

Environmental Chemical Exposures as Risk Modifiers for Liver Disease and Cancer



Juliane I Beier, PhD

Department of Medicine, GI, Liver and Nutrition Division

Department of Environmental and Occupational Health

Pittsburgh Liver Research Center

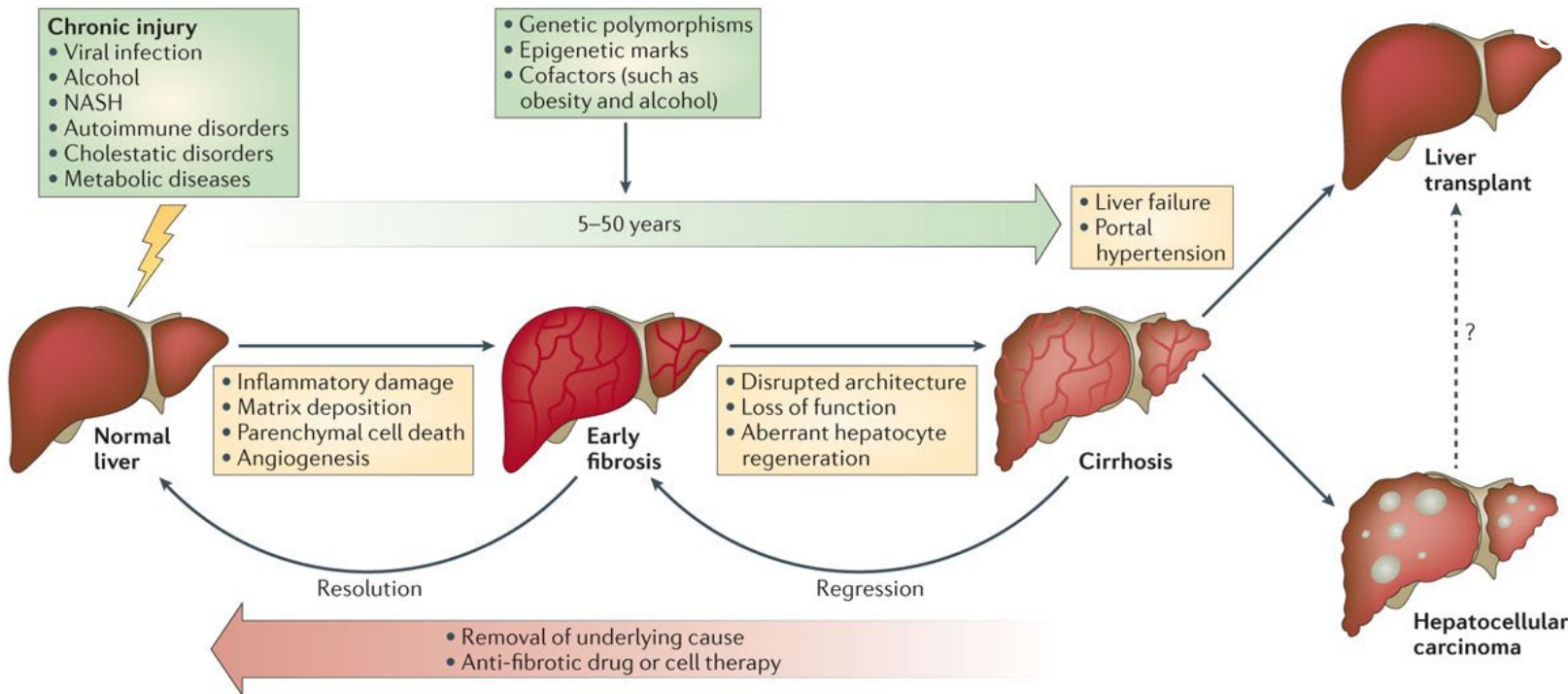
University of Pittsburgh



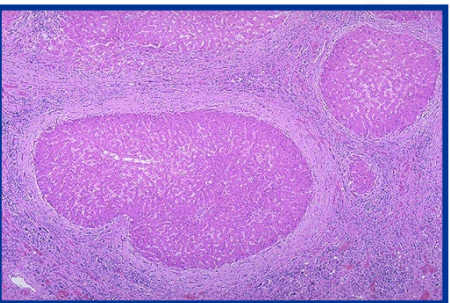
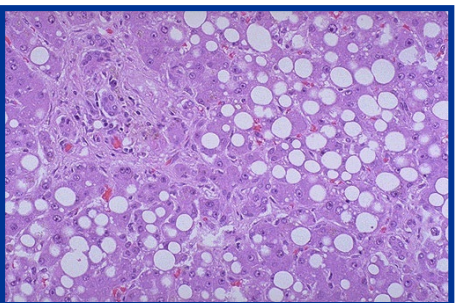
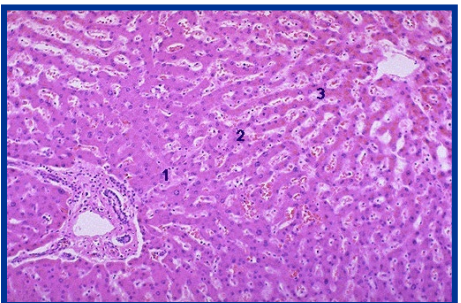


Key events in steatotic liver disease (SLD)

Shared natural history



- Caused by:**
- virus
 - alcohol (ALD)
 - obesity (MASLD)
 - toxic chemicals (TASLD)



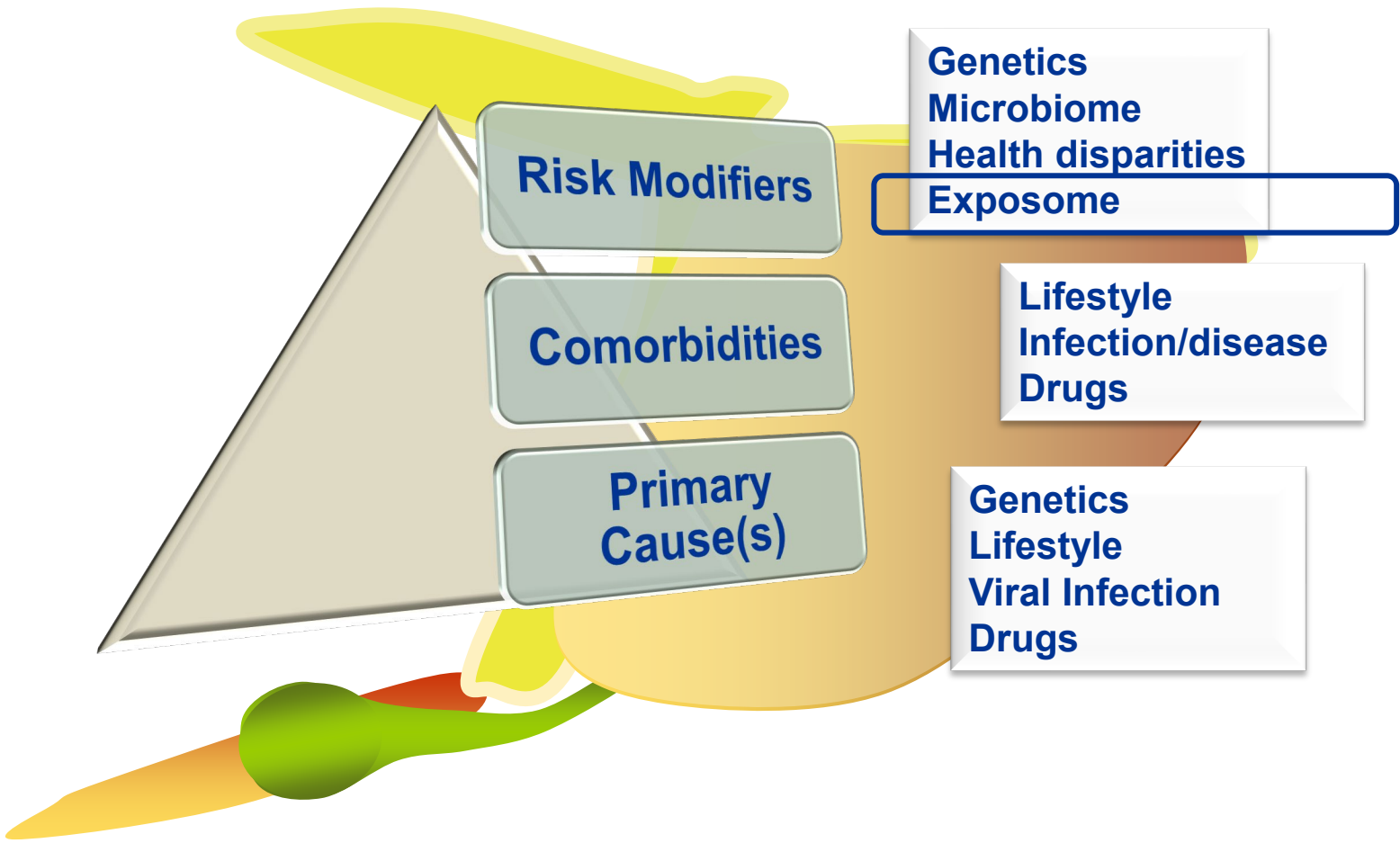
Nature Reviews | Immunology

Major detoxifying organ
Silent disease



Risk factors of steatotic liver disease

Drivers of inter-individual risk



Environmental toxicant: vinyl chloride (VC)



How VC came on the 'radar'

1974

- Cluster of hepatic angiosarcoma diagnoses in workers in Louisville, KY
- Occupational exposure to VC recognized as cause

1975

- OSHA set stricter exposure guidelines
- Exposure to high VC concentrations eliminated

2010

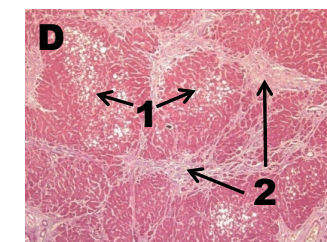
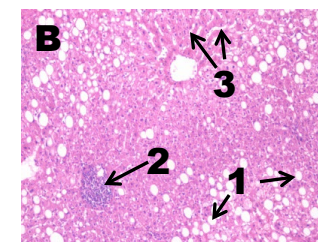
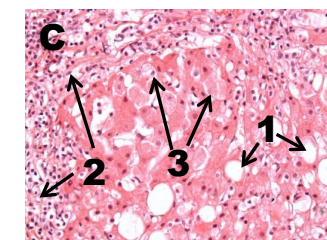
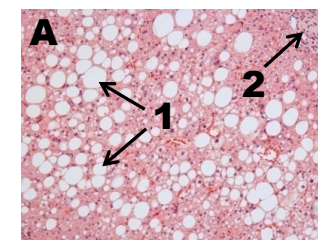
- Cave et al. described 'Toxicant-associated steatohepatitis' (TASH)
- VC-induced non-cancerous liver injury

2023

- Current OSHA threshold still at <1 ppm/day
- #4 on the ATSDR Substance Priority List
- Risk for low-level, chronic exposure in humans unknown



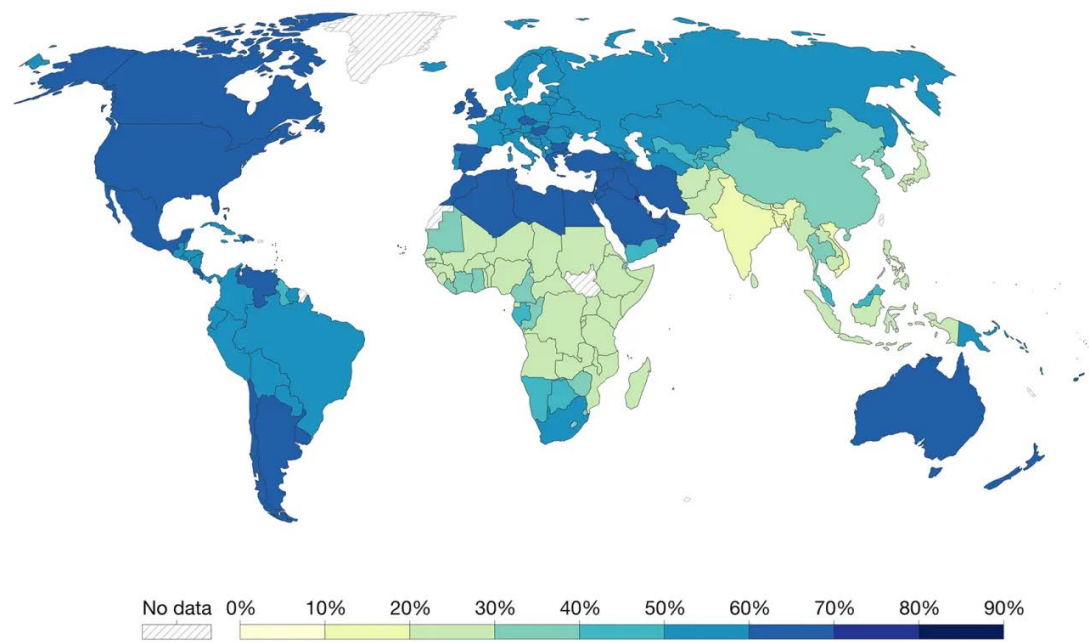
TASH



Tamburro et al., *Hepatology*, 4:413-8.
Kielhorn et al., *Environ Health Perspect*, 108: 579-88.
Hsiao et al. *J Occup Environ Med*, 46, 962-966.
Maroni et al. *J Occup Environ Med*, 60, 60-65.
Cotrim et al., *Liver Int*, 24, 131-135.
Cave et al., *Hepatology*, 51:474-81.



Low conc. VC - a risk modifier for liver damage?



Source: WHO, Global Health Observatory

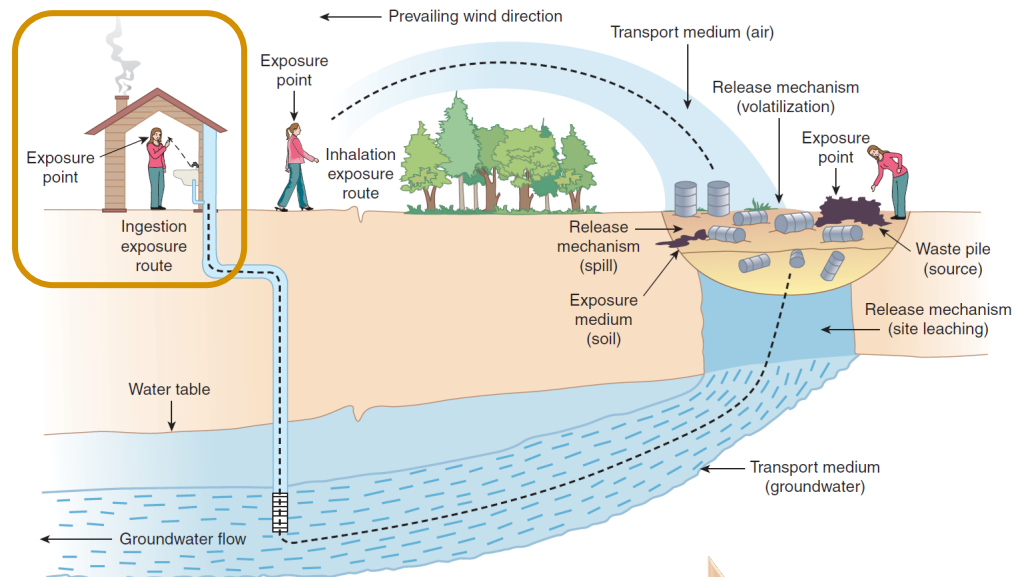
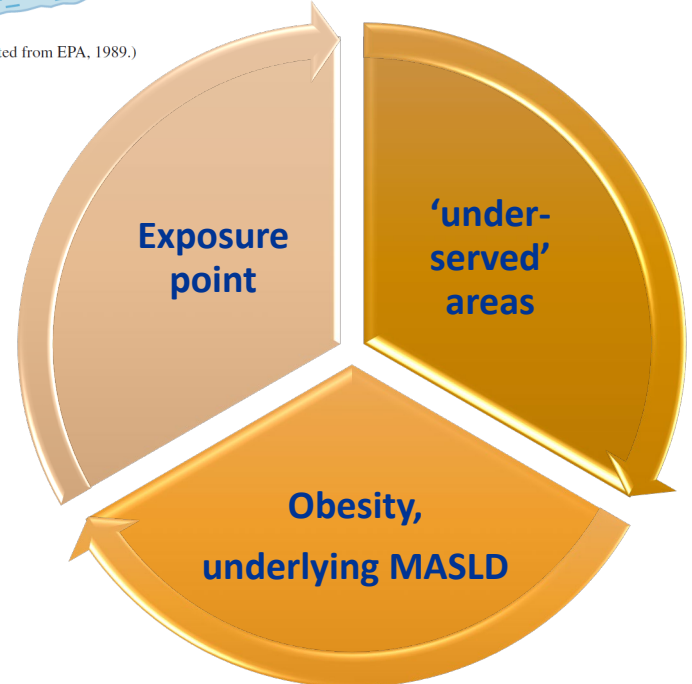
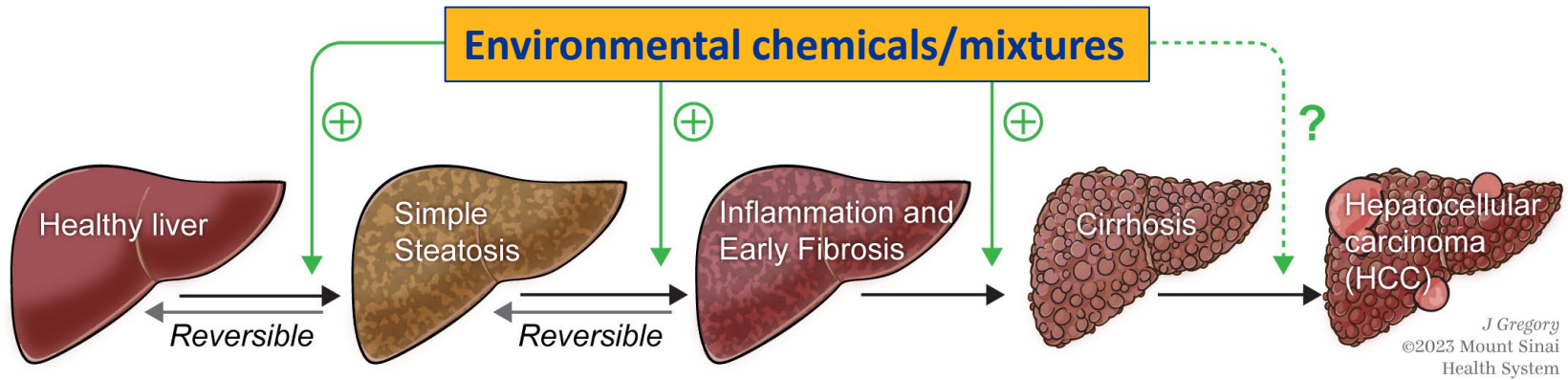
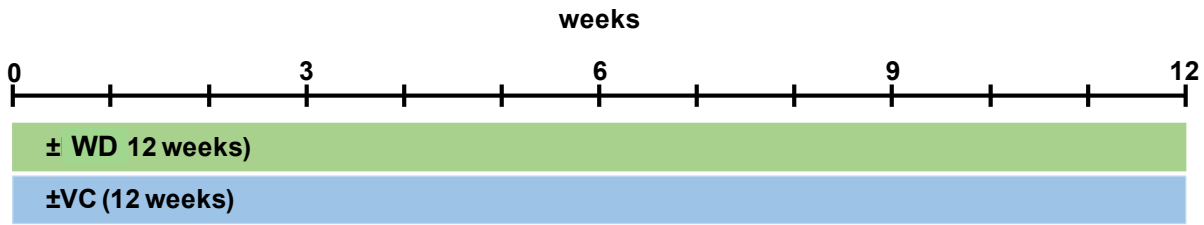


Figure 24-1. Solvent exposure pathways and media. (Adapted from EPA, 1989.)





Low VC exposure enhances MASLD



Lang et al. *Hepatol Commun.* 2(3), 270-284.
Lang et al. *J Vis Exp.* 155, e60351.
<https://www.jove.com/v/60351/vinyl-chloride-high-fat-diet-as-model-environment-obesity>

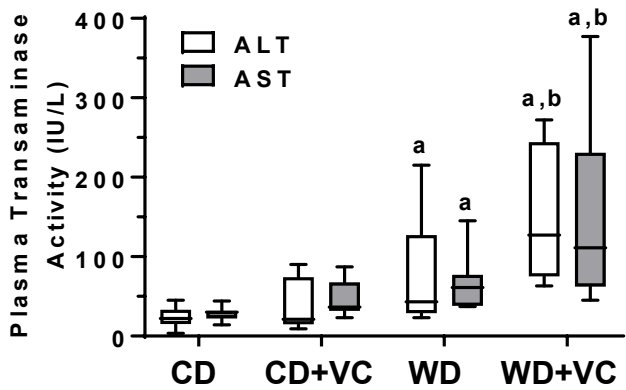
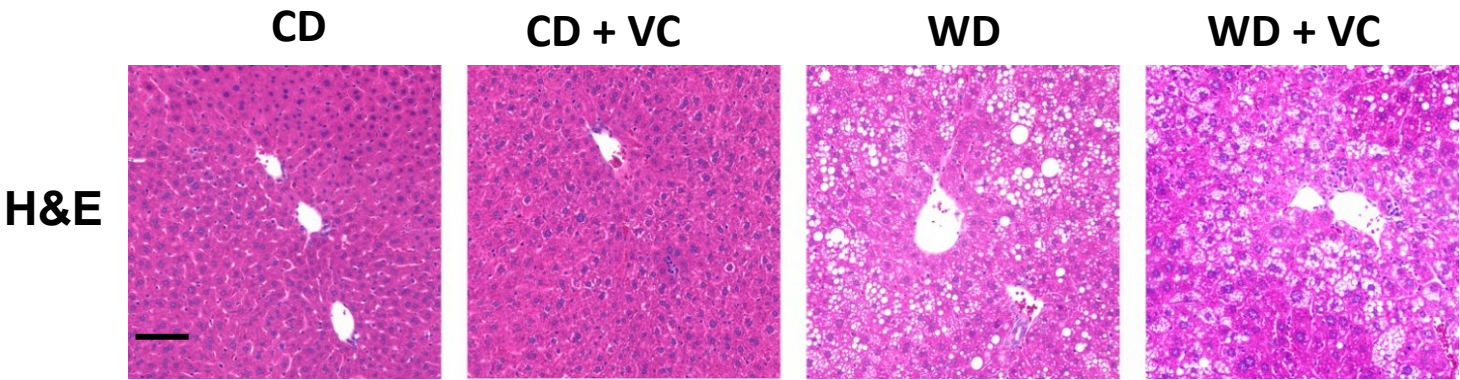


VC concentration:
 0.85 ± 0.1 ppm

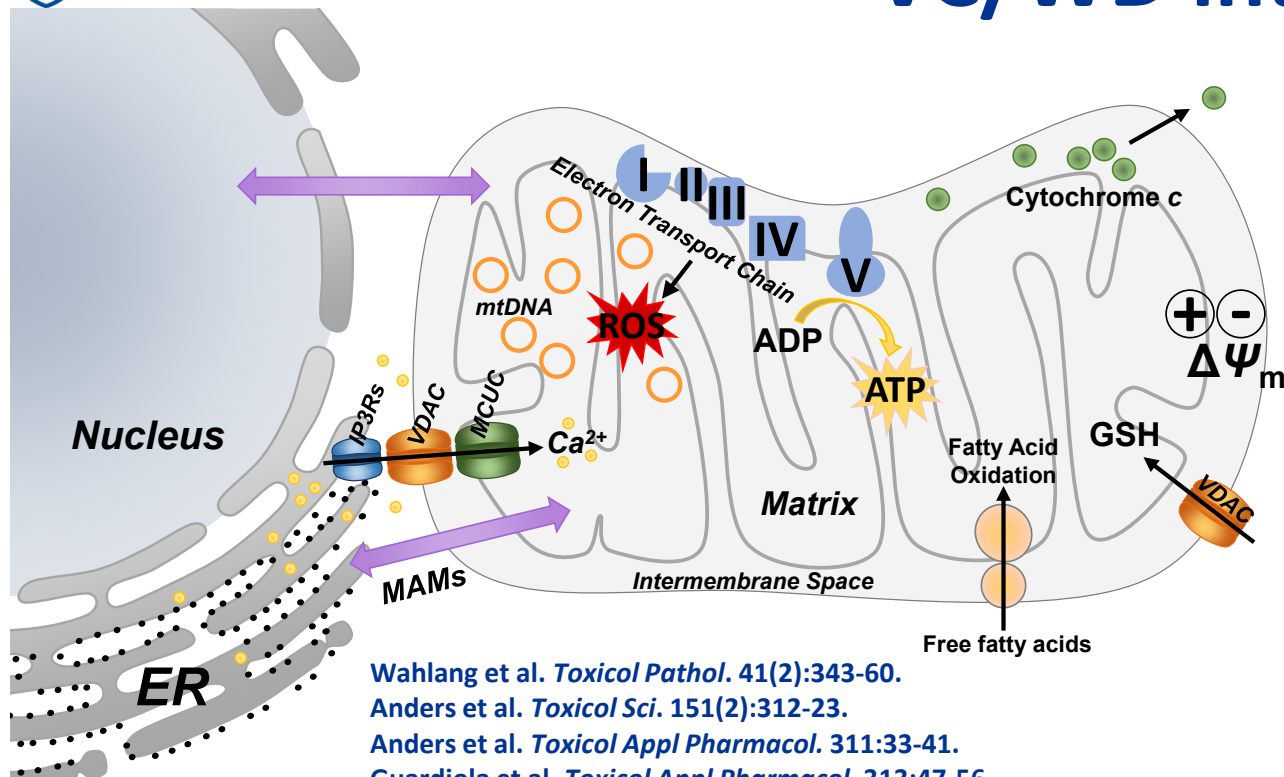


Western-style diet:

- 42% fat
- 43% carbohydrate
- 15% protein



VC/WD interaction



Wahlang et al. *Toxicol Pathol.* 41(2):343-60.
 Anders et al. *Toxicol Sci.* 151(2):312-23.
 Anders et al. *Toxicol Appl Pharmacol.* 311:33-41.
 Guardiola et al. *Toxicol Appl Pharmacol.* 313:47-56.
 Lang et al. *Hepatol Commun.* 2(3), 270-284.
 Liang et al. *Chem Res Toxicol.* 31(6):482-493.
 Lang et al. *Biol Chemistry.* 399(11):1237-1248.
 Chen et al. *Redox Biol.* 24:101205.
 Wahlang et al. *Curr Envir Health Rpt.* 6(3):80-94.
 Lang et al. *Toxicol Appl Pharmacol.* 114745.
 Wahlang et al. *Toxicol Sci.* 174(1):79-91.
 Lang et al. *J Vis Exp.* 155, e60351.
 Werder et al. *Food Chem Toxicol.* 39:111242.
 Kaelin et al. *Toxicol Appl Pharmacol.* 115068.
 Schneggelberger et al. *Acta Pharm Sin B.* 11(12):3756-3767.
 Beier et al. *Acta Pharm Sin B.* 11(12):3768-3778.
 Ge Y et al. *Toxicol Sci.* 193:103-114.
 Liu S, et al. *Toxicol Appl Pharmacol.* 468:116514.

Injury and cell death

- Inflammation/Inflammasome activation ✓
- Generation of ROS/RNS ✓
- Necrosis/necroptosis ✓
- Autophagy ✓

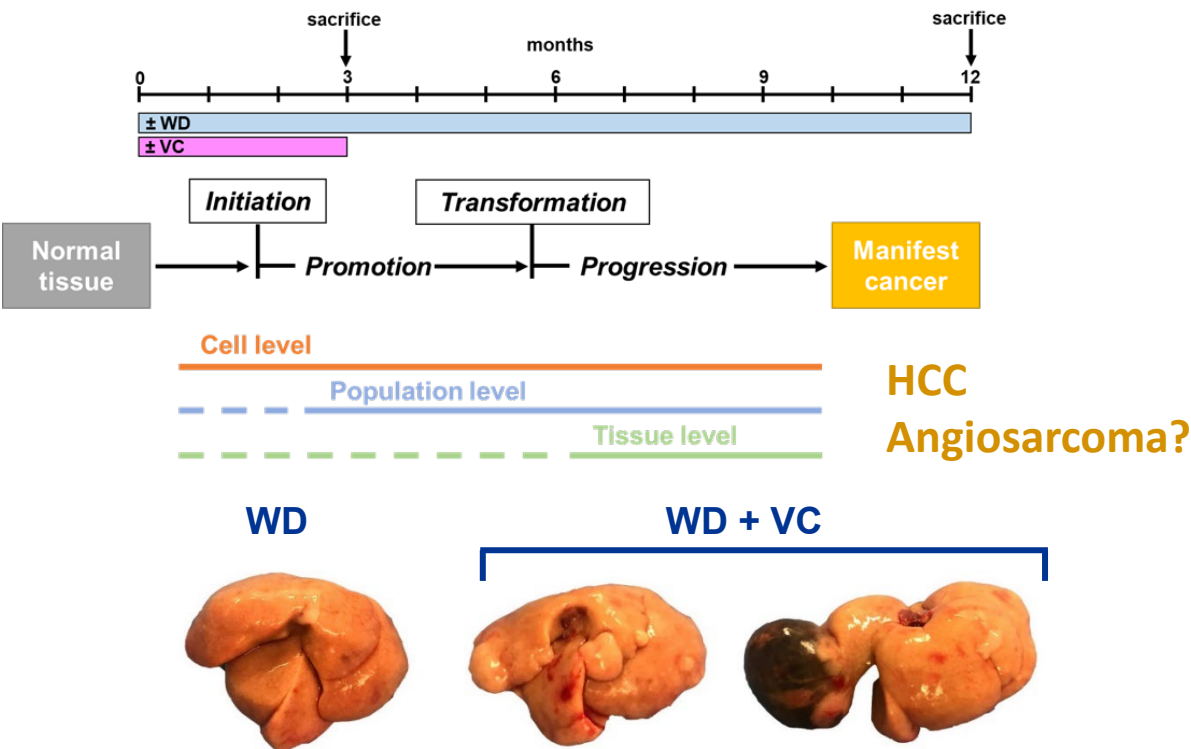
Metabolic dyshomeostasis

- Glycogen depletion ✓
- Steatosis ✓
- ER stress ✓
- Loss of ATP ✓
- Mitochondrial damage ✓
- MAM miscommunication ✓
- Cholesterol trafficking ?
 - To be continued...

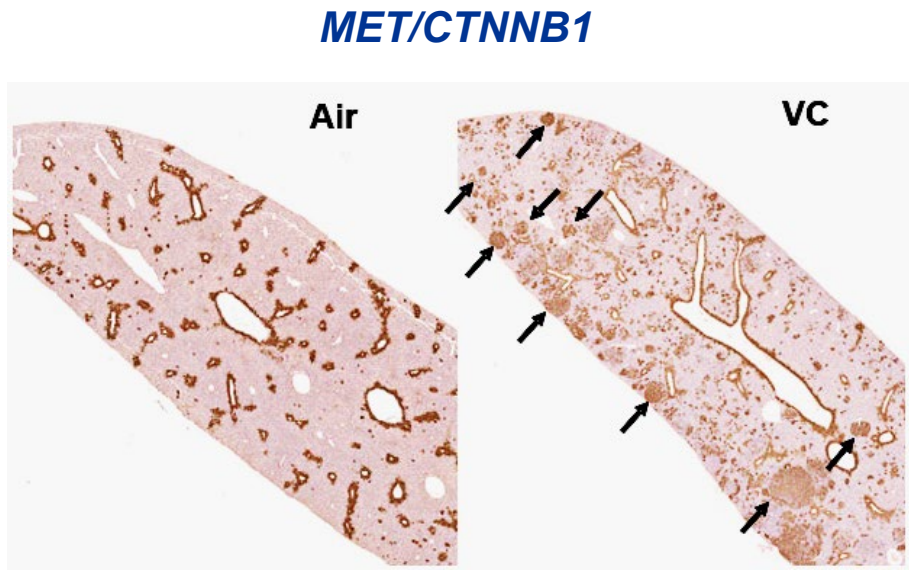
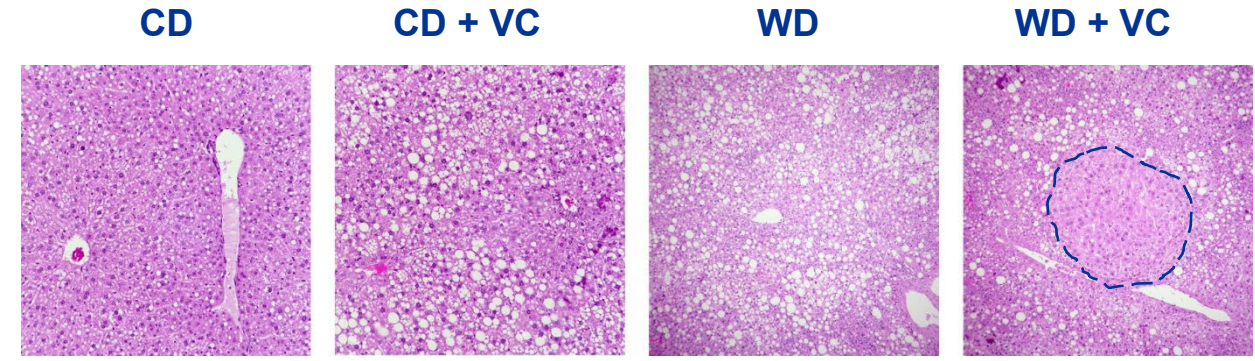
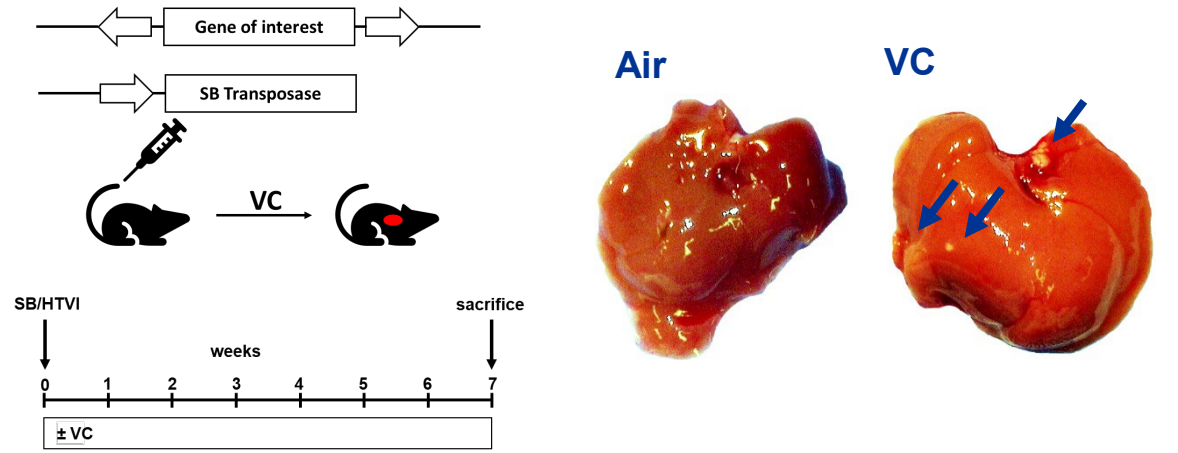


VC-induced tumor formation

age-out ("outside-in")



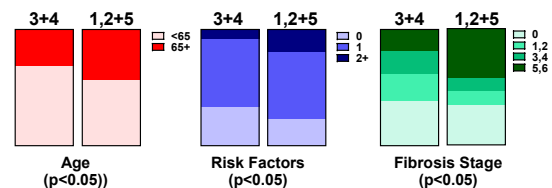
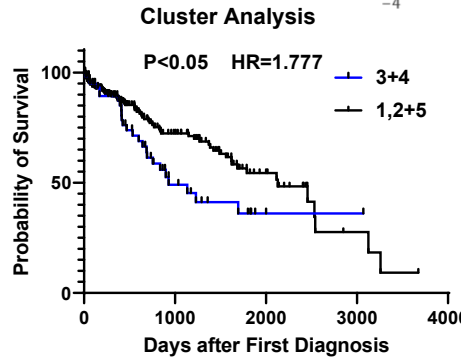
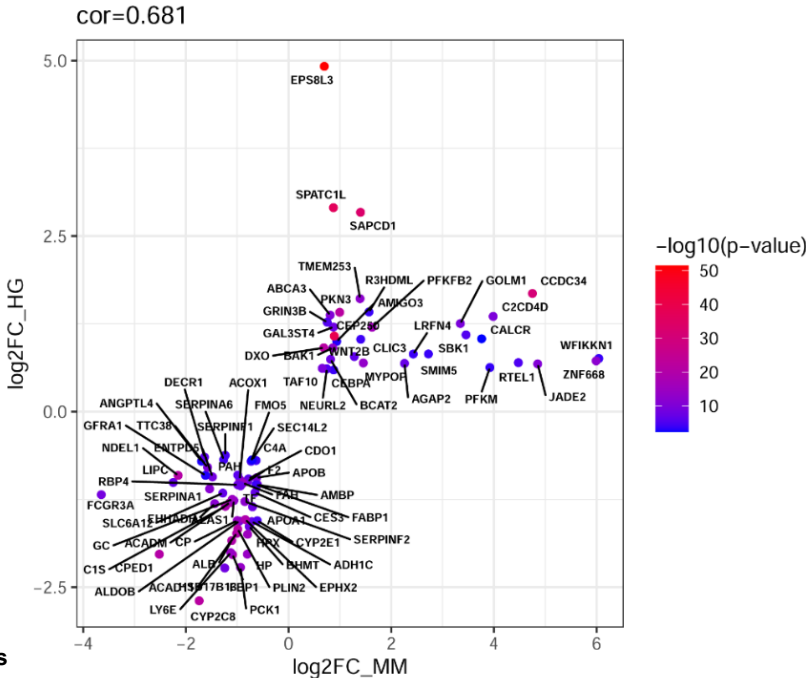
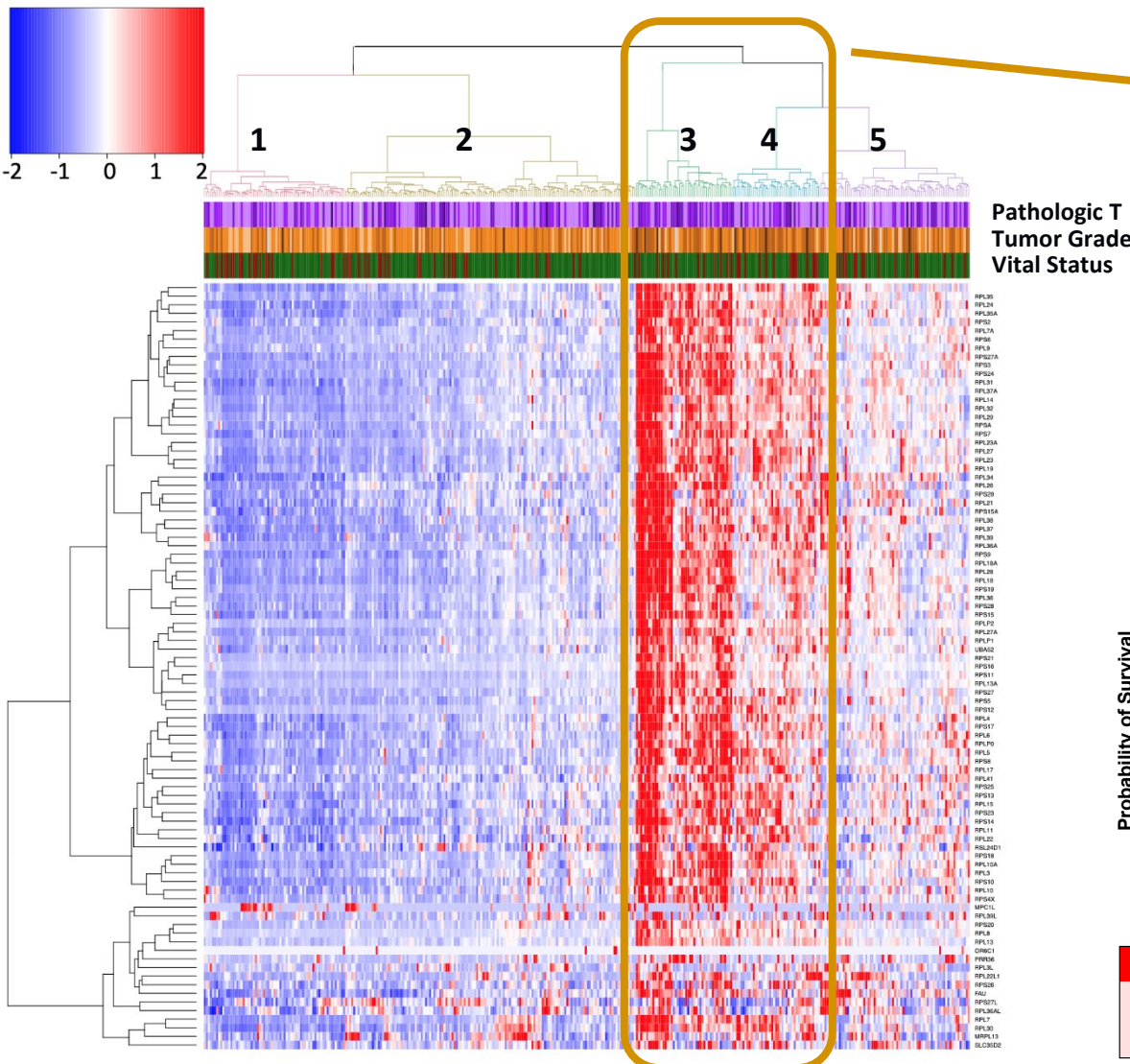
Met/b-cat ("inside-out")





Does this relate to humans?

filtered by GO:ribosomal processing





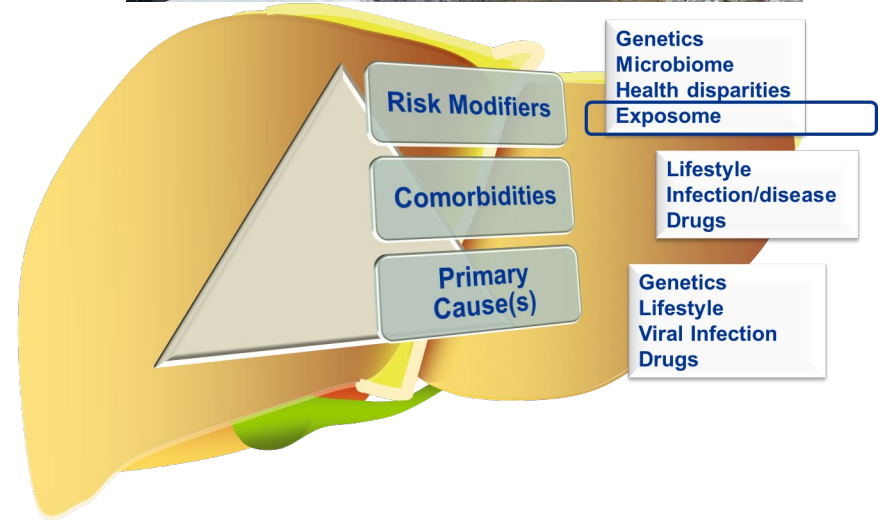
Environmental toxicant-enhanced disease

- Other underlying diseases/factors?

- ALD ?
- Cardio-vascular disease?
- Viral infections?
- Lung diseases?
- Pregnancy?
- Childhood exposure?

- Other environmental chemicals:

- Metals (arsenic, lead, cadmium...)
- Polychlorinated biphenyls (PCBs)
- Per- and Polyfluoroalkyl Substances (PFAS)
- Volatile organic compounds (VOCs)
- Dioxins



Tan M, et al. *Toxicol Appl Pharmacol.* 2011; 257(3):356-64.
Wahlang B, et al. *Toxicol Appl Pharmacol.* 2014; 279(3):380-390.
Marques E, et al. *Toxicol Appl Pharmacol.* 2020; 408:115250.
Cichocki JA, et al. *Toxicol Sci.* 2017; 159:102-113
Yang L, et al. *Mol Nutr Food Res.* 2021; e2000811
Beier et al. *Acta Pharm Sin B.* 11(12):3768-3778.
Share.america.gov

Environmental toxicant-enhanced disease

• Other underlying diseases/factors?

- ALD ?
- Cardio-vascular disease?
- Viral infections?
- Lung diseases?
- Pregnancy?
- Childhood exposure?

• Other environmental chemicals:

- Metals (arsenic, lead, cadmium...)
- Polychlorinated biphenyls (PCBs)
- Per- and Polyfluoroalkyl Substances (PFAS)
- Volatile organic compounds (VOCs)
- Dioxins

Table 1 Factors that influence the development and severity of liver diseases.

Liver disease	Genetics ^a	Lifestyle/comorbidities ^b	Environmental toxicants ^c	Microbiome ^d
Inherited liver diseases	+++ ^{2,3}	+ ⁴	—	+ ³
Biliary atresia	++ ^{5,6}	+(+) ⁵	++ ⁷	+ ⁸
Primary biliary cholangitis	++ ⁹	—	++ ^{10–15}	+ ¹⁶
Primary sclerosing cholangitis	++ ^{17,18}	—	—	+ ^{19,20}
Autoimmune hepatitis	++ ^{21–24}	++ ^{21–24}	+ ^{23–25}	++ ²⁶
Direct DILI	+ ^{27–29}	++ ^{30–32}	+ ^{33–35}	++ ³⁶
Idiosyncratic DILI	+ ³⁷	+ ³⁸	—	—
Viral hepatitis	++ ^{39,40}	++ ^{41,42}	+(+) ^{43,44}	—
NAFLD/MAFLD	++ ⁴⁵	+++ ⁴⁵	++(+) ^{46–49}	++(+) ^{50,51}
ALD	++ ⁵²	+++ ⁵²	—	+++ ^{51,53}
TAFLD/TASH	—	—	+++ ^{46,54}	+ ⁵⁵

—, no known association or not classifiable. Evidence inadequate in humans and limited in experimental models.

+, possible association. Limited evidence in humans and in experimental models.

++, probable association. Limited evidence in humans and sufficient in experimental models.

+++ , known association and/or primary cause. Clear cause and effect association is known.

^aSexual dimorphism, familial associations, linkage disequilibrium, etc.

^bViral infections, metabolic syndrome, alcohol, underlying liver disease, etc.

^cExposure to environmental/occupational chemicals or toxins, natural or anthropogenic, that was not self-administered.

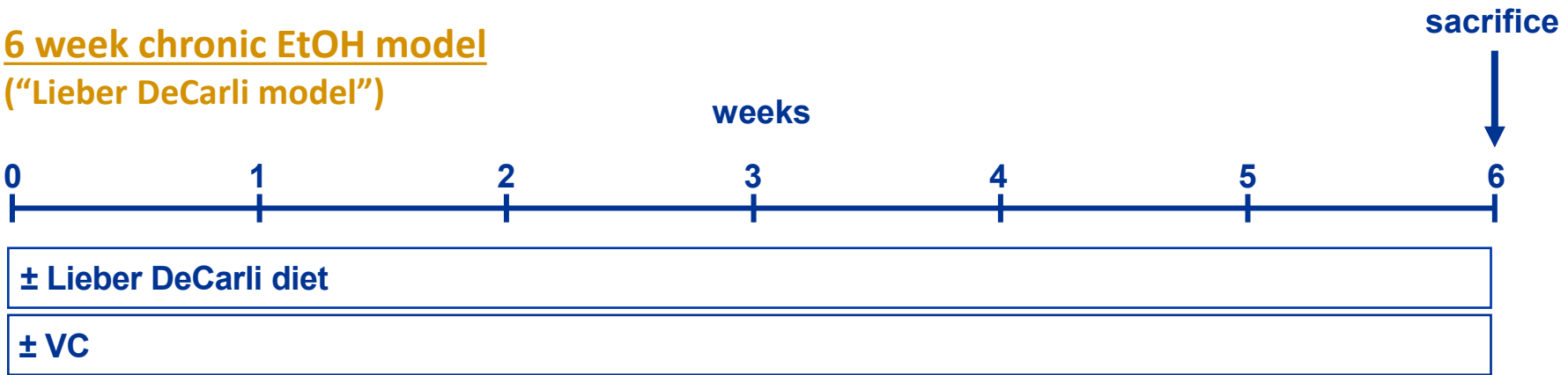
^dAltered microbiome/dysbiosis in diseased patients or in animal models.

Tan M, et al. *Toxicol Appl Pharmacol.* 2011; 257(3):356-64.
Wahlang B, et al. *Toxicol Appl Pharmacol.* 2014; 279(3):380-390.
Marques E, et al. *Toxicol Appl Pharmacol.* 2020; 408:115250.
Cichocki JA, et al. *Toxicol Sci.* 2017; 159:102-113
Yang L, et al. *Mol Nutr Food Res.* 2021; e2000811
Beier et al. *Acta Pharm Sin B.* 11(12):3768-3778.
Share.america.gov

Other underlying disease

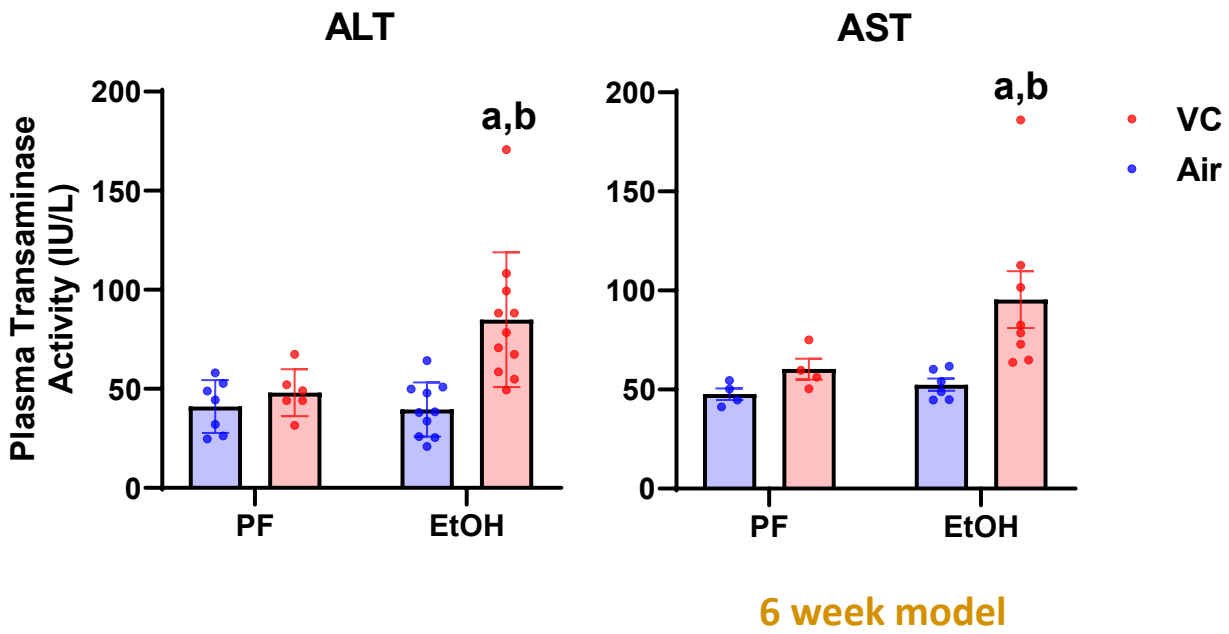
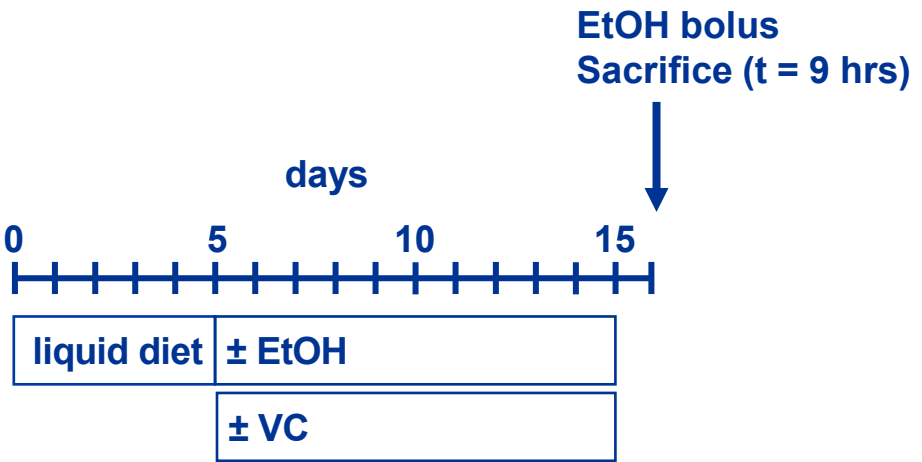
ALD

6 week chronic EtOH model ("Lieber DeCarli model")



EtOH = alcohol

10 + 1 model ("acute on chronic model", "NIAAA model", "Gao binge model")

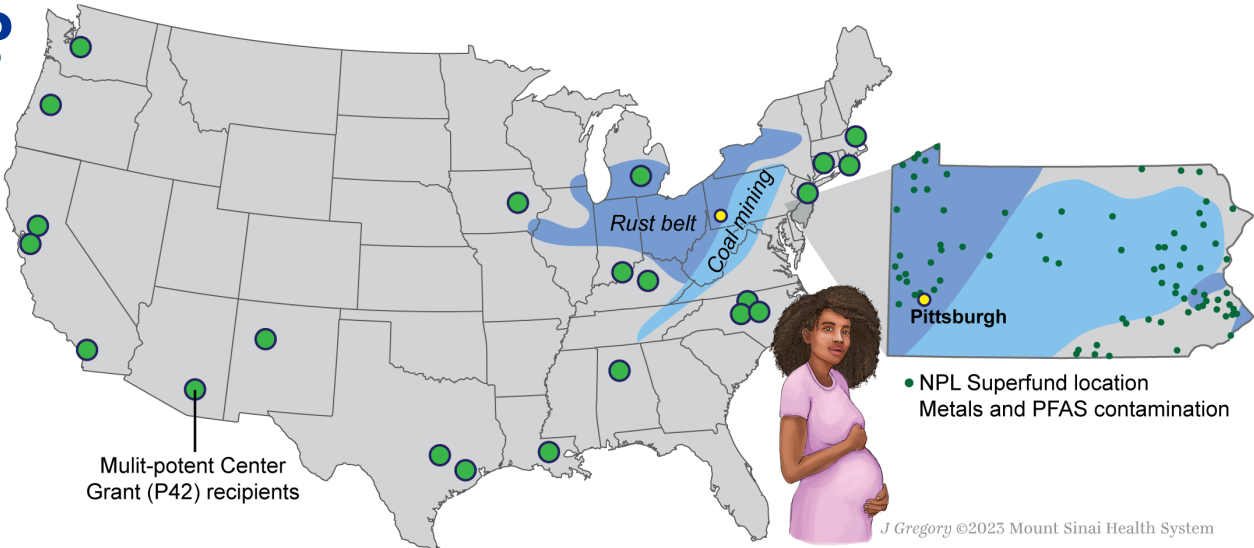




Environmental toxicant-enhanced disease

- **Other underlying diseases/factors?**

- ALD ?✓
- Cardio-vascular disease?
- Viral infections?
- Lung diseases?
- Pregnancy?
- Childhood exposure?



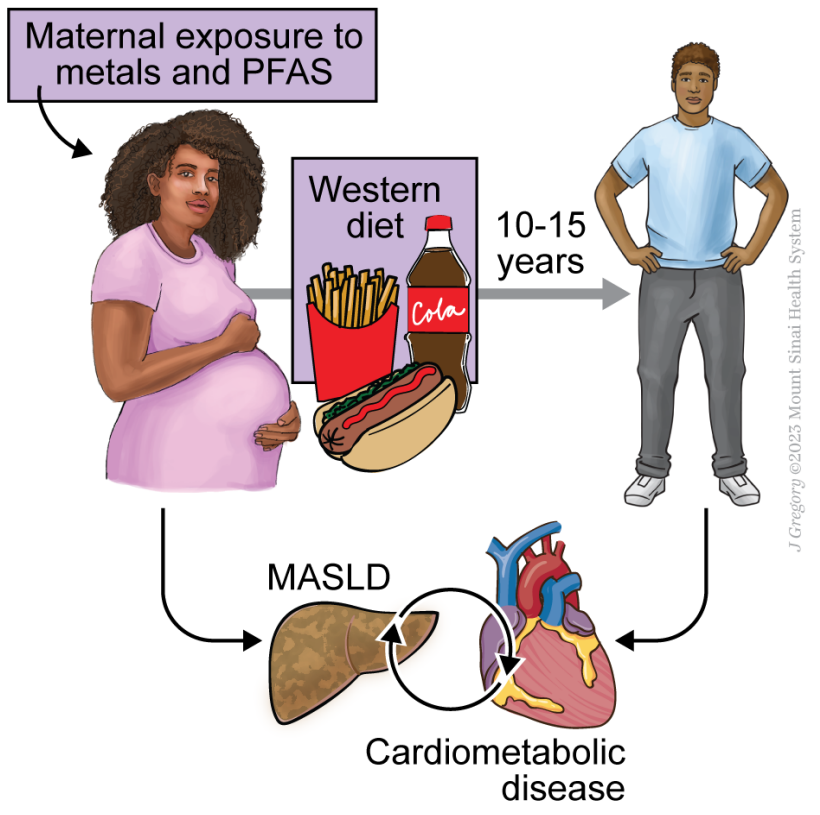
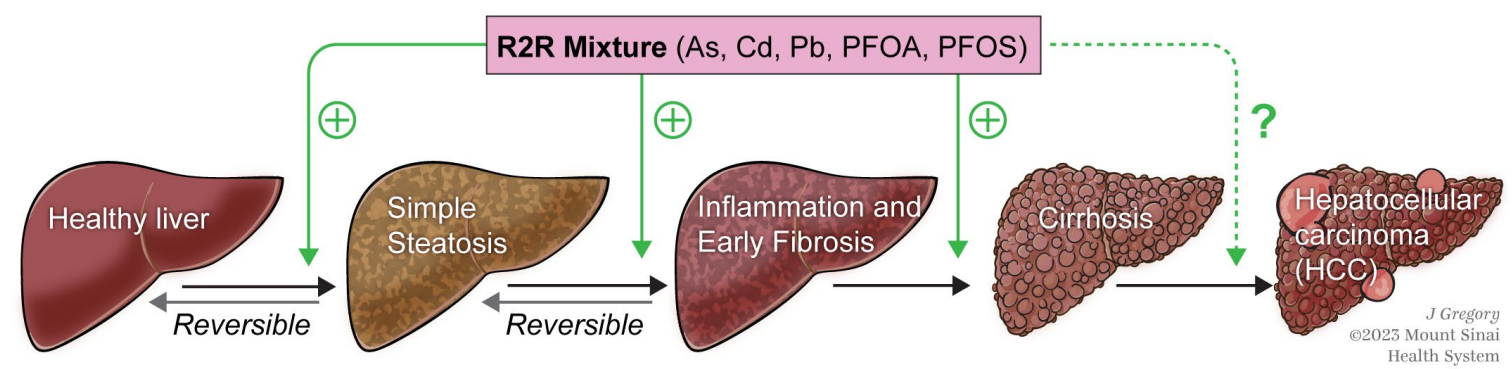
- **Other environmental chemicals:**

- Metals (arsenic, lead, cadmium...)
- Polychlorinated biphenyls (PCBs)
- Per- and Polyfluoroalkyl Substances (PFAS)
- Volatile organic compounds (VOCs)
- Dioxins

Tan M, et al. *Toxicol Appl Pharmacol.* 2011; 257(3):356-64.
Wahlang B, et al. *Toxicol Appl Pharmacol.* 2014; 279(3):380-390.
Marques E, et al. *Toxicol Appl Pharmacol.* 2020; 408:115250.
Cichocki JA, et al. *Toxicol Sci.* 2017; 159:102-113
Yang L, et al. *Mol Nutr Food Res.* 2021; e2000811
Beier et al. *Acta Pharm Sin B.* 11(12):3768-3778.
Share.america.gov
etc



Upcoming studies





East Palestine Community

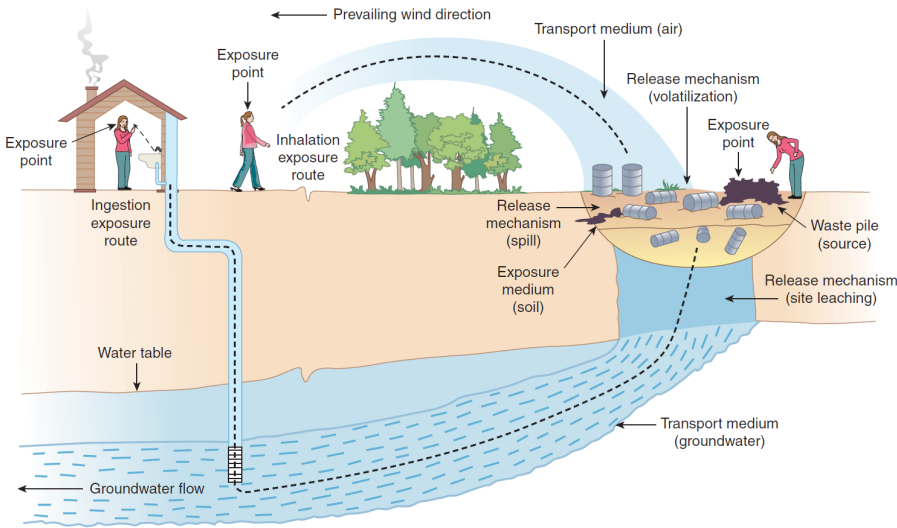


Figure 24-1. Solvent exposure pathways and media. (Adapted from EPA, 1989.)

Thank you, community leaders!



Acknowledgements

Beier/Arteel Lab

Jiang Li

Charis-Marie Vanderpuye

Pooja Muddasani

Dexi Chen

Former Lab members

Olivia Bannister

Meera Bhargava

Aisha Bhutta

Regina Schnegelberger

Avinash Kumar

Anna Lang

Liya Chen

Lisanne Anders

Brenna Kaelin

Gavin Poff

Austin Krueger

Max Rakutt

Karl Hempel

Heegook Yeo

Collin McKenzie

East Palestine Community

Pitt Collaborators

Silvia Liu

Paul Monga

Michael Jurczak

Donna Stolz

Sruti Shiva

Francisco Schopfer

Melanie Scott

Brett Kaufman

Maureen Lichtveld

Aaron Barchowsky

Outside Collaborators

Xiang Zhang (UofL)

- Liqing He (UofL)

Matt Cave (UofL)

- Banrida Wahlang (UofL)

Wen-Xing Ding (KUMC)

Grant support:

- **NIDDK R01 DK133454**
- **NIEHS R21 ES031531**
- **PLRC**

