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RESEARCH ARTICLE

Invited Perspective. Per- and Polyfluoroalkyl Substances, Hepatotoxicity, and Liver Disease: Evidence and Clinical Responses

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ABSTRACT

Background: This perspective concerning hepatoxicity of per- and polyfluoroalkyl substances (PFAS) aims to provide a current understanding of the damage and reasonable clinician responses to the needs of concerned patients and affected communities.

Methods: Search strategy included PFAS and the following: human liver toxicity/disease; relevant biomarkers including transaminases, lipids, uric acid; predictive equations (for liver disease), liver imaging modalities, and histologic findings. Experimental data concerning liver outcomes and disrupted hepatic metabolic pathways was also reviewed. Recommended clinical approaches to patients and communities was sought in both the National Library of Medicine and relevant organizational websites.

Results: Several PFAS reliably cause adverse changes in human liver biomarkers, with strong consistency between human and experimental data. Adverse population changes include human transaminases, cholesterol and LDL cholesterol, and uric acid. This biomarker triad suggests that mechanisms and outcomes are or resemble metabolic associated steatotic liver disease, which is found across species following experimental PFAS exposure. Human imaging studies and sparse human histologic studies mostly support the inference that the toxicant damage is or resembles a pathway that can lead from steatosis to more serious stages of liver disease due to disrupted liver metabolism of fatty acids. Advice to patients and clinicians was reviewed from various agencies and nonprofits organizations including a committee of the US National Academies of Sciences, Engineering, and Medicine, and the nonprofit/university collaboration PFAS REACH.

Discussion: Converging lines of evidence indict PFAS as human (and trans-species) hepatotoxins and mostly support a metabolic associated steatotic liver disease continuum as the nature of the injury. Increases in abnormal transaminases and sparser imaging and biopsy findings support that the damage is clinically important and a contributing cause of a public health problem. It is still challenging to decide which of many definitively disrupted metabolic pathways is/are most important to the injury. Many PFAS in use remain virtually unstudied, a research and public health emergency. Simple clinical responses to the concerns of the most heavily contaminated patients and communities, which are within the capabilities of most clinical offices, are reviewed.

Keywords: Per- and polyfluoroalkyl substances (PFAS); Liver Diseases; Liver steatosis; Non-alcoholic fatty Liver disease (NAFLD); Alanine aminotransferase (ALT); review

Abbreviations:

alanine aminotransferase (ALT)
fibrosis-4 index for liver scarring/fibrosis (Fib-4)
homeostatic model assessment for insulin resistance (HOMA-IR)
metabolic dysfunction associated steatotic liver disease (MASLD)
odds ratio (OR)
nonalcoholic fatty liver disease (NAFLD)
US National Health and Nutrition Survey (NHANES)
NLR family pyrin domain containing 3 inflammasome (NLRP3)
per- and polyfluoroalkyl substances (PFAS)
perfluoroheptane sulfonic acid (PFHpS)
perfluorohexanesulfonic acid (PFHxS)
perfluorooctanoic acid (PFOA)
perfluorooctanesulfonic acid (PFOS)
toxicant-associated fatty liver disease (TAFLD)
vibration-controlled transient elastography (VCTE)

Introduction

Current evidence indicates that per- and polyfluoroalkyl substances (PFAS) are hepatotoxins and suggests that liver toxicity of PFAS is or resembles nonalcoholic fatty liver disease (NAFLD), now called metabolic dysfunction associated steatotic liver disease (MASLD). An exogenous environmental source of such toxicity is important for two reasons. MASLD is a rapidly advancing international epidemic, affecting an estimated 30 percent of the world's population.[1-3] The histologic phenotypes of the disease range from often subclinical steatosis to steatohepatitis, and may progress to fibrosis and cirrhosis. Despite increased awareness of MASLD as a source of morbidity and mortality, it is understood to be seriously underdiagnosed, especially in its earliest, most reversible phases.[2,4] Second, PFAS have become ubiquitous environmental toxins,[5] and can be detected in the blood of almost all humans (and wildlife species) from around the world.[6-8] Clinical understanding of the contribution of PFAS to liver disease provides opportunities for improved individual and population health.

PFAS are synthetic, multiply fluorine-substituted carbon compounds with enduring environmental persistence due to the strength of their carbon-fluorine bonds ("forever chemicals").[9,10] PFAS have myriad industrial uses and appear in household and personal products, including nonstick cookware, disposable food containers, water repellant garments, paint, carpets, drapes and upholstery, cleaning products, skin applications including cosmetics, sunscreens, and deodorants, ski wax and other waxes, as well as medications, medical devices and anesthetic agents.[8] Occupational groups (including firefighting, electroplating, coated paper and other coating product manufacture, and some hobbies) and residence in communities with contaminated water have the greatest exposure risks.[11,12] Nevertheless, PFAS are ubiquitous, present in numerous foods including vegetables, meat, and especially fish and seafood.[13] Migration from food packaging materials is an important and potentially avoidable source of exposure.[14,15] A number of PFAS are biomagnified in the food chain and bioaccumulative in species, including humans.[16] PFAS are also in household dust (including PFAS originating from surface applications and from topically applied cosmetics),[17,18] and are internal contaminants of almost all of humans internationally.[6,8]

Their chemical stability belies extraordinary biological activity. PFAS interact with numerous human nuclear receptors,[19,20] disrupt fatty acid metabolism,[21] and increase reactive oxygen species.[22] They cause immune dysregulation and endocrine disruption,[23-25] potentially explaining epidemiologic findings of increased risks of human carcinogenesis such as testicular cancer and kidney cancer.[26-29] They are associated with diminished bone mineralization,[30-32] a risk for osteoporosis, and with increased risk for bone fracture in longitudinal study.[33] Exposure is associated with hypertensive disorders of pregnancy including preeclampsia,[34-36] as well as population-level alterations in childhood growth and development.[37,38] Among the catalogue of risks, there is increasing evidence that PFAS accumulate in liver and that liver is a primary target organ for the toxic effects of PFAS.[39-41]

PFAS and Clinical Biomarker data of Liver Function: A systematic review of 23 relevant human studies in multiple geographies found evidence of adverse effects on liver enzymes and incorporated data from eight adult studies in formal meta-analysis of the historic longer chain compounds. Alanine aminotransferase (ALT), the most liver-specific of transaminase biomarkers, was adversely associated with long-chain PFAS exposure (for perfluorooctanoic acid (PFOA), representative z-score =6.20, p=0.001).[42] Adverse human population associations extend to other transaminases, as well as to the apoptosis biomarker cytokeratin 18 m30.[25,42,43] Transaminase

and other biomarker evidence of PFAS liver damage also pertain to children and adolescents.[44-47] Biological coherence is seen in parallel liver function and histologic data from toxicologic studies across species.[25,42,48-52]

The "C8 Health Project" addressed the topic of liver injury based on abnormal ALT values in a large adult population (n=47,092).[53] The population was exposed to widely varying levels of PFOA contamination in six contiguous water districts, from "background" levels of exposure in one unaffected area to very high levels of internal contamination, and also included exposed workers from teflon manufacturing. Using historic statistically-derived cutoffs (ALT>45IU/L in men, >34IU/L in women) a near-monotonic increase of abnormal value (Odds Ratio (OR) 1.10; (95% C.I. 1.07,1.13) was found for each additional unit of measured log serum PFOA after multivariable adjustments.[53,54] Trends for abnormal values were stronger in the overweight and obese, but the PFAS association to abnormal values was significant in all weight groups.[55]

PFAS internal exposures similarly affect total and LDL cholesterol, as well as uric acid including increased risk of hyperuricemia in studies of multiple populations, including children, adolescents, and adults including women during the menopausal transition.[25,42,56-64] The triad of higher liver enzymes, worse lipid profiles, and higher uric acid is the pattern of biomarker elevation also seen in populations afflicted by MASLD, notably in the setting of metabolic syndrome.[65,66] (NAFLD or MASLD has also been termed toxicant-associated fatty liver disease (TAFLD) when the contributing cause may be contaminant such as PFAS.[67]) Population researchers have sought evidence that PFAS hepatotoxicity is due to or resembles the progressive damage of MASLD, beginning with simple steatosis and progressing to hepatocyte inflammation, fibrosis and cirrhosis.

Prediction scores for MASLD combine several clinical and/or biochemical parameters in order to more accurately predict MASLD state. The fibrosis-4 index for liver scarring/fibrosis (Fib-4) has been used to predict population-wide hepatotoxicity of environmental and dietary exposures in general.[68,69] In US National Health and Nutrition Survey (NHANES) data, serum PFAS mixture was associated with worse Fib-4 scores but not with the (NAFLD) liver fat score; the pattern of findings suggested that the risk was more closely related to fibrosis than to steatosis.[70] In contrast, the hepatic steatosis index developed specifically for Asian patients was used to evaluate 546 newly diagnosed acute coronary syndrome patients in Hebei Province, China. The study detected linear associations of serum perfluorooctanesulfonic acid (PFOS), perfluorohexanesulfonic acid (PFHxS), and total PFAS to the predictive index at PFAS serum exposure levels considered representative of the Chinese population (median PFOS was 5.59 ng/mL, serum concentrations of other PFAS were lower).[71]

Before accepting predictive equation data for steatosis vs fibrosis at face value, understanding a complexity of serum PFAS concentrations may be helpful. PFAS are bound in vivo to albumin,[72,73] and serum PFAS concentrations are predictably lower in those with low albumin and especially lower when there is microscopic albuminura.[74] Further, liver diseases including MASLD increase the risk of albuminuria.[75] The (NAFLD) Liver Fat Score and Hepamet Fibrosis score, which incorporate serum albumin as a predictive factor, may therefore suffer from attenuation bias when the population-wide goal is to interrogate the specific causation role of PFAS. The Fib-4 score and the Asian Hepatic Steatosis Index, which do not incorporate albumin in their predictive equation, may therefore be more likely to be useful in PFAS settings and showed associations to steatosis as well as fibrosis.[70,71]

PFAS and Liver Imaging data: In clinical settings, suspected MASLD can be diagnosed with abdominal ultrasound, magnetic resonant imaging or computerized tomography, or increasingly with vibration-controlled transient elastography (VCTE), a specific ultrasound technique that uses a mechanically generated shear wave and liver fat to predict liver stiffness.[76] Harvard University investigators interrogated NHANES 2017-18 data for the subpopulation with both serum PFAS measures and results of VCTE (n=1,135). Evidence of MASLD (n=448) was based on a controlled attenuation parameter (CAP, or fatty change) score ≥285 dB/m (a score representing high degree of fatty liver change) and a high likelihood of fibrosis with liver stiffness measurements ≥8.6 kPa.[77] Significant associations to CAP scores (per log transformed standard deviation increase in PFAS) were found for PFOA and for PFHxS (OR 1.13; 95% C.I. 1.01-1.26) with stronger associations present for those with the comorbid risk of heavy alcohol intake (≥2 drinks/day for women and ≥3

drinks-day for men)). Associations were also stronger for obese participants.[77]

PFAS exposure was also associated with imaging evidence of MASLD in children. In a study of 244 NHANES adolescent participants, 41 met CAP score criteria for MASLD.[78] Perfluoroheptane sulfonic acid (PFHpS) was significantly associated with MASLD, and most ORs for other PFAS were >1 but not statistically significant.[78]

PFAS and Liver Biopsy and Histology data: Liver biopsy remains a key method for diagnosing MASLD and for grading and staging disease severity. Experimental data across species show that PFAS reliably induce lipid droplet accumulation and steatosis in hepatocytes.[25,79,80] High fat diet combined with PFAS exposure increases the experimental hepatoxicity.[81] Explanations for steatosis seen across species have been proposed based on experimental data in vivo and in vitro. These include (and are not limited to) activation of NLR family pyrin domain containing 3 (NLRP3) inflammasome, multiple nuclear receptor activations disrupting glycerophospholipid metabolism and shifting the hepatocyte response from fatty acid oxidation to hepatic triglyceride accumulation, disruption of gut microbial metabolites, triggering of Wnt/ß-catenin/NFKß signaling, induced insulin resistance possibly by alterations in the phosphatidylinositol-3 kinase pathway, and disruption of microRNAs and chemical composition of liver extracellular vesicles.[40,56,82-89]

Human biopsy-based studies concerning PFAS and nonneoplastic liver disease are likely sparse because the procedure carries a risk of bleeding and is generally reserved for serious cases in which the result of biopsy would also affect management.[90] Among 74 children with biopsy-proved MASLD, higher serum PFAS (per each interquartile range) and especially higher serum PFHxS were associated with increased risk for nonalcoholic steatohepatitis (NASH, OR: 4.18, 95% CI: 1.64-10.7), lobular inflammation (OR 2.87, 95% CI: 1.12-7.31). and higher (NAFLD) activity score (β-coefficient 0.46; 95% CI: 0.03, 0.89).[91] A contrasting study of 161 morbidly obese adults within a bariatric surgery population found serum PFAS to be inversely associated with evidence of hepatocellular inflammation.[92] The authors noted similar inverse associations to polychlorinated biphenyl (PCBs) and hexachlorocyclohexane, and discussed whether impaired enterohepatic circulation following surgical procedures for obesity could lead to decreased retention of long half-life serum pollutants such as PCBs and PFAS in the morbidly obese, explaining the inverse results.[92] A French study of 100 biopsy proven NAFLD patients measured 17 PFAS and found and perfluorododecanoic acid (chain length C=12) was associated with significant fibrosis and perfluorohepatanoic acid with advanced fibrosis.[93] The importance of these isolated findings in the context of multiple comparisons will need further study. In a cohort of 105 individuals already known to have biopsy-proven NAFLD, serum PFAS concentration was associated with bile acid and lipid metabolic pathways, and with population clinical variables such as liver fat content, and with homeostatic model assessment for insulin resistance (HOMA-IR) in females.[94] The authors reported similar findings in including sex-specific differences in hepatocyte lipid content in a murine model.[94]

For the related topic of liver cancer, a case-control comparison of 50 incident hepatocellular carcinoma (HCC) cases and matched controls nested within the longitudinal Multiethnic Cohort Study population found that high serum PFOS concentrations (>55ug/L, a high contamination level that pertains to <1% of the population) was associated with 4.5-fold increase in the risk of HCC (95% C.I. 1.2-16.0).[95] This finding is based on small numbers, and did not visualize an effect when exposure was evaluated as a continuous variable, pointing to possible non-monotonic effects. In addition, a lifetime exposure model cohort within the C8 Health project (with a still smaller number of liver cancer cases) did not dichotomize low versus high exposure and detected no relationship to HCC for the related compound PFOA.[96] The authors of this PFOA study discussed the potential for underestimation bias when the lifetime exposure enrollment model begins with a survivor cohort of an often lethal cancer.[96]

Discussion of Current Knowledge, Literature Gaps, and Research Needs for PFAS and Liver Disease.

Mechanisms of PFAS hepatoxicity: Historic "long-chain" PFAS such as PFOA, PFOS, and PFHxS are consistently associated with adverse changes in a variety of human clinical biomarkers of liver toxicity and also with predictive equations for MASLD in humans.[25,42,54,55,58,70,71] There are parallel confirmatory experimental findings of consistent presence of steatosis and disruption of lipid and uric

acid metabolism across species following PFAS exposure,[25,42,97,98] although reproducing the specific experimental finding of higher serum cholesterol requires attention to species, dietary conditions, and can benefit from additional investigation of 'humanized' models for energy handling.[19,99-101] Multi-omics approaches identify suspect mechanisms, including (and not limited to) disruption of the pentose-phosphate shunt and compromised fatty acid signaling and degradation pathways,[102,103] and disruption of bile acid handing with dysregulated glucose metabolism pathways.[94] Thus, experimental data firmly support and human population data including biomarkers, imaging, and liver biopsy mostly support that the liver damage of PFAS exposure is likely consistent with or similar to a steatosis mechanism, while the extent of the damage and the most important pathways (out of multiple candidate pathways suggested in the literature) are only partially amenable to human population exploration with biomarker findings.

Imaging for liver steatosis and fibrosis: Emerging human imaging VCTE data also support a PFAS exposure effect on steatosis and inflammation/fibrosis as indicated by CAP scores in NHANES data.[77,78] The initial introduction of VCTE data to the 2017-2018 NHANES cycle, after more than fifteen years of population declines in historic long-chain serum PFAS levels (such as PFOA and PFOS), means that investigations using this resource are limited to a narrower exposure range than many previous studies. The research gap of few available studies and a narrow range of exposure means that similar studies in populations with a wider range of exposure and longitudinal study design are desirable.

Progression and severity of liver disease in humans: While experimental data across species support a role for PFAS increasing the risk and severity of MASLD, sparse human biopsy data are conflicting. Associations to liver disease progression in at-risk children,[91] conflict with inverse associations to lobular inflammation in a bariatric surgical population for adult morbid obesity.[92] A suggested role for inverse causation due to enhanced excretion patients with altered gut anatomy and disrupted enterohepatic circulation following bariatric surgery could explain the inverse adult association.[92] Medications such as cholestyramine that disrupt enterohepatic circulation do markedly decrease serum PFAS,[104] so the proposed explanation is plausible, but unproved. An intriguing study in a high exposure worker population found that modeled cumulative PFAS exposure in a region with serious contamination was associated with both liver cancer and liver disease mortality, but conclusions are tempered because comorbid risk factors (such as alcohol) could not be measured and the extent of histologic clarification of cirrhosis deaths is uncertain.[105] PFAS-associated disrupted metabolomic pathways in a cohort proven to have NAFLD, along with greater steatosis in the females, support a role for these toxicants in either the origin or the exacerbation of liver disease.[94] Finally, PFAS and human liver cancer data are intriguing but conclusions cannot be drawn.[95]

Research gaps: 1) To what extent do PFAS initiate early stages of liver disease, and to what extent do they contribute to disease progression? Early stages of MASLD are greatly underdiagnosed, while more severe MASLD (and other diseases with late stages characterized by serious morbidity and mortality) face serious study design challenges including enrollment bias and underestimations.[4,96,106-108] Case-control imaging studies nested in existing longitudinal populations with historic, wider-ranging PFAS measures hold some hope for providing an early answer to this question. 2) What can we learn about the risks of PFAS in understudied populations, including populations with higher a priori risks of liver disease such as native Americans, LatinX, and Indian subcontinent populations and environmental justice communities? 3. How do lifestyle and individual risk factors interact with the risk of PFAS? It is understood that risk intervention approaches to diet and exercise decrease morbidity and mortality in steatotic liver disease in general,[109,110] and preliminary but far from extensive experimental and population evidence suggests that appears to be the case for PFAS.[87,111,112] In addition, there are already important hints in the literature that the risks of PFAS and alcohol or obesity may be additive, and we need to know more. 4) Which of many experimentally-supported mechanisms for hepatoxicity are most important? The bewildering biological activity of these chemically stable compounds gives the problem of multiple signals; identifying the most important from multiple candidates is a need.

Hepatoxicity of PFAS "replacements," an overarching research gap: Proliferating "replacement compounds" are generally PFAS with shorter carbon chains and shorter half-lives. These are increasingly present in food, water, soil, and

humans.[113] These replacements may not be bioaccumulated. Convenient serum biomarkers as surrogate representatives of exposure are often unavailable and exposure estimates are therefore complex. Human studies addressing the hepatotoxicity of compounds with short half-lives are sparse, needed, while after-the-fact exploration of hundreds or thousands of compounds is inadequate to the task of protecting the public. For PFAS in current or contemplated use, the pace of industrial development in critical industries and proliferation of introduced compounds will exceed the available funding for research. The hope that replacement compounds will reliably and sufficiently be less hepatotoxic than predecessor compounds is a slender thread for hanging consequential decisions about environmentally persistent compounds that find their way into water, food, and household dust, especially considering the known hepatoxicity of analogous compounds. Replacement compounds can demonstrably share characteristic toxicity risks with better-studied predecessors and may in some cases augment or even add risks not previously recognized.[85,101,114-121] Policy debates in the absence of reliable predictive data are problematic. The expanding knowledge of unfortunate outcomes for the compounds we already know, and the strong likelihood based on experimental findings that many replacement compounds will adversely affect humans (and other species), deserve substantial scrutiny. Understanding which mechanisms are most important to liver disease is critical if there is to be hope of using experimental studies for policy decisions concerning which (if any) of these enormously useful compounds are relatively safer and safe enough.

A research facilitation need is clear in all circumstances and potentially acceptable to most industrial manufacturers and PFAS users. Secrecy regarding PFAS molecules in production and use needs to end. Delayed recognition that these too have been released to the environment, as well as the disinformation tactic of artificially high detection limits as public reporting values, can only increase suspicion, increase adverse effects, and increase downstream healthcare consequences and environmental clean-up costs, with associated potential liability across domains of cost and reputation of manufacturing and user industries. The pace and efficiency of research will improve and public distrust will decrease when environmental pollutant reporting and detection strategies keep pace with new PFAS-reliant processes and pollutants.

Roles and responses of clinicians

Clinicians may not have to become expert in yet another topic with its own rich literature in order to interact successfully and safely with patients concerned about PFAS exposure. Trust with the concerned patient can be built by the simple acknowledgement of the substantial evidence of PFAS toxicity without committing to specific outcomes if the clinician is not knowledgeable. For liver toxicity, the topic of this perspective, the evidence is quite strong.

Second, exposure concerns of patients such as those living in contaminated communities, or in specific occupations or avocations, or even those with specific diets (such as high consumption of freshwater species) can be acknowledged. These patients and communities may also want specific data about their internal contamination. A committee empaneled by The US National Academies of Science, Engineering, and Medicine (NASEM) at the request of the US Centers for Disease Control and Prevention (CDC) has provided open source (https://nap.nationalacademies.org/catalog/26156/guidance-on-pfas-exposure-testing-and-clinical-follow-up) clinical guidance for this circumstance, encouraging clinicians to inquire about exposure.[122] This begins with a conversation aimed at determining how a patient might be exposed to PFAS. The exposure assessment includes consideration of dietary exposures, local advisories that might include fish, game, or water contamination, and an occupational medicine consultation if there is a work component. (From experience, we also recommend a consultation with a consultant who is comfortable with broader environmental topics, such as an occupational physician, when clinical time or expertise is unequal to the task of an exposure history.) NASEM then recommends offering PFAS testing to patients whose history suggests elevated exposure.[122] Considerations for this recommendation will include when and if exposure ended, as most elevations in blood levels will be gone or greatly diminished after 3-4 half lives. However, experience suggests that residents in exposure communities can remain anxious if merely reassured in the absence of data. The considerable problem of the cost of testing if there is no payment source, and potential difficulty of finding a collaborating laboratory, can make

PFAS internal contamination testing a difficult task from patient and clinician perspective. From experience, when patients who may be in high exposure groups seek testing, clinical attempts to remove barriers to testing support patient autonomy and sense of well-being.

What about risk mitigation? NASEM guidance includes a lipid panel for patients whose summed serum PFAS is higher than 2ng/mL one time commencing ages 9-11, and once every 4-6 years after age 20, with recommendations that dyslipidemia testing could begin as young as age 2 for patients with ≥20 ng/mL summed serum PFAS levels.[122] Recommended minimum ages and periodicities for preventive screening tests are characterized by national variations, and comorbid risk factors such as obesity can influence thinking. The reasonable goal is to reduce risk, not to rigidly follow helpful recommendations which are intended to be general. Although lipid screening tests are recommended in many countries for all patients, it is known that many do not get tested in some nations,[123] and the concern for PFAS testing can be a 'teachable moment" in the clinician-patient relationship that improves performance for lifestyle interventions and medication adherence.

NASEM does not make additional recommendations about other aspects of PFAS and liver disease for the individual, and is also clear that such testing is not precluded but instead the outcome of clinician-patient discussion.[122] PFAS-REACH, a US federally funded collaboration of several nonprofit organizations and universities led by Silent Spring Institute does recommend consideration of liver disease for high-PFAS exposure populations. The medical screening recommendations can be found at the PFAS Exchange Resources page website (https://pfas-exchange.org/resources/) and includes transaminases for highly exposed patients.[124]

Limited yet demonstrably useful lifestyle interventions characterize our current responses to early stages of MASLD and are equally appropriate when PFAS are part of the risk picture, and they have known favorable risk profiles. These include lifestyle modifications and targeted weight loss, physical activity, and dietary changes. As with lipid management, which is more likely to engender early pharmacologic therapy, the natural patient concern about PFAS and liver disease is a potential motivator. Its additional contribution to liver risk factors may improve the patient-clinician success in the rewarding but difficult topic of lifestyle intervention to prevent advancement of MASLD. It may further be useful to patients to know that there is preliminary yet unsurprising evidence that exercise, for example, decreases risks for PFAS and liver-related topics in adolescents.[125] Dietary changes that are well-understood to be first-line interventions for reducing the risk of hyperlipidemia and MASLD in general, such as high fiber diet, can also modestly reduce PFAS uptake and increase PFAS excretion.[111,126,127] Pharmacologic treatments are generally reserved for those with who have evidence of steatohepatitis or fibrosis,[2] although obesity is increasingly a pharmacologic target of its own in some countries.

Patients may inquire about means to hasten excretion of these bio-persistent chemicals with their long half-lives. Although PFAS exposures are ubiquitous and unavoidable, they can be decreased by food and personal product mindfulness such as avoidance of freshwater fish from contaminated regions, avoidance of prepackaged foods with nonstick wrappers, and consideration of which of the numerous personal and household products contain PFAS. Detailed exposure reduction advice is available from NASEM,[122] and excellent succinct consumer advice is available from many reliable consumer sites. Concerning more aggressive means of PFAS excretion, a clinical trial in firefighters showed that each successive serial phlebotomy provides modest decreases in serum PFAS.[128] From experience with patients from the most affected communities, self-nomination as a regular voluntary blood donor has been a logical and likely cost-effective patient response to internal contamination, although also an ethical topic not addressed by blood donation agencies since the blood PFAS is directly transferred to unknown recipients. One affected community appears to be considering a coordinated phlebotomy approach to decreasing serum PFAS.[129] Bile acid sequestrants such as cholestyramine appear to greatly enhance excretion of PFAS and especially sulfonate PFAS such as PFOS,[104] and may be reasonable considerations with an uncharacterizable risk/reward profile, especially for patients who also need a secondary lipid lowering drug.

Finally, clinicians can add PFAS to their list of known public health concerns, and provide advocacy for steps that reduce environmental releases or dietary and personal exposures. Clinicians can advocate for resources that support delivering uncontaminated water where PFAS have already

infiltrated source water, and that mitigate risks in those already exposed.

Conclusion:

The ubiquitous environmental and internal contaminants PFAS are definitively hepatotoxic to humans (and other species). This is shown by consistent alterations in liver enzyme biomarkers across experimental species and in numerous human populations, with convincing meta-analysis findings.[42] The toxicity either is or resembles MASLD, as shown by a triad of biomarker data including transaminases, cholesterol and LDL cholesterol, and uric acid; by emerging liver imaging data;[77,78] and by sparser and not fully consistent biopsy data.[91,94] Experimental studies show that a number of pathways are affected.[25,39,42,56] Clarifying which of these pathways is most important is a consequential research need because "replacement" PFAS (which are also "forever chemicals") are being introduced into use, and therefore into the environment and into humans (and other species) at a rapid rate.[7,8,10,130] Predictive studies of which, if any, may be nontoxic to the liver are essential. Trade secrecy delays recognition of environmental releases and is societally expensive. There are several roles for clinicians including public health advocacy for clean water and medical care of exposed workers and residents of contaminated communities. It is not necessary for clinicians to become PFAS experts to follow the simple PFAS avoidance and monitoring guidance presented by the several authoritative websites provided in the text. A healthy high-fiber low-meat diet can decrease exposure and enhance excretion, and unhealthy foods often have more PFAS (and freshwater fish from contaminated areas and some seafoods are examples of generally healthy foods that can contain more PFAS). Specialists can provide additional discussion concerning enhanced excretion. PFAS exposure causes liver damage, and it may also provide those so affected with an additional motivation for early and safe interventions which decrease risk.

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Conflict of Interest

Alan Ducatman has been paid as a consultant to attorneys for the citizens of several cities who have received medical monitoring benefits attendant to PFOA contamination of drinking water.
Lida Chatzi has no conflicts to declare.

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