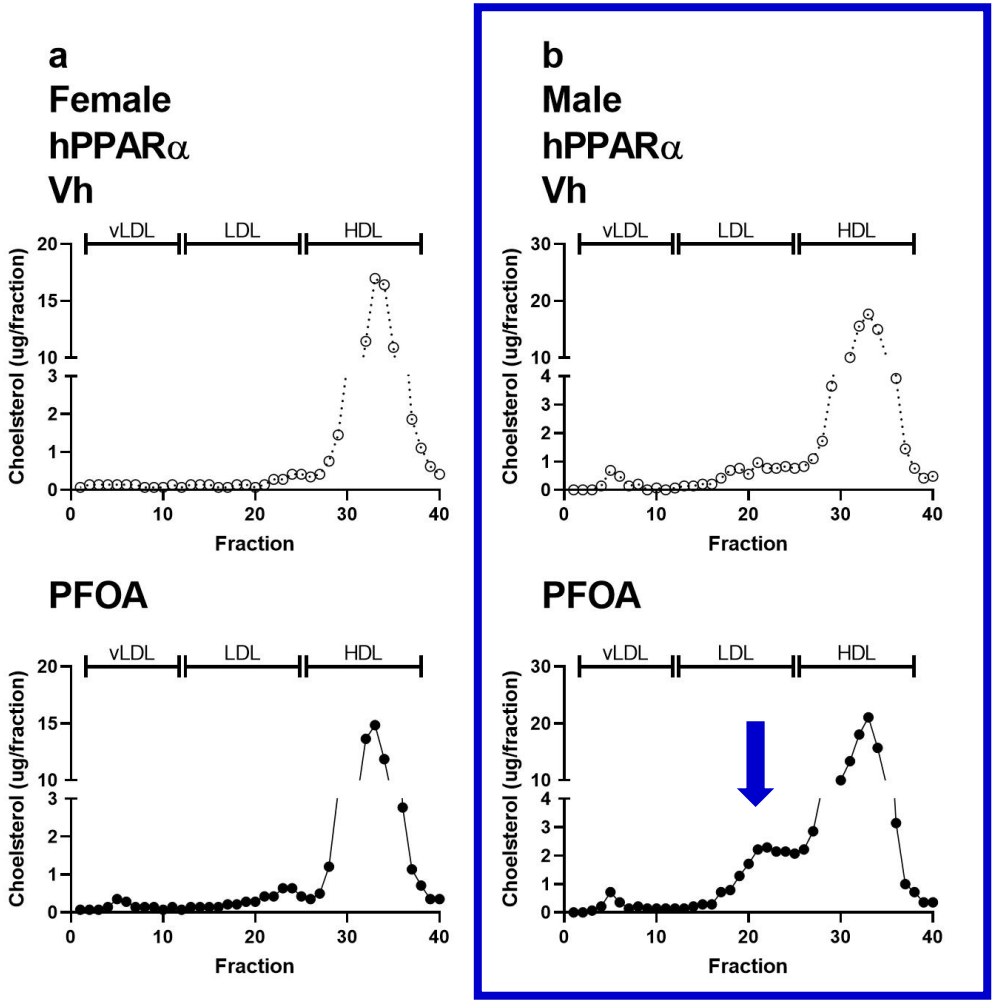






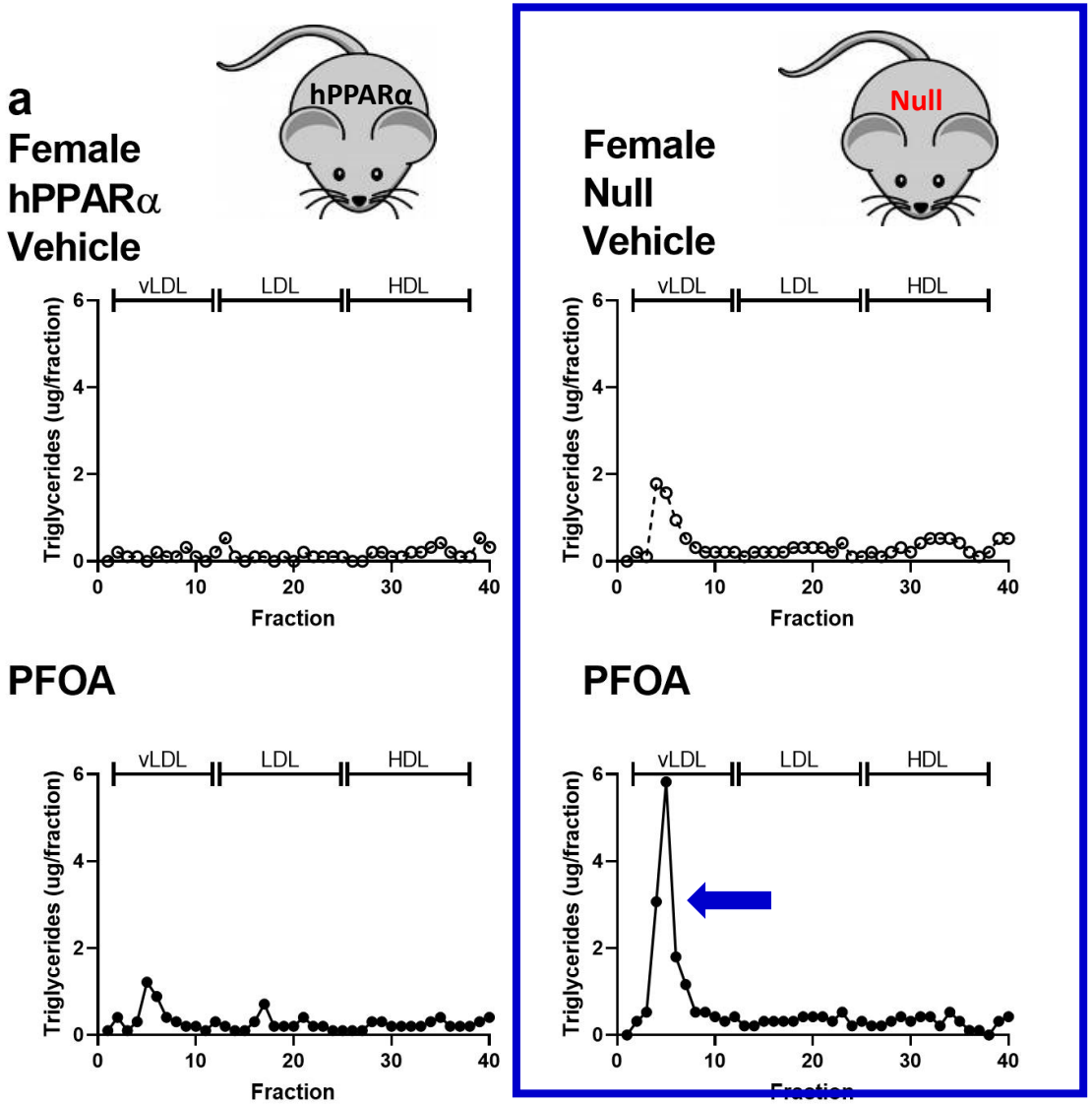
PFOA increases serum LDL-c, particularly in male hPPARα mice.





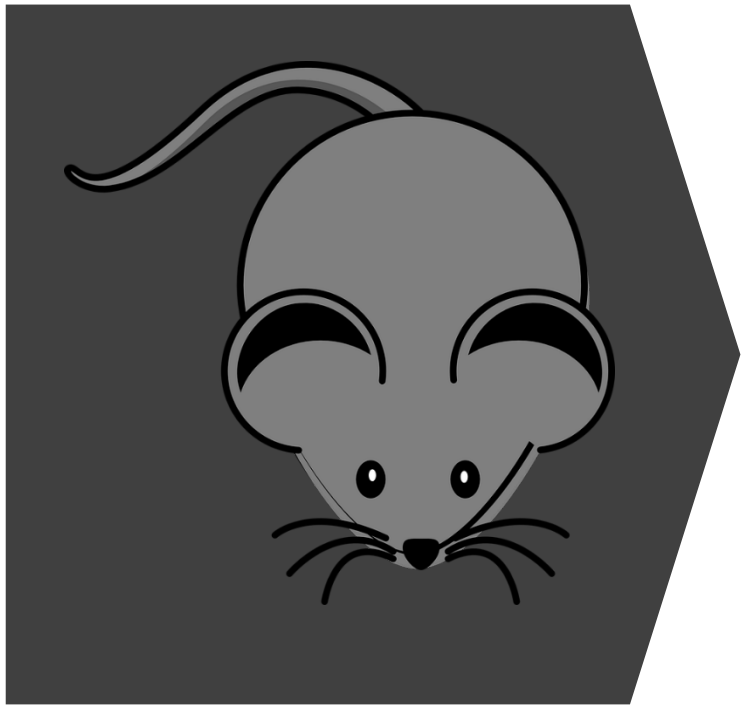
Schlezinger et al., 2020. PMID: 32822737
Also see: Rebholz et al., 2016. PMID: 26942110

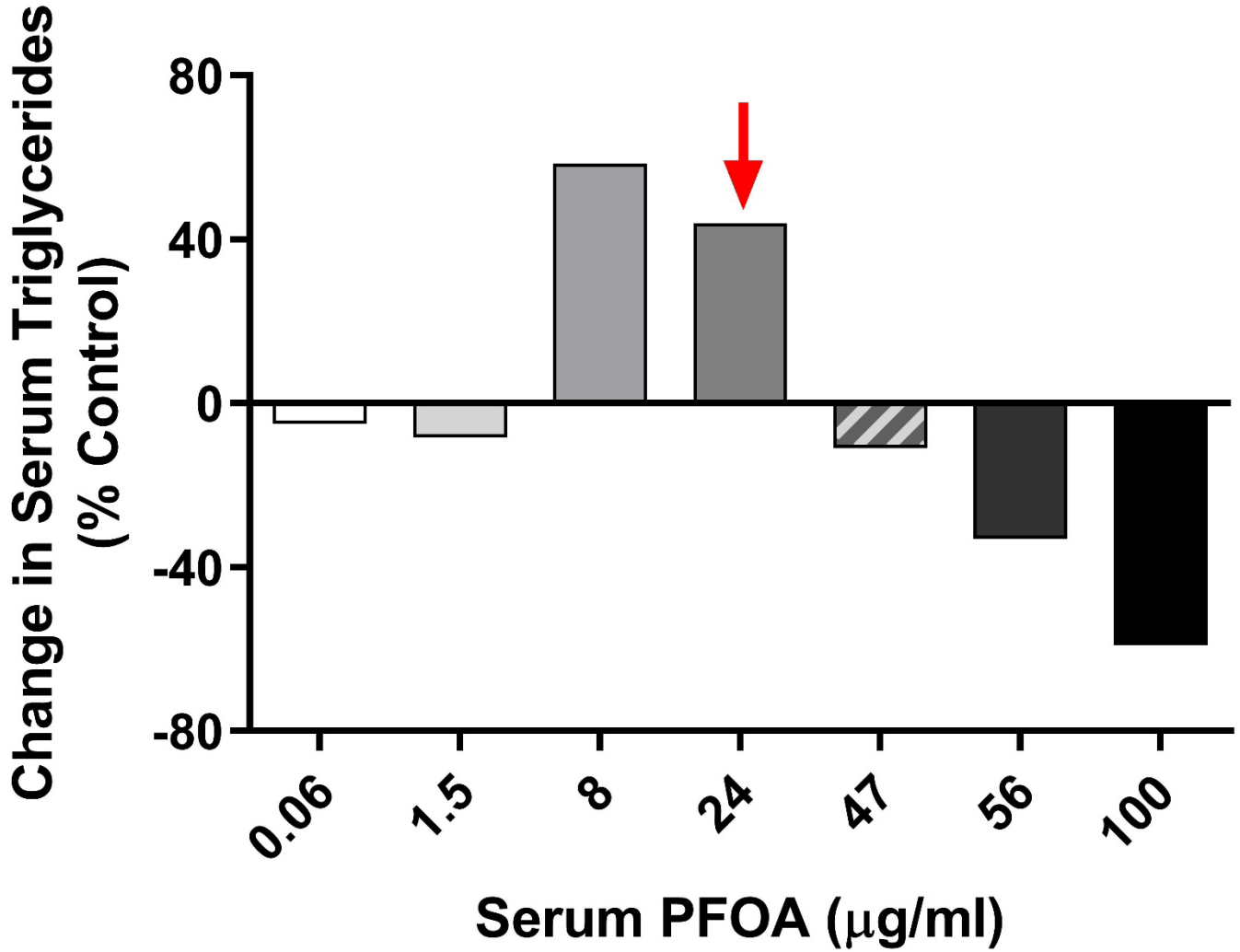
Human PPARα is a stronger regulator of PFOA's effect on serum triglycerides in females than males.



Schlezinger et al., 2021. PMID: 34252412

Do inconsistencies in results from rodent studies imply that the epidemiology is incorrect?

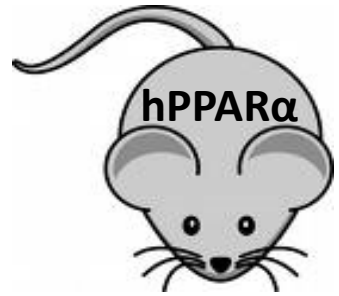




Yan et al., 2014. PMID: 24459700
Pouwer et al., 2019. PMID: 30657992
Loveless et al., 2006. PMID: 16448737
Schlezinger et al., 2021. PMID: 34252412

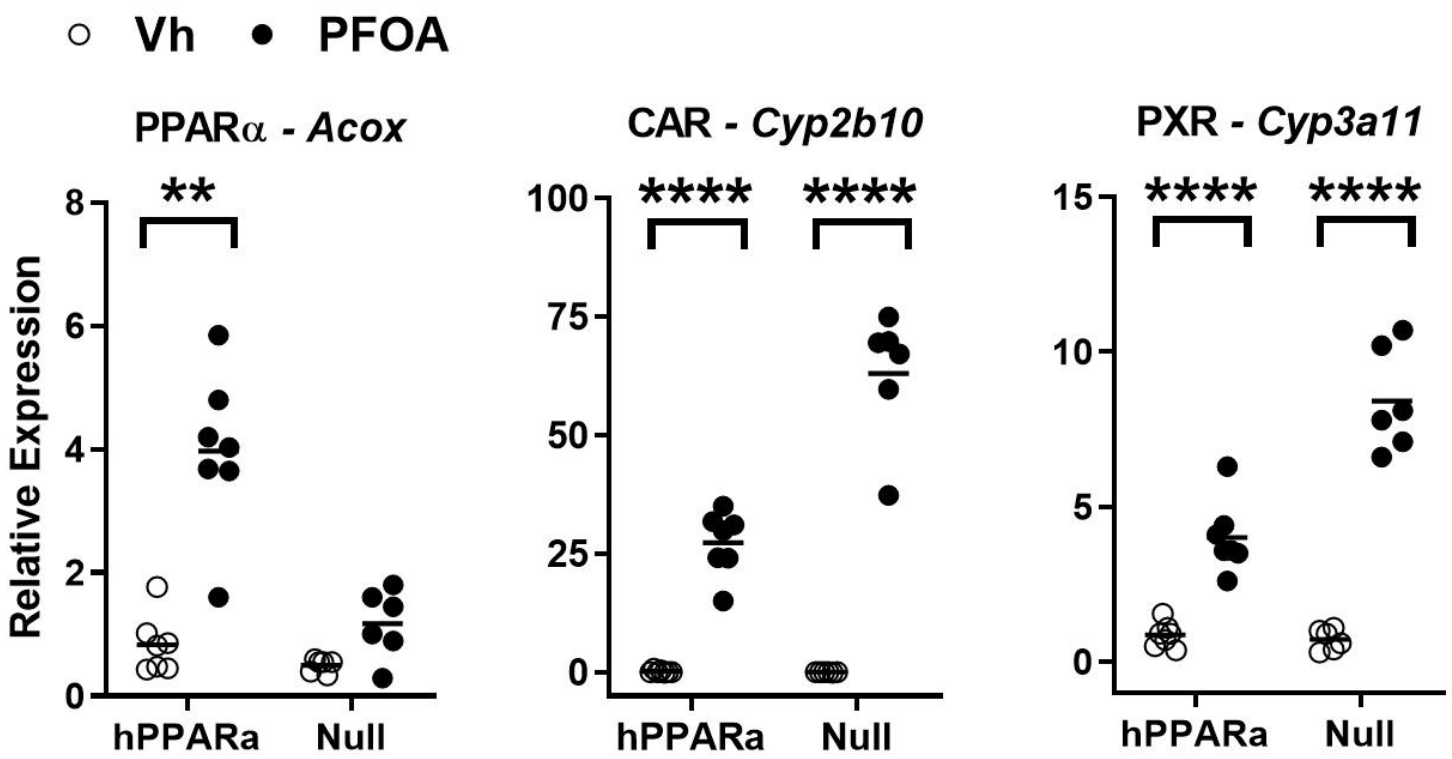
Data are from male mice only.

PFAS activate at least three nuclear receptors that regulate lipid homeostasis



% hPPARα-dependence of PFOA-induced hepatic gene expression:
57% (male)
59% (female)*

Female



It is NOT all about PPARα! The proportion of effect that PPARα contributes will depend upon the PFAS!

Schlezinger et al., 2020. PMID: 32822737

Conclusions

- **In mice expressing human PPARα, subchronic exposure to PFOA,**
  1) **disrupts liver lipid homeostasis in a PPARα- and sex-dependent manner**
  2) **Increases serum cholesterol and triglycerides in a PPARα- and sex-dependent manner**
- **Activation of PPARα alone cannot explain the dose-dependent effects of PFOA on serum lipids**
- **Mouse data do NOT contradict human data when…**
  1) **human relevant doses are used**
  2) **human relevant diets are used**

Acknowledgements:

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Tom Webster

Boston University

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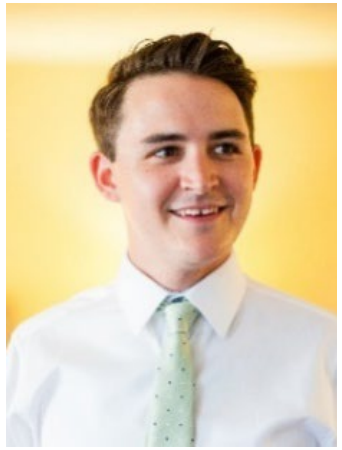
Örebro University



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