Published in final edited form as:

Hepatology. 2020 November ; 72(5): 1518–1521. doi:10.1002/hep.31549.

Environmental Pollution and the Developmental Origins of Childhood Liver Disease

Matthew C. Cave

Department of Medicine, Division of Gastroenterology, Hepatology, and Nutrition; Department of Pharmacology & Toxicology; and the Department of Biochemistry and Molecular Genetics; University of Louisville School of Medicine, Louisville, KY, 40202, USA

The Superfund Research Center, the Center for Integrated Environmental Health Sciences, Alcohol Research Center and the Hepatobiology and Toxicology Center, University of Louisville, Louisville, KY, 40202, USA

The Robley Rex Veterans Affairs Medical Center, Louisville, KY, 40206, USA

The Liver Transplant Program at UofL Health - Jewish Hospital Trager Transplant Center, Louisville, KY, 40202, USA

Environmental hepatology is an emerging field focused on the environmental contribution to liver health and disease. Although lifestyle choices such as drugs, alcohol, diet and exercise are major environmental influences; the potential contribution of chemical pollutants is less clear. Nonetheless, accumulating evidence suggests that these exposures may increase liver disease risk, with the greatest evidence occurring for non-alcoholic fatty liver disease (NAFLD) (1, 2).

In this issue of *Hepatology*, Stratakis, *et al.* present rigorous environmental epidemiology research, “Prenatal Exposures to Perfluoroalkyl Substances Associated with Increased Susceptibility to Liver Injury in Children”. Gestational exposures to a mixture of perfluoroalkyl substances (PFAS) were positively associated with higher liver enzymes and increased liver injury risk during childhood (median age 8.2 years). Moreover, these developmental exposures were associated with an altered serum metabolome. Latent variable analysis identified a profile for at risk children characterized by high prenatal PFAS exposures and disrupted amino acid and glycerophospholipid metabolism. The study’s major results are illustrated in Figure 1. The most likely explanation for the observed liver injury is NAFLD, based on the results of previously published pediatric and adult PFAS exposure cohort studies (3, 4) and rodent models of gestational and adult PFAS exposures (1, 2, 4–6). Several novel concepts believed to be important for hepatologists and liver investigators are raised by Stratakis, *et al.* First, the underappreciated, but potentially significant, environmental contribution to chronic liver disease is highlighted. Even more concerning is the possibility that *in utero* exposures to environmental pollutants could increase liver

Matthew C. Cave, M.D., Professor, University of Louisville School of Medicine, Kosair Charities Clinical and Translational Research Building Rm 507, 505 S. Hancock St., Louisville, KY, 40202, USA, matt.cave@louisville.edu, Phone (502) 852-6189, Fax (502) 852-8927.

Competing Financial Interests: The author declares no competing financial interests relevant to this editorial.

disease risk by altering post-natal metabolism. Should the identified associations subsequently be confirmed as causal, this knowledge has the potential to profoundly impact the understanding of liver disease pathogenesis and potentially patient care and policy.

In order to better contextualize these data, overviews of environmental liver disease and PFAS are required. In a manuscript published in *Hepatology* in 2010, our group coined the term, toxicant-associated steatohepatitis (TASH), to describe the fatty liver disease occurring in vinyl chloride workers in the absence of other risk factors (7). This report provided proof-of-concept that high-level occupational chemical exposures could cause steatohepatitis. Cross-sectional cohort studies were then conducted which identified specific low-level environmental contaminants (including PFAS) which were associated with liver injury and suspected fatty liver disease (1, 2). Model systems elucidated mechanisms by which specific pollutants either caused hepatic steatosis or interacted with lifestyle factors to increase the severity of diet-induced nonalcoholic steatohepatitis (NASH) (1, 2). Thus, the lines between NASH and TASH were blurred. Chemical pollutants have been associated with other related metabolic diseases including: type 2 diabetes (T2D), obesity, hypercholesterolemia and metabolic syndrome (MetS). In 2017, the metabolism disrupting chemical (MDC) hypothesis (2) postulated that “environmental chemicals have the ability to promote metabolic changes that can result in obesity, T2D or fatty liver in animals including humans; these metabolic alterations may play an important role in the global epidemics of obesity, T2D and MetS.” MDCs exert their effects at low doses, may have non-monotonic dose responses, and may exhibit sexually dimorphic effects (2). Like maternal nutritional status (Barker’s hypothesis) and other endocrine disrupting chemicals (EDCs) such as diethylstilbestrol, MDCs may act at prenatal windows of susceptibility to promote disease onset later in life. This concept is now called the developmental origins of health and disease (DOHaD) hypothesis. The developmental origins of several metabolic diseases, including NAFLD, have been demonstrated for several pollutants including PFAS at least in model systems (2, 5). Proposed mechanisms include hepatic exposure-induced epigenetic changes and transcriptional reprogramming. In this issue of *Hepatology*, Stratakis, *et al.* present the first evidence implicating PFAS in the developmental origins of human liver disease.

PFAS are emerging chemicals of concern. Widespread use began in the 1970s for myriad industrial and household consumer applications including non-stick cookware (e.g., Teflon®); products that confer resistance to grease, stains (e.g., ScotchGuard®) or water; and firefighting foams. Some PFAS have been released into the environment, where they persist due to their high thermodynamic stability and resistance to degradation. PFAS have been called ‘forever chemicals’ due to their decades long half-lives. Human exposures typically occur through ingestion of contaminated water or food, although transplacental exposures occur (8). Most people from industrialized countries have detectable PFAS in blood (8). While the human health effects of PFAS require further investigation, several PFAS are MDCs associated with hypercholesterolemia, obesity, diabetes and liver disease in animal models and/or human studies (1–5). More recently, PFAS pollution has garnered considerable attention from community residents, scientists, government agencies and media outlets. This is related, in part, to the 2019 Hollywood feature film, ‘Dark Waters’, and the detection of higher-level PFAS contamination in drinking water near some US military installations and surrounding communities. The 2018 National Defense Authorization Act

authorized the Center for Disease Control and Prevention's Agency for Toxic Substances and Disease Registry (CDC/ATSDR) to investigate PFAS exposures and health effects (including liver injury) in communities near military bases or industrial facilities affected by contaminated drinking water. While these studies are ongoing, ATSDR has recently released scientific and clinical guidance on PFAS based on currently available information (8). The United States Environmental Protection Agency (EPA) has recently published research on PFAS and fatty liver disease (6), and federal maximum contaminant level standards are under development for some of these substances.

Thus, Stratakis, *et al.* present timely and relevant environmental health data. Their manuscript is the first linking prenatal PFAS exposures to subsequently increased liver disease risk (DOHaD) and possible NAFLD in a human cohort. Other results were consistent with the MDC hypothesis, suggesting possible mechanisms. These include: (i) an altered serum metabolome consistent with metabolic disruption; (ii) observable effects with low-level exposures; (iii) some non-monotonic dose responses; and (iv) sexually dimorphic effects. The increased liver disease risk was independent of obesity, suggesting that the hepatic effects of prenatal PFAS exposures were independent of any potential obesogenic effects of these substances. The observed alterations in amino acid and glycerophospholipid metabolism were similar to the groups' recent publication linking childhood PFAS exposures to pediatric NAFLD histologic severity (3).

While "Prenatal Exposures to Perfluoroalkyl Substances Associated with Increased Susceptibility to Liver Injury in Children" could have a transformative impact in the field, it may point only to the tip of the iceberg. The developmental origins of liver disease, as well as the broader field of environmental hepatology, warrant broader recognition and further investigation. While considerable resources are justifiably being diverted to address the ongoing coronavirus global pandemic, the timing may soon be right for the AASLD and its members to become increasingly involved with environmental health science research. Collaborative opportunities may exist with government organizations (e.g., NIEHS, EPA, CDC/ATSDR, etc.) already working in this area. Perhaps the National Institute of Environmental Health Sciences Translational Research Framework (9) could be applied to achieve environmental impact while promoting liver health. Interactions between environmental contaminants and traditional liver disease risk factors (e.g., diet, ethanol, viral hepatitis, etc.) require further investigation, and stronger disease biomarkers (e.g. histology or imaging) should be used when possible. Likewise, interventions to mitigate the adverse health effects of MDCs have recently been proposed (10), but the efficacy of these strategies specifically for the treatment of liver diseases warrants investigation.

Acknowledgements:

This editorial was supported, in part, by funding from the National Institute of Environmental Health Sciences (R35ES028373, P42ES023716, P30ES030283 and R21ES031510), the National Institute on Alcohol Abuse and Alcoholism (5P50AA024337) and the National Institute of General Medical Sciences (P20GM113226).

References:

1. Wahlang B, Jin J, Beier JI, Hardesty JE, Daly EF, Schnegelberger RD, Falkner KC, et al. Mechanisms of Environmental Contributions to Fatty Liver Disease. *Curr Environ Health Rep* 2019;6:80–94. [PubMed: 31134516]
2. Heindel JJ, Blumberg B, Cave M, Machtinger R, Mantovani A, Mendez MA, Nadal A, et al. Metabolism disrupting chemicals and metabolic disorders. *Reprod Toxicol* 2017;68:3–33. [PubMed: 27760374]
3. Jin R, McConnell R, Catherine C, Xu S, Walker DI, Stratakis N, Jones DP, et al. Perfluoroalkyl substances and severity of nonalcoholic fatty liver in Children: An untargeted metabolomics approach. *Environ Int* 2020;134:105220.
4. Bassler J, Ducatman A, Elliott M, Wen S, Wahlang B, Barnett J, Cave MC. Environmental perfluoroalkyl acid exposures are associated with liver disease characterized by apoptosis and altered serum adipocytokines. *Environ Pollut* 2019;247:1055–1063. [PubMed: 30823334]
5. Trevino LS, Katz TA. Endocrine Disruptors and Developmental Origins of Nonalcoholic Fatty Liver Disease. *Endocrinology* 2018;159:20–31. [PubMed: 29126168]
6. Das KP, Wood CR, Lin MT, Starkov AA, Lau C, Wallace KB, Corton JC, et al. Perfluoroalkyl acids-induced liver steatosis: Effects on genes controlling lipid homeostasis. *Toxicology* 2017;378:37–52. [PubMed: 28049043]
7. Cave M, Falkner KC, Ray M, Joshi-Barve S, Brock G, Khan R, Bon Homme M, et al. Toxicant-associated steatohepatitis in vinyl chloride workers. *Hepatology* 2010;51:474–481. [PubMed: 19902480]
8. Agency For Toxic Substances and Disease Registry: An Overview of the Science and Guidance for Clinicians on Per- and Polyfluoroalkyl Substances (PFAS) In. <https://www.atsdr.cdc.gov/pfas/docs/clinical-guidance-12-20-2019.pdf>; 2019.
9. Pettibone KG, Balshaw DM, Dilworth C, Drew CH, Hall JE, Heacock M, Latoni AR, et al. Expanding the Concept of Translational Research: Making a Place for Environmental Health Sciences. *Environ Health Perspect* 2018;126:074501.
10. Sargis RM, Heindel JJ, Padmanabhan V. Interventions to Address Environmental Metabolism-Disrupting Chemicals: Changing the Narrative to Empower Action to Restore Metabolic Health. *Front Endocrinol (Lausanne)* 2019;10:33. [PubMed: 30778334]

The Developmental Origins of Childhood Liver Disease

Figure 1: Prenatal exposures to the environmental pollutants, perfluoroalkyl substances (PFAS), were associated with metabolic disruption and increased risk for childhood liver disease.