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Invited Perspective: PFAS and Liver Disease: Bringing All the Evidence Together

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In this issue, Costello et al.[1] provide a meta-analysis for associations between per- and polyfluoroalkyl substances (PFAS) and human clinical biomarkers for liver injury. They simultaneously considered PFAS effects on liver biomarkers and histological data from rodent experimental studies. This integrative assessment addresses an important need.

Based on concordance between population and experimental findings, the authors concluded there is convincing evidence that perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), and perfluorononanoic acid (PFNA) are hepatotoxic to humans. The authors note that, although the exact mechanisms of toxicity are uncertain, they likely feed into pathways that induce nonalcoholic fatty liver disease (NAFLD)—a reasonable hypothesis, given the abundant literature concerning PFAS and lipid disruption. Others have called attention to the similarity of experimental PFAS-induced steatosis and human biomarkers following PFAS exposure[2,3]; Costello et al.[1] are the first to provide a needed methodical approach to literature-wide statistical assessment of liver data.

An important consideration is that the global epidemic of NAFLD is estimated to affect $\sim 25\%$ of the human population,[4] although this figure may still be an underestimation of the prevalence of early preclinical stages, which do not invariably progress.[4,5] Because the diagnosis requires clinical suspicion along with laboratory and imaging studies, and because it is formally made with invasive techniques, NAFLD is underdiagnosed and preventive opportunities are often lost.[5] The strong association of NAFLD to alanine amino transferase (ALT), the biomarker of choice in this systematic review by Costello et al.,[1] diminishes the possibility that population findings are attributable to unmeasured confounding by alcohol intake.[6] This work firmly puts PFAS exposure on the list of persistent pollutants, such as polychlorinated biphenyls,[7] that cause hepatotoxicity and whose mechanism is linked to steatosis.[8]

Global PFAS risk evaluations have sometimes minimized the potential importance of PFAS associations to liver (or lipid) biomarkers because the mean is still within the normal range, or because findings lack consistency.[9] Because of underlying experimental and human study design heterogeneity, the work by Costello et al.[1] conveys more about the consistency than the strength of association within and across species. Population research naturally features inconsistency, but this systematic review paints a picture of consistency of effect. We hope the totality of evidence will encourage thoughtful future use of characterizations of consistency or its absence.

Characterizations about the size and importance of biomarker findings are most logically framed as data. ALT in populations has a positively skewed distribution.[10] The adverse modification of this distribution with PFAS exposure is illustrated in the massive population evaluated by the C8 Health Project, wherein a 6% mean population-wide increase in ALT attributed to PFOA after multiple adjustments led to a 16% increase in above-normal ALT across five quintiles of PFOA exposure.[11] Further, as noted by Costello et al.,[1] experimental PFAS studies have documented adverse histological liver findings (often sex-specific) in the absence of large adverse changes in clinical biomarkers. From a public health perspective, changes in liver transaminases are consistently relevant to the health of populations and are also part of the algorithmic approach to liver disease diagnoses.[5,6]

Two recent papers underline the ongoing importance of PFAS hepatotoxicity. Developmental exposure to low doses of PFOA and GenX caused enhanced histological liver lesions, vesicular fat content, and insulin resistance in young adult mice on a normal diet in a sex- and dose-dependent manner, without altering serum ALT or aspartate aminotransferase (AST).[12] Further, an analysis of liver biopsy material from people undergoing bariatric surgery showed that some PFAS were significantly correlated with liver fat content, insulin resistance, and liver disease status in a sex-dependent manner.[3] As suggested by Costello et al.,[1] future PFAS research should report data on both males and females for the various health outcomes.

The conclusion that PFAS cause hepatoxicity in humans in no way contradicts the advocacy by Costello et al.[1] for needed research. Important knowledge gaps in the population literature include whether the documented higher transaminases, disruptions in lipid/bile acid metabolism, and higher uric acid represent PFAS-induced liver damage from steatosis per se or from some other liver processes. This damage will be difficult to study, because the diagnosis of NAFLD is seldom made during early disease.[5] Other important questions raised by this review are *a*) whether overweight/obese individuals and those with diabetes are more susceptible to PFAS hepatoxicity, *b*) which "replacement" or emerging PFAS can cause liver damage, and *c*) whether high vs. low doses cause different kinds of liver toxicity. GenX, a current replacement for PFOA, has shown significant hepatotoxicity in several recent experimental studies,[12–14] suggesting it may not be a safe replacement. A significant challenge will be deciding which of the multiple metabolic pathways altered by PFAS[13] are most important and predictive for induction of liver damage and for progression of liver disease, so that emerging PFAS may be screened for hepatotoxicity prior to entering the market.

Looking beyond these stated research needs, people living or working in communities with high exposure to PFAS want to know what can be done to protect themselves right now. For existing exposures, promising PFAS research suggests that lifestyle interventions, useful for NAFLD in general, may be helpful.[15] This work needs to be replicated, because affected populations are aware that the pace of our research is not addressing

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their legitimate concerns. The meta-analysis by Costello et al.[1] underscores the urgent need for further research and for immediate and reasonable public health action.

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