



# Why should we care about pollutants and metabolic health in liver disease?

## Parish MASH Meeting

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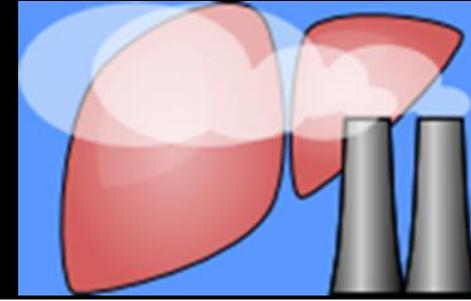
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# Disclosures



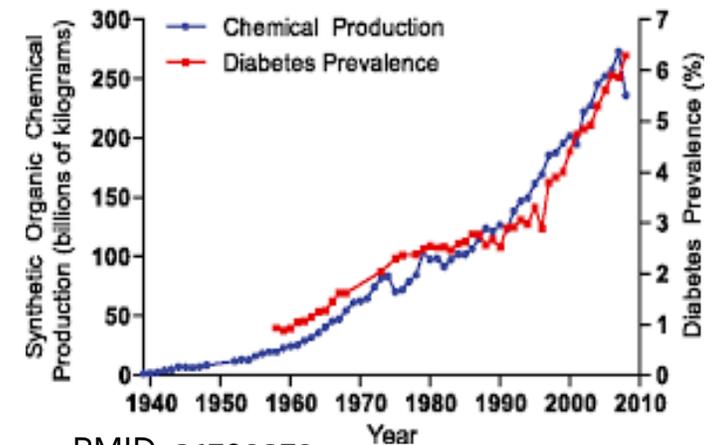
Dr. Cave has no COI related to this presentation. Off-label investigational use is discussed. Dr. Cave's research is supported by the US National Institutes of Health (R35ES028373, R01ES032189, R21ES035475, P42ES023716, P30ES302883, P20GM155899) and the US Department of Defense (HT9425-23-1-1056). His institution receives research support from Intercept, Cymabay, Akeru, Altimmune, Galectin, and Durect on his behalf. He reports paid consulting and/or speakers bureau agreements with Intercept, Madrigal, Ipsen, and Novo Nordisk. Dr. Cave's spouse is an employee of AbbVie.



“As the tide of chemicals born of the industrial age has arisen to engulf our environment, a drastic change has come about in the nature of the most serious health problems.”

- Rachel Carson, *Silent Spring* (1962)

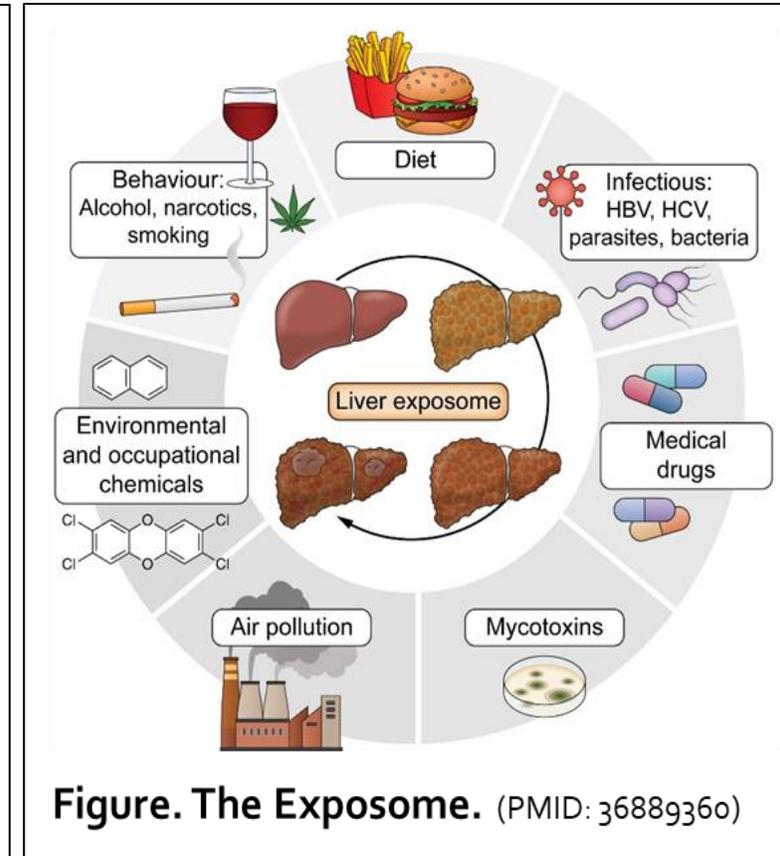
Diabetes vs. Chemical Production



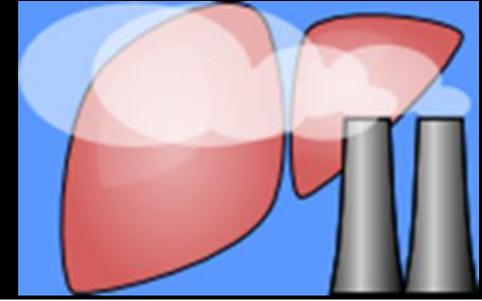
PMID: 21709279

# Pollution and diabetes, obesity, and liver diseases

- **'Endocrine-disrupting chemicals'** (EDCs - 1991): Chemicals associated with diabetes, thyroid disease, etc. (PMID: 34452693, 37956907)
- **'Exposome'** (2005, 2014): cumulative effect of environmental exposures and biological responses. (PMID:31701542, 35395240)
- **'Obesogens'** (2006): Chemicals associated with obesity. (PMID: 35395240)
- **'Toxicant-associated steatohepatitis'** (TASH - 2010, TASLD - 2023): chemicals and steatotic liver disease. (PMID:19902480, 37623845)
- **'Metabolism-disrupting chemicals'** (MDCs, 2016) promote metabolic changes that can result in obesity, type 2 diabetes, or fatty liver. (PMID: 27760374)



# Sources of endocrine and metabolism disrupting chemicals



<p><b>Food production</b></p> <p>Agricultural chemicals Food additives Packaging materials</p>		<p>Pesticides Bisphenols Phthalates Organotins</p> <p>Per- and polyfluoroalkyl substances (PFASs)</p>
<p><b>Industrial activity</b></p> <p>Air pollutants Industrial chemicals and by-products Water contaminants</p>		<p>Polychlorinated biphenyls (PCBs) Particulate matter (PM) Ozone Nitrogen oxides Fracking fluids Dioxins</p> <p>Toxic metals (As, Hg, Pb, Cd, etc.) Polyaromatic hydrocarbons (PAHs)</p>
<p><b>Personal and home care</b></p> <p>Personal care products Cleaning supplies Flame retardants Solvents and coatings</p>		<p>Phthalates Bisphenols 'Fragrances' PFASs Triclosan</p> <p>Polybrominated diphenyl ethers (PBDEs) Parabens</p>
<p><b>Medical care</b></p> <p>Medical products and equipment</p>		<p>Pharmaceutical agents Phthalates Bisphenols Polymers</p>

>1000 known EDCs  
>50 known obesogens

**Search the TEDX List**

Select "Chemical Name/Number" OR "Filters" below to search, or [show all chemicals](#). [ABOUT THE LIST](#)

CHEMICAL NAME OR CAS NUMBER

FILTERS

Click a heading to select options.

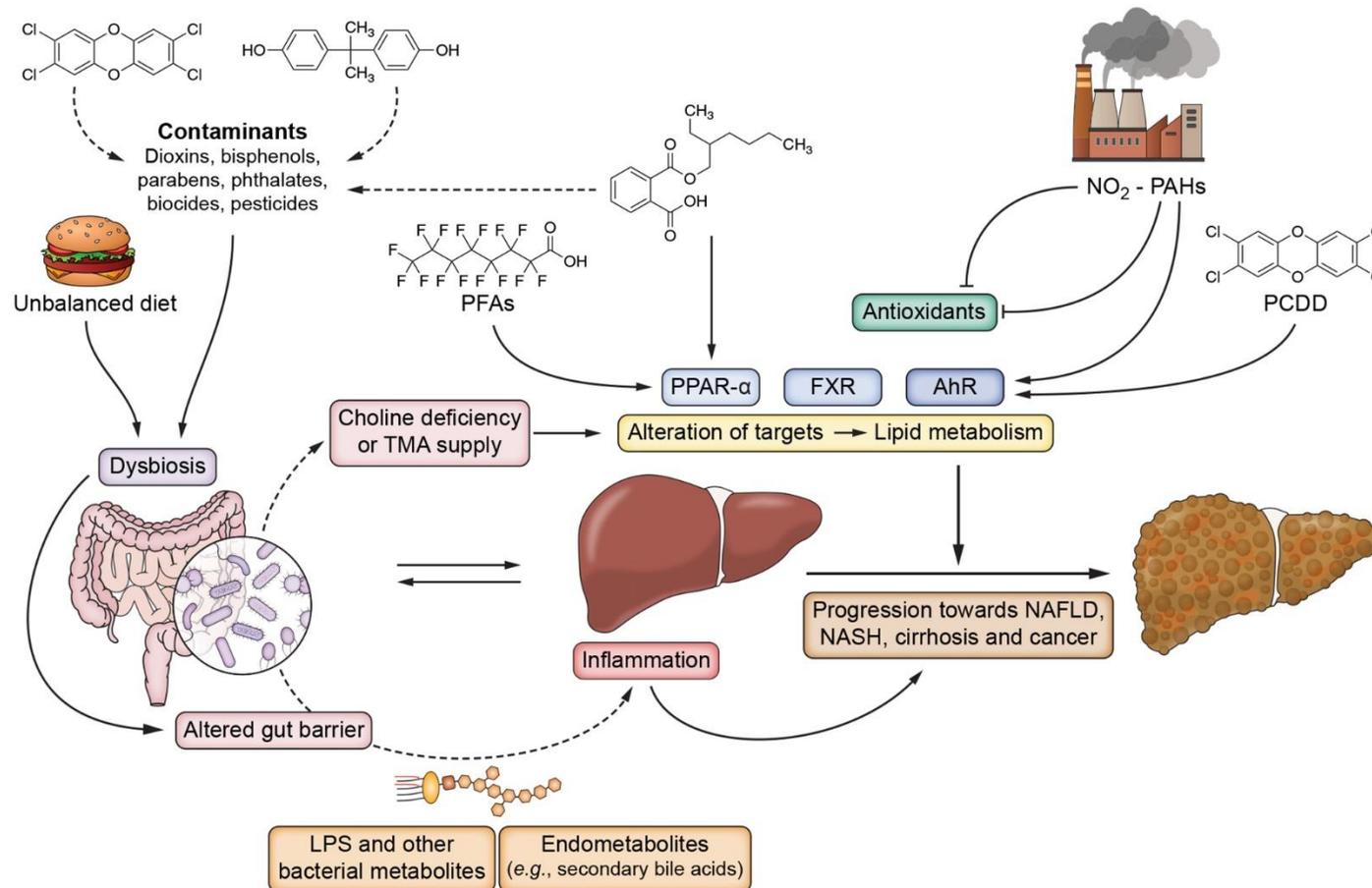
Last updated September 2018

[endocrinedisruption.org](http://endocrinedisruption.org)



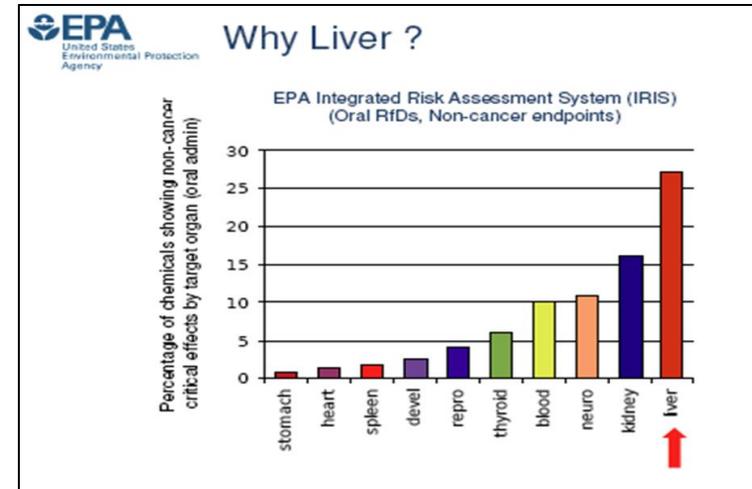
# Mechanisms of environmental pollutants in MASLD

Chemical pollutants work at low-doses through mechanisms including nuclear receptors and microbiome to reprogram hepatic gene expression, disrupt metabolism, and promote MASLD.



# Key concepts in occupational and environmental hepatology

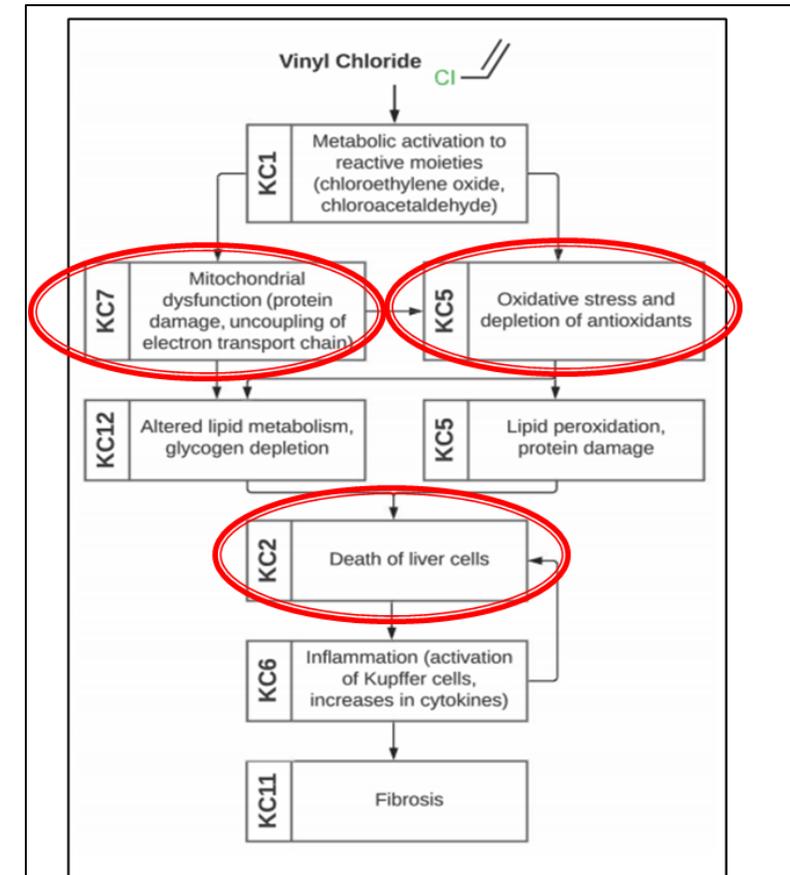
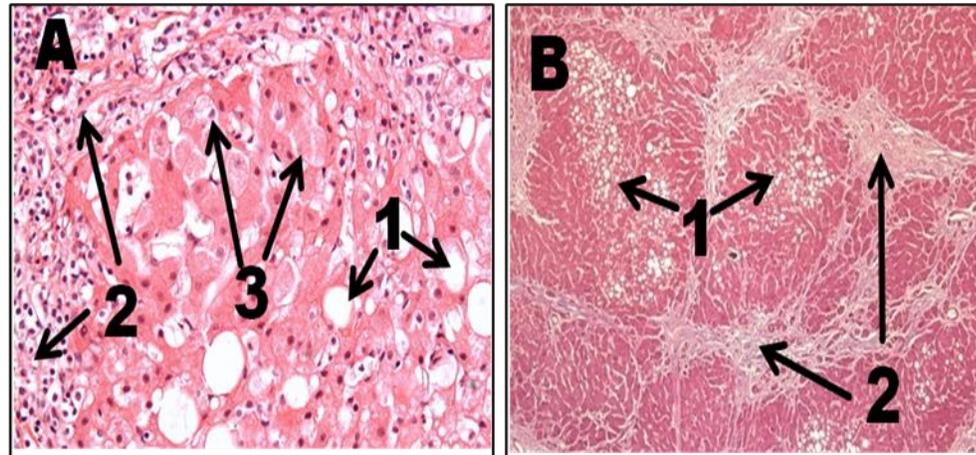
- Liver is the #1 target organ for toxic chemicals.



- 9 of the top 10 pollutants on ATSDR's substance priority list are associated with MASLD.
- Environmental justice: disparities in exposures (e.g., age, race/ethnicity, sex, geography).
- Differential hepatic response to exposures: race/ethnicity (PMID: 36937989); sex (PMID: 37074385); diet-dependent effects; windows of susceptibility (DoHAD); and gene x environment interactions.
- **Pollution has been associated with MASLD development, severity, and complications.**
- **Environmental pollutant exposures can also be considered as disease modifiers in MASLD.**

# TASH due to OCCUPATIONAL chemical exposures & the reverse-translational approach to elucidation of mechanism

- **TASH** identified in 25 lean, non-drinking, highly-exposed vinyl chloride workers from Louisville's Rubbertown Complex.
- Steatosis (84%), steatohepatitis (80%), and fibrosis (55%)
- **TASH** associated with hepatocyte necrosis, antioxidant depletion, insulin resistance & adipocytokines.



**Fig.** Animal models elucidated VC's mode of action in TASH as summarized by a key characteristic approach.

# Adult NAFLD and ENVIRONMENTAL chemical exposures & the exposome-wide association study (EWAS) approach

- In 2010, the prevalence ORs for NAFLD and 196 pollutants were determined in adult NHANES.
- Reviews of the current EWAS approach were recently published in *Hepatology* and *J Hepatol*.

Polychlorinated biphenyls, lead, and mercury are associated with liver disease in American adults: **NHANES 2003-2004**.

Cave M, Appana S, Patel M, Falkner KC, McClain CJ, Brock G.

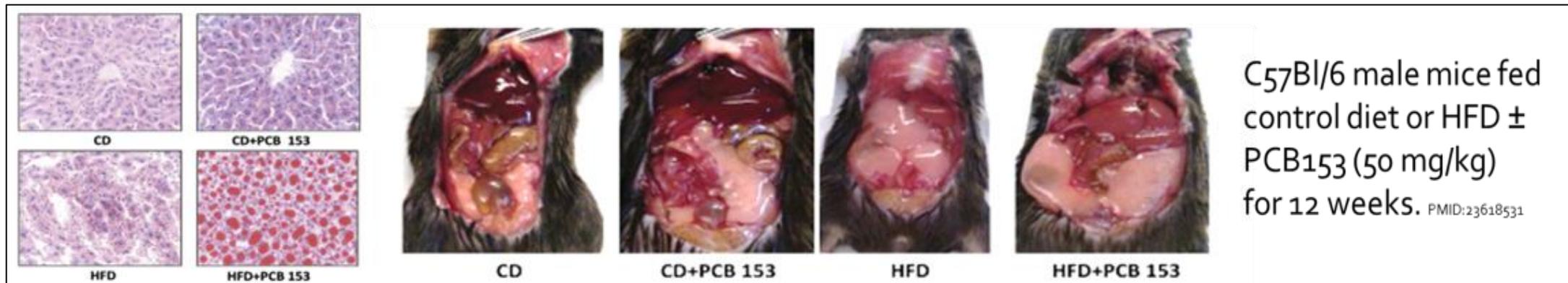
Environ Health Perspect. 2010 Dec;118(12):1735-42. doi: 10.1289/ehp.1002720.

Insecticide and metal exposures are associated with a surrogate biomarker for non-alcoholic fatty liver disease in the National Health and Nutrition Examination Survey 2003-2004.

Wahlang B, Appana S, Falkner KC, McClain CJ, Brock G, Cave MC.

Environ Sci Pollut Res Int. 2020 Feb;27(6):6476-6487. doi: 10.1007/s11356-019-07066-x. Epub 2019 D

Pollutant	Adjusted Odds Ratio for 'Unexplained ALT Elevation' by Exposure Quartile				P <sub>trend-adj</sub>
	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	4 <sup>th</sup>	
PCBs (non-dioxin-like)	Ref	0.8	2.4	4.5	0.001
PCBs (dioxin-like)	Ref	2.2	4.4	7.6	<0.001
Heptachlor epoxide	1.4	1.3	1.9	2.6	0.001
Dieldrin	1.6	1.8	2.2	3.1	0.007
Trans-nonachlor	0.7	1.6	1.7	1.6	0.050
Mercury	1.1	2.0	2.2	1.6	0.014
Lead	Ref	1.2	1.5	1.6	0.014

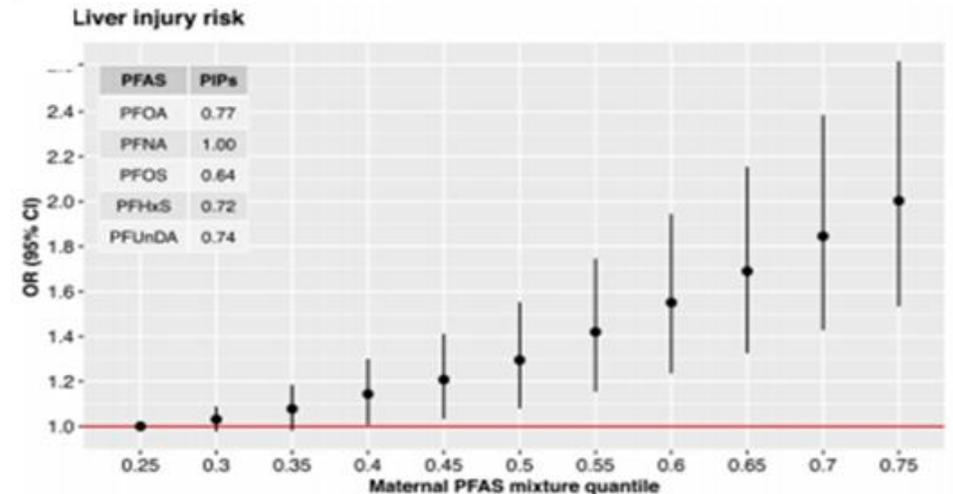
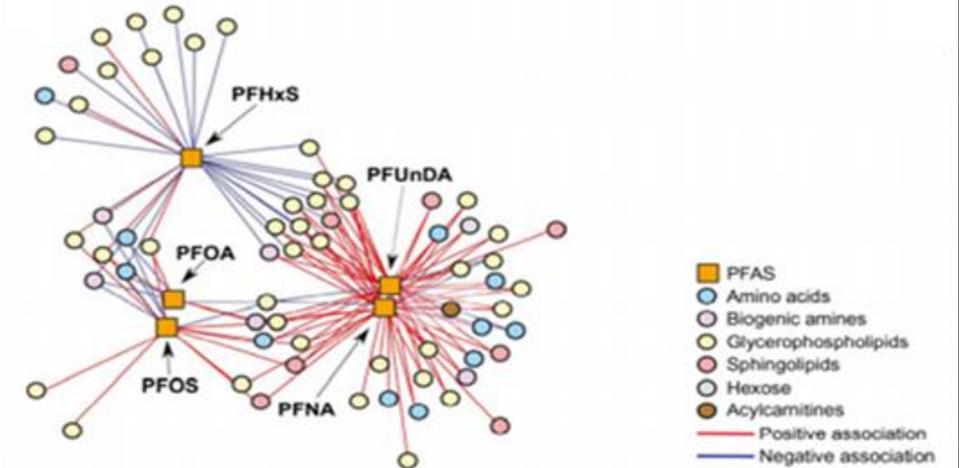
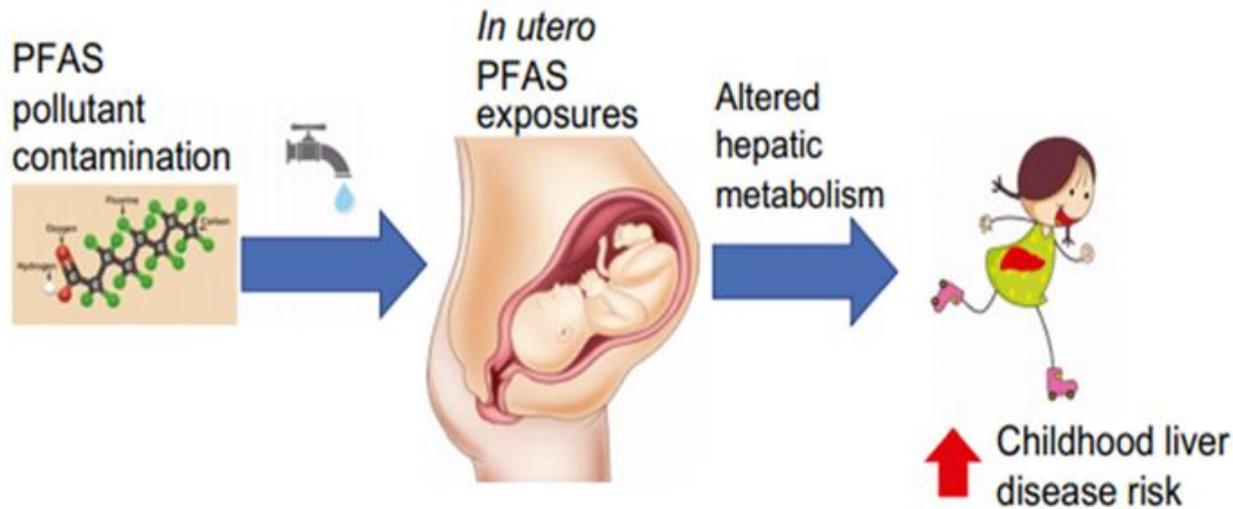


# Pediatric MASLD prevalence ORs by gestational ENVIRONMENTAL PFAS exposures with metabolome-wide association study (MWAS)

> *Hepatology*. 2020 Nov;72(5):1758-1770. doi: 10.1002/hep.31483. Epub 2020 Oct 19.

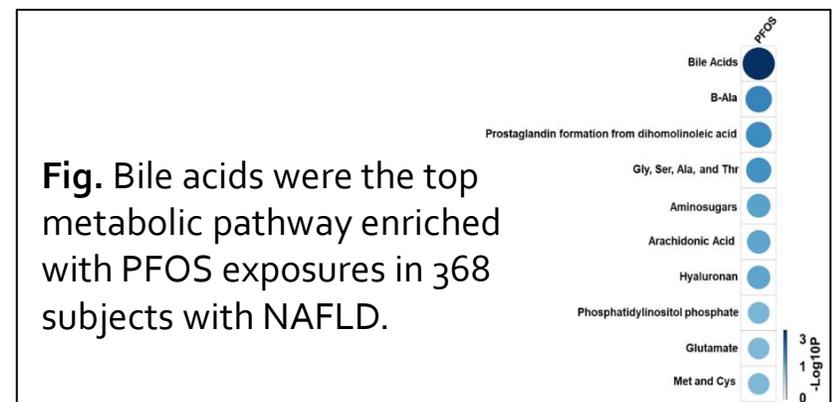
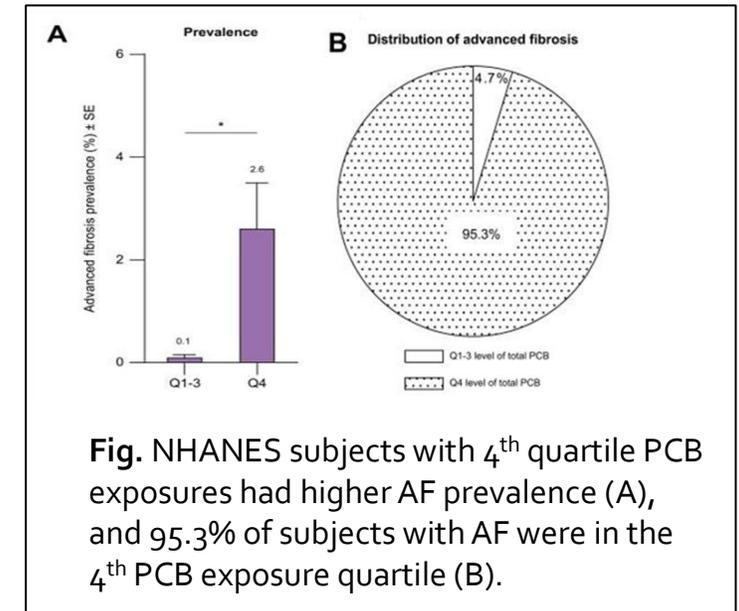
## Prenatal Exposure to Perfluoroalkyl Substances Associated With Increased Susceptibility to Liver Injury in Children

### The Developmental Origins of Childhood Liver Disease



# Liver disease SEVERITY and chemical exposures

- **PCBs** and metals were associated with advanced fibrosis in adult NHANES 1999-2018 (n=47,422). PMID: 36937989
- In adults with NAFLD, **PFAS** were positively associated with the severity of steatosis, steatohepatitis, and fibrosis using **histologic** (n=100-105, PMID: 37776622, 34627976) or **elastographic biomarkers** (n=696-14000, PMID: 37323015, 36968216, 38764062, 39150893).
- Pathway analysis of MWAS vs. **PFAS** (n=105 NAFLD subjects) demonstrated enrichment in **bile acid** and lipid metabolic pathways (PMID: 34627976). We recently confirmed the **bile acid** findings for PFOS (n=368 NAFLD subjects). (Samala N, Chalasani N, Smith MR, Cave MC et al., unpublished)



# MASLD complications and chemicals

## HCC

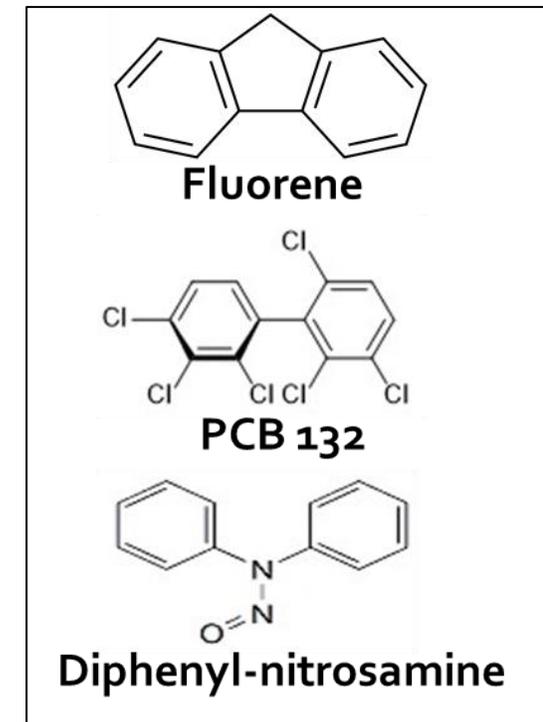
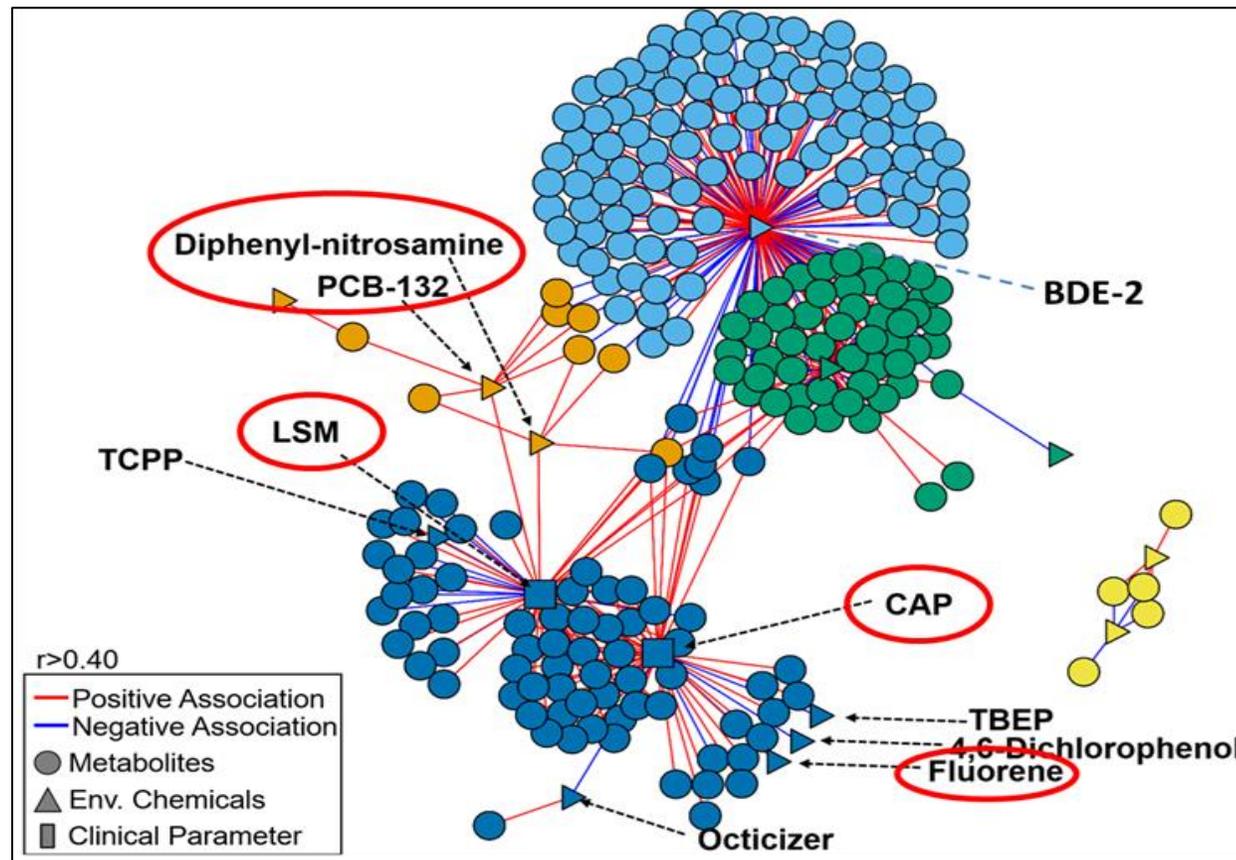
- Aflatoxins have long been associated with HCC. (PMC3496858)
- Many pollutants associated with MASLD were determined by IARC to be human carcinogens (e.g., PFAS, PCBs, vinyl chloride, etc.).
- Limited data on pollutants, including PFAS (PMID: 36111068), and HCC (PMID: 29199597).

## Cardiovascular events

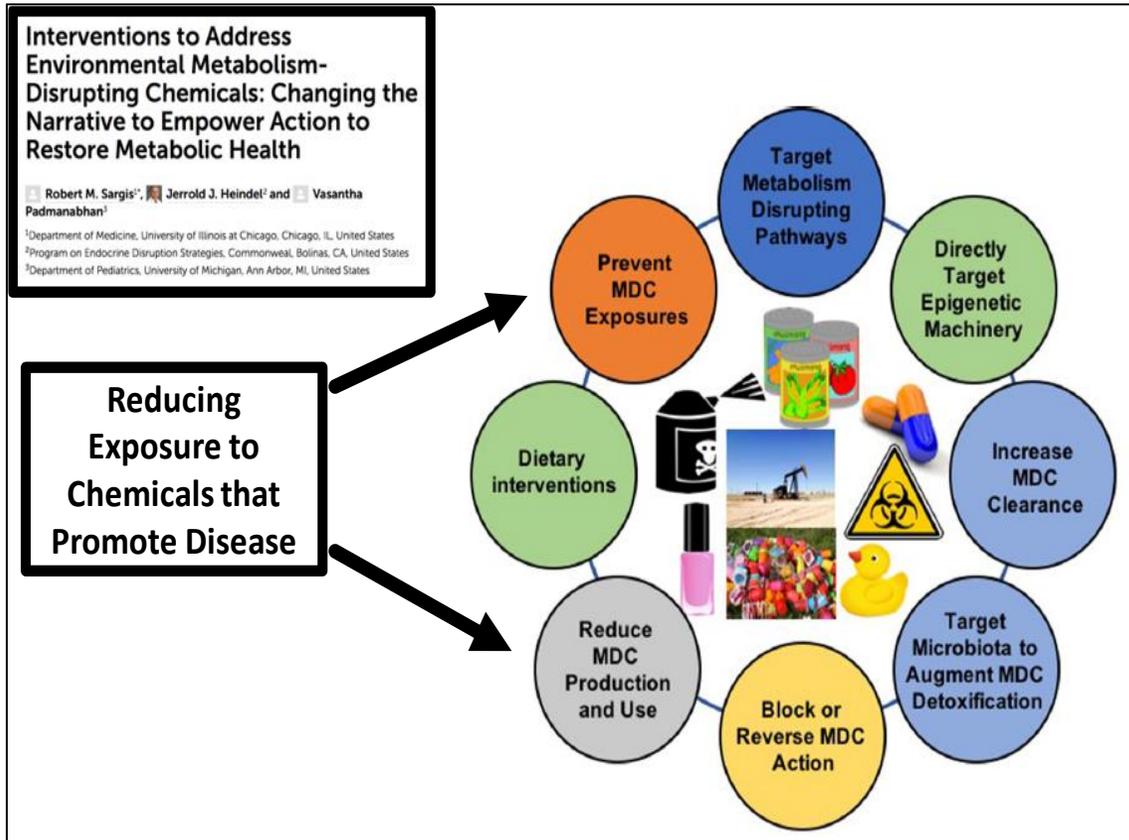
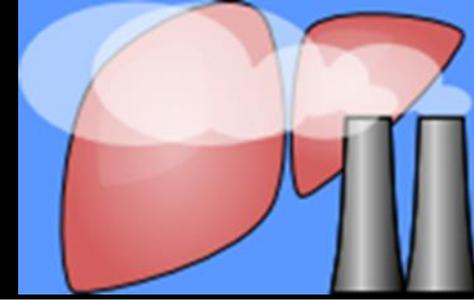
- Dioxins associated with increased TMAO. (PMID: 29353125)
- PFAS and acute coronary syndrome in NAFLD patients. (PMID: 37722302)

# The untargeted multi-omics approach

- Network analysis (xMWAS) of biomarkers (NAFLD severity, exposures, and metabolites (n=134 NAFLD cases))
- 4 pollutants were significantly associated with CAP and 6 with LSM. Fluorene, PCB 132 and diphenyl-nitrosamine were positively associated with both VCTE biomarkers.

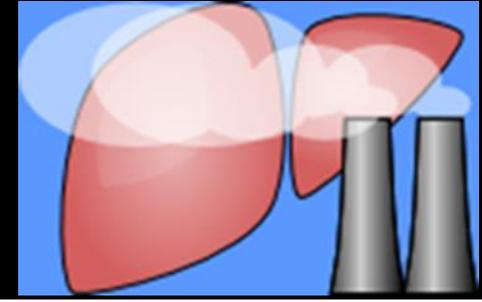


# What can you do?



- **Reduce MDC exposures:** An organic diet intervention reduced pesticide and oxidative stress biomarkers in children. (PMID:31483785)
- **Increase MDC clearance:**
  - 1) GI elimination: Olestra (PMID:24629911), cholestyramine (PMID: 6175768), and fermentable fibers (PMID:15519386) increased the fecal elimination of MDCs in human subjects.
  - 2) Renal elimination: A randomized clinical trial demonstrated enhanced urinary excretion of MDCs with the combination of a thiazide diuretic and an SGLT2 inhibitor. (PMID: 33065070)

# Conclusions



- **We should care about pollutants and metabolic health in liver disease.**
- Pollution is a disease modifier associated with MASLD development, severity, and complications.
- Barriers exist to implementation of environmental health science in clinical hepatology practice.
- Longitudinal data are required on pollution and fibrosis progression, HCC development, response to therapy, decompensation, survival, and GxE.
- The exposome is an important new concept in hepatology which could be incorporated in a future precision medicine approach to liver health.



# Acknowledgments



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