

Dr. Suhair Shallal  
Designated Federal Officer  
Science Advisory Board Liaison for Environmental Protection Agency Scientific Advisory Board PFAS  
Review Panel Docket

Pursuant to FRL 9222-01-OA

Dear Dr Shallal and PFAS Review Panel Members:

I am Alan Ducatman, MD, MS, board certified in Internal Medicine and in Occupational Medicine. I am a long-time consultant for “Best Doctors in America,” recipient of awards from my professional society, a former member of the American Board of Preventive Medicine (ABPM), which designs the process leading to board certification in Occupational Medicine and Preventive Medicine, and a former member and chair of the Residency Review Committee in Preventive Medicine. I have been a member and chair of the Board of Scientific Counselors for the Agency for Toxic Substances and Disease Registry (ATSDR).

I am also a PFAS clinical researcher, with more than 30 peer publications concerning PFAS exposure and health effects, including emphasis on the relationship of biomarkers to clinical population outcomes.. I have provided invited PFAS presentations in multiple venues including hospital grand rounds, professional society meetings of clinical and toxicology colleagues, for water management colleagues, to ATSDR, the US Government Accounting Office, and to a committee of the US National Academy of Sciences, Engineering, and Medicine (NASEM).

Clinicians provide their conflicts of interest. I have been a paid and volunteer consultant to communities seeking redress from PFAS water contamination, with emphasis on obtaining clean water and evaluating the desirability and implementation of medical monitoring following internal contamination from water sources. Notwithstanding that conflict, my research is straightforward and continues to document either the presence or absence of health effects from PFAS exposure, depending on the data.

This letter has two purposes.

1. I wish to provide support for the general conclusions concerning derivation of a Reference Dose that will be used in development of a Maximum Contaminant Level Goal (MCLG) for PFOA (CASRN 335-67-1) in the recently released draft document. The Reference Doses reached are supported by the science. They correctly identify the presence of plausible human hazard at very low levels of exposure. Implementation of regulatory approaches will need to carefully consider feasibility of reproducibly measuring contamination and actually cleaning delivered drinking water to affected populations. Actual attainment of cleaner water is the goal, and how to set a standard that delivers maximum benefit from attainable and sustainable technologies will require planning across disciplines. The MCLG is science-based. What the science behind the MCLG means for enforcement and investment will be an important exploration. I hope a conclusion can be reached expeditiously. Exposed populations need the support.

2. The two new draft documents contain problematic assertions and incomplete reviews. With limited time, I have responded to a specific topic, the relationship of PFOA exposure to hepatotoxicity. I think more attention could be given to PFOS and liver toxicity, and to noncancer kidney toxicity in both documents. However, I support EPA's choice of a sensitive human endpoint other than hepatotoxicity as the basis for the PFOA Reference Dose. However, because EPA is a trusted source of information on health risks of environmental contaminants, it is important that misunderstandings, misleading statements, and unsupported assumptions and conclusions be addressed by document reviewers. The following sections of this letter provide details about the discussion of hepatotoxicity of PFOA in the draft document and suggestions for reconsideration. Additionally, EPA ought to be aware that the state of California (California Office of Environmental Health Hazard Assessment, 2021) used liver endpoints as the basis for a PFOA Reference Dose to be used for a health-based drinking water value. In general, the California document may be useful to the US Environmental Protection Agency (EPA).

### **3.3.3 Human Evidence for Hepatic Effects of PFOA:**

Summary: the liver discussion appropriately contains both human and experimental data sections. Both human and experimental sections have mostly reasonable factual data but each suffers from consistent confusion between the goal of choosing a different endpoint, which is acceptable, and the inappropriately expressed need to dismiss the science and current understanding of hepatotoxicity following PFOA exposure in order to emphasize a different endpoint. In pointing out that there is more or more easily useable evidence for some other human health outcome in the development of reference standards, the current EPA verbiage concerning liver outcomes is problematically misleading. First, hepatotoxicity in children is different than hepatotoxicity in adults in one specific way. If the insults are chronic and not acute, the findings are far more likely to be seen and likely to be consistent in adults. Second, a reader of the current draft document and its summary might not understand that independent, medium-to-high-confidence adult studies looking at alanine aminotransferase (ALT) consistently show higher ALT levels in association to PFAS exposure, and that this finding is further consistent with multiple lines of experimental evidence and also consistent with other lines of human evidence, such as the lipid data in populations. The reader also might not understand that elevated ALT in a population is indeed reliable and widely accepted

evidence that the population has sustained clinical damage to liver function. These problems then pervade the document subsections.

#### **Concern about the summary 3.3.3.1.3 Summary Population Findings:**

First, the distinction between adult and childhood studies should be clearer. Liver disease from chronic exposures is present in either adults or children, but temporally easier to find in adults because the development of liver disease from chronic exposures takes time and pertains to larger population subsets. Adult studies in independent hands show that ALT is reliably related to PFAS exposure. In particular, because steatosis or “fatty liver” is the underlying and verifiable histopathological finding across exposed animal species, reviewers are asked to consider the time that finding takes to develop in humans and how much more likely it is to be seen in adults. (Well done studies do show the outcome in children. It simply requires much more attention to study design.) Accordingly, I have focused my comments on the adult studies because the goal is to show that PFAS do indeed cause hepatotoxicity.

For adult studies, the landmark Darrow et al (2016) study with its longitudinal component, model of cumulative exposure, tens of thousands of participants, inclusion of both workers and residents, and most importantly featuring a broad range of PFOA exposure from background levels to very high levels of exposure, is confusingly compared to a study with a different design and range of exposures (Jain and Ducatman, 2019).

A reader of this section of the EPA document might believe that the results of the (Jain and Ducatman 2019) contradict the study by (Darrow et al., 2016). There is no contradiction, since the Jain and Ducatman study investigated the relationship between PFOA and ALT at the far lower general population range of exposure (in NHANES data) and considered the impact of a comorbid risk factor in a way that was different than in the Darrow et al. (2016) study. The population in the Jain study was a fraction of the size of the Darrow et al. study, and, additionally, it did not have a longitudinal component and a cumulative exposure component. The more important difference is that Jain and Ducatman carefully emphasized that their work was about the levels of PFAS in the recent NHANES dataset. "...Recent Low Exposures..." is even in the title of the publication. It is this limited range of exposure in NHANES data, which comes from the general population, compared to C8 population data, which comes from communities with elevated exposure from drinking water, that explains the difference in findings. The language in the draft EPA takes the finding of additional risk in a susceptible population and somehow

leaves the impression that that the identification of a comorbid susceptibility somehow contradicts to the Darrow et al. (2016) study. Both studies find the essential relationship, while the Jain and Ducatman study had no means to follow it to higher dose exposures. The tables and figure in Darrow et al (2016) demonstrate the importance of the capability to compare high and low exposure groups.

In addition, the discussion in the draft EPA PFOA document can lead the unwary reader to conclude that there is a difference regarding the impact of obesity as a comorbid risk factor between Jain and Ducatman (2019) and (Darrow et al. 2016). It is the additional susceptibility of the overweight and obese, and not the basic relationship of PFAS to higher ALT across all stratifications of body mass index (BMI) that needs replication. This was investigated in the Jain and Ducatman (2019) study but not by Darrow et al (2016). Such investigation is an easy target for future research but does not reflect on the basic point. The ALT association is present in large studies by independent researchers, including Jain and Ducatman (2019), and clearest when there is a wide range of population exposure.

EPA has asked for additional studies that it may have missed. EPA should consider the increase in ALT related to PFAS in Yamaguchi et al. (2013), a paper which is not cited in the draft EPA document. This cross sectional study recognized in 2013 an important point that is not clear from the EPA review. The undesirable liver transaminase findings and the undesirable increased lipid findings in relationship to PFAS exposure were both noted in (Yamaguchi et al. 2013). The authors understood that the transaminase and lipid findings are related rather than separate considerations. They both reflect evidence of clinically important liver damage. This point appears in reviews such as in (Fenton et al. 2020) but is not acknowledged in the EPA draft document, which questions the clinical significance of liver damage for reasons that are unclear. The need to account for and better integrate the multiple lines of human population evidence of liver toxicity with the multiple lines of experimental evidence of human toxicity is presented in more detail below.

The idea that we need more demonstrations that higher ALT will lead to more ALT above clinically relevant cutoffs is expressed in the EPA document. It ignores that there is already more than one demonstration and more importantly it ignores that the relationship is a mathematical function. If ALT is elevated, more ALT will above a cutoff will be detected in a sufficient size population. Further, the number above the cutoff will be greater if more appropriate clinical cutoffs are used. Details are presented below.

### **3.3.3.2 Animal evidence**

### 3.3.3.2.3 Histopathology and 3.3.3.4 Evidence integration

In general, the sections on animal evidence should more clearly discuss that abnormalities consistent with steatosis and even steatohepatitis are found in multiple animal species after PFOA (and PFOS) exposure, including vacuolization, lipid droplets, both pathway and ultrastructural evidence of interrupted bile acid metabolism, and other histopathologic findings. The consistency of these findings with the consistently recorded higher ALT associated with PFOA (and PFOS) in human population studies should be noted more clearly. The deleterious liver enzyme (such as ALT) findings in humans and animals are also consistent with deleterious uric acid findings in humans and animals and especially with deleterious cholesterol findings in humans and the best designed animal studies. (That is, when the right animal models is used by independent researchers, the increases in cholesterol seen in humans are also seen in animals.) Awareness of the individual relationships is already partly but not fully addressed in the EPA draft document. The important point is that their interrelated and clear relationship to liver toxicity should be included. Disrupted cholesterol metabolism is not instead of liver toxicity, it is direct evidence of liver toxicity.

The following summary sentence about ALT in the EPA draft document is misleading in two ways. ***“However, the associations were not large in magnitude, and it is unclear whether the observed changes are clinically adverse”*** (p.147, EPA draft document for PFOA). The two concepts contained in this sentence are misleading for the assertion that the changes associated with PFOA are small, and incorrect for the assertion that there is an absence of clarity concerning clinical adversity of these changes. A discussion of why these assertions are misleading and/or incorrect and why the basic summary needs to be rewritten follows:

- The EPA draft document acknowledges that adult population studies by several different researcher groups reveal the association of PFOA and abnormal liver transaminases, notably but not exclusively ALT. The study best able to characterize the average percent change in ALT is Darrow et al. (2016 ). The fully adjusted longitudinal model resulted in a 6% increase from the lowest to highest quintile of PFOA exposure, and other studies show similar increases. This ALT increase is for a single contaminant in a population that has been considered with multiple adjustments for other risk factors. I am a clinician and have spent a career mitigating effects of toxic exposures. From a clinical population perspective, this population effect is remarkable and thought-provoking, not “small” as EPA has characterized in its draft. The clinical purpose of the ALT test is to compare the outcome to the normal range. For several reasons (Sherman 1991), a

6% population-wide increase will predictably move more than 6% of the population outside of the normal range and have an outsize effect on those above any chosen cut-off for several mathematical reasons that will apply across populations, just as was seen in Darrow et al. (2016), who also reported a 16% increased risk of above-normal ALT (45 IU/L in men and 34 IU/L in women) from the lowest to highest quintile of PFOA exposure. Further, the total number affected will increase if more modern, lower ALT cutoffs are used, a point discussed in more detail under the discussion of ALT normal ranges (below).

- The EPA draft document (p. 147) makes the point that the Darrow et al. findings concerning increased risk of above-normal ALT are not replicated in other studies, implying that the finding may not be reliable. Here is the misleading sentence: ***“One study reported higher odds of elevated ALT with PFOA exposure (Darrow, 2016), but due to the lack of this type of analysis in other studies, it is not possible to assess consistency.”*** This reservation is incorrect because it ignores a parallel finding from Gallo et al. (2012), and it is also mathematically naïve. It is unclear why the EPA document does not mention that Gallo et al. (2012) also reported an association of PFOA with an increase incidence of exceeding the cutoff values for ALT. The 16% increase in above cut-off values from the Darrow et al. (2016, 3749173) longitudinal model is larger than the 10% increase based on cross-sectionally measured associations reported by (Gallo et al. 2012), and it is likely more reliable based on a more robust study design in the reenrolled study subpopulation followed by Darrow et al (2016). (EPA appears to have made a decision to include only recent evidence. It is up to the review committee if this is acceptable. From a clinical perspective, provided studies meet quality metrics, it is indefensible.) The increases of 10-16 % in those considered abnormal with the normal/abnormal cut-offs applied to ALT (45 IU/L for men and 34 IU/L for women) in Darrow et al. (2016) and (Gallo et al. 2012) are important for cost, burden of disease, and clinical understanding by treating clinicians. These findings in two studies (derived from the same population but with different total enrollments, models, and time periods) are an indication that the association of PFOA with clinically defined elevated ALT is well established. Furthermore, the increase in individuals above a chosen clinical cut-off is a mathematical function. Provided the underlying association exists, the outsize effect on cutoffs is predictable. Although the percent increase in individuals with ALT above these cutoff values was not evaluated in the other populations with reported associations of PFOA and increased ALT, it will inevitably recur and be replicated if studied in populations showing the association. That is, other populations with similar ALT increases will still operate within the realm of mathematics for cut-offs. The EPA

draft supposition that the clinical implications might be mathematically different for other populations with similar elevations in ALT is not based on a clinical understanding of the population science. Further, the Darrow et al (2016) and Gallo et al (2012) understate the impact, as noted below.

- The lab normal/abnormal cutoffs of 45 IU for men and 34 for women used by Darrow et al., (2016) and (Gallo et al. 2012) are actually conservative understatements. They are based on antiquated (albeit still reported) “lab normal” values, which vary among laboratories and which are statistically and not clinically derived. They are historical artifacts and unrelated to modern guidelines for ALT cut-offs used for the purpose of early detection or following of incipient liver diseases, especially those due to steatosis. Modern guidelines from authoritative medical professional organizations such as those of the American College of Gastroenterology (ACG) and the American Association for the Study of Liver Disease (AASLD) use lower cutoffs (Kwo, Cohen and Lim 2017, Park et al. 2019). For example, the ACG cutoffs for the normal range are 29 to 33 IU/l for men, 19 to 25 IU/l for women, as stated in in the next bullet, and the AASLD cutoffs are lower still. These lower cut-offs will identify greater (not smaller) numbers for clinical consideration and counseling based on very real risks, and they will show a larger impact of PFOA on the total number and even the percentage above population cutoffs (that is, a larger number of individuals will be in the group deserving consideration for further evaluation based on guidelines. For clinical reasons related to comorbid risks, this is more likely to occur in the obese. (It is not at all surprising that Jain and Ducatman (2019) showed that the ALT association is higher in the obese, but the finding should indeed be replicated. (No reader should think that the greater association in obesity suggests that the overall association is due to confounding. That has been investigated in multiple studies and is not the case.) Furthermore, the increase in the already substantial burden for the entire population is modeled in (Darrow et al.,2016)). The EPA document provides inappropriately dismissive language for the ALT findings, possibly based on a misunderstanding of the clinical use and the impact of what the document terms “small” increases. More importantly, the EPA draft document ignore the well-understood implications these data hold for liver health and disease in exposed populations (Ioannou, Boyko and Lee 2006a, Ioannou et al. 2006b, Kwo et al. 2017), discussed below.
- The sentence in the EPA draft document that inappropriately characterizes the increase in ALT as “small” also raises the second question of whether the finding is clinically significant. As discussed above, the language ***“it is unclear whether the observed changes are clinically adverse”*** is

demonstrably inappropriate for the population impact. Here is a reflection on the clinical and population meaning of higher population ALT from the American College of Gastroenterology (ACG) Practice Guidelines. *“Multiple studies have demonstrated that the presence of an elevated ALT has been associated with increased liver-related mortality. A true healthy normal ALT level ranges from 29 to 33 IU/l for males, 19 to 25 IU/l for females and levels above this should be assessed”* (Kwo et al. 2017). These sentences from the relevant clinical specialty organization (ACG) are carefully and appropriately phrased. In its document, the ACG communicates that a single liver function test alone does not make a diagnosis in any individual, and the ACG is not implying that it is used alone. However, the ACG is clear about the clinical impact on a population basis - higher ALT in a population is assuredly associated with poorer liver health and increased liver mortality (Kwo, 2017). The clinical understanding that populations with higher ALT have a clinically consequential liver outcomes is so well understood that it is painful for me, as a clinician, to read the current language in the EPA draft document. The information linking elevated ALT to worse liver outcomes (Ioannou et al. 2006a) and other health outcomes (Ioannou et al. 2006b) is not new or controversial (Kwo et al. 2017). Language that seeks an exemption for PFOA (and other PFAS or any toxin with similar consistent adult associations) should be reviewed very carefully.

- The EPA SAB PFAS review committee has strong expertise and is likely already aware that the charge questions are problematic, reflecting confusion at EPA about how to consider changes in biomarkers on a population basis. A charge question suggests that increased ALT indicates hepatocellular injury only when it is greater than 2x the normal value. The statement, disguised as a question, has multiple problems and reflects neither clinical thinking for individuals nor population-based clinical thinking, instead mixing them together and failing either consideration in a confusing way. It is well known that ALT values above the normal range are potentially clinically important in individuals at less than 2x the normal range. A brief review of the normal range follows. There are at least 3 different normal ranges that can be applied to individuals (lab normal values, which vary from laboratory to laboratory, and those of the relevant clinical professional specialty societies, AASLD, ACG). The existing PFAS and liver biomarker studies such as (Gallo et al. 2012) and (Darrow et al. 2016) used the lab normal value for ALT, which is the highest cutoff and least able to sensitively detect disease. Importantly, the question in front of EPA is about population effects, and not the much more complex question of use in clinical algorithms. The population effects are easier to understand and important. There is zero doubt



that elevations of ALT are meaningful in populations (Kwo et al. 2017), whether considered as percent increases or as increases above the normal range. The charge question stating that the associations are not large inadvertently usurps the committee's responsibility to consider whether the language in the draft document is appropriate and supplies its own conclusion. The conclusion which has been inadvertently supplied about that significance of ALT in the inappropriately framed question is scientifically misleading and not consistent with the modern interpretation of individual laboratory tests, whether the question is for individual clinical care or from a clinical population perspective. Modern thinking about Increases in ALT above lab normal levels understands that such deviations are common, not always associated with liver disease, but still worthy of consideration by clinicians who use modern algorithms for decision-making (Kwo et al. 2017). More importantly, the assertion that has been inadvertently supplied in the question is markedly inconsistent with how we think about clinical population transaminase data. Populations with higher ALT have more liver disease (Kwo et al. 2017) and other risks (Ioannou et al., 2006a; Ioannou et al., 2006b). The question is improperly framed and misleading.

- A causal association of PFOA to higher ALT in humans is augmented by solid data concerning liver injury following PFAS exposure in animals across species, summarized in many papers including (Roth et al. 2021). Experimental findings include and are not limited to liver enlargement, steatosis, and elevated liver enzymes, and disruptions in lipid/bile acid metabolism. These outcomes are already largely acknowledged by the EPA draft document, but they are not reasonably paired with the reasonably consistent human evidence to reach a defensibly worded conclusion. The animal data and human data are strongly in parallel for clinically adverse liver effects.
- The additional evidence concerning experimental markers of liver damage is also not reflected in a reasonable way in EPA's summary statements. For example, (Bassler et al. 2019) reported that PFOA was associated with cytokeratin markers of hepatocyte apoptosis in humans. Evidence of specific metabolic pathways in humans (and animals) were noted by (Sen et al. 2021), discussed in more detail below.
- A different section of the EPA draft document acknowledges parallel data which richly documents the even more extensive and consistent association of PFOA (and other PFAS) exposure to deleterious effects on human lipid metabolism. It has not acknowledged that these data are also evidence of hepatotoxicity and highly consistent with the liver enzyme data. These liver associations

can be regarded as certain or near certain to be causal based on human and experimental data. In considering whether the liver is affected by PFOA, the EPA draft document has not considered this acknowledged metabolic lipid disruption in relationship to clinically adverse effects in the liver. The lipid/bile acid data also support the existence of clinical liver damage. Lipids are both made and metabolized in the liver. Pathway information is supplied by numerous experimental studies, and specific human bile acid pathways are discussed by Sen et al (2021), who paired the human data in 105 NAFLD participants to experimental data in order to show the underlying liver metabolism. They showed that PFOS, PFOA, PFHxS, and P:FNA were positively associated to liver fat content and to measures of hepatic inflammation. (Only PFOS was associated with cirrhosis per se in the population studied. We really do not want to wait for cirrhosis before understanding that liver disease is bad. Increased steatosis and increased inflammation are also evidence of toxicity.) They also provided evidence that experimental murine data reveal similar bile acid pathway disruption for the several PFAS including PFOA and PFOS studied (Sen et al., 2021). The relationship of cholesterol to liver metabolism is very well known, discussed in simplified contexts such as “WebMD” (Morgan, 2021). The fact that disturbances in cholesterol homeostasis lead to NAFLD and to accumulation of lipids in hepatocytes (Malhotra et al. 2020) is basic knowledge. EPA is already aware that the lipid effect of PFAS exposure is seen in hepatocyte across experimental species following PFAS exposure, and EPA is already aware that there is concomitant lipid evidence in humans, as reviewed in (Fenton et al. 2020) and other reviews. EPA simply needs to acknowledge that the relevant organ is the liver (However, a detail should be mentioned. The ability to make cholesterol becomes impaired in end-stage liver disease, complicating the cross-sectional study of the relationship of cholesterol to cirrhosis or liver cancer or diseases that cause secondary liver failure (Ghadir et al. 2010, Wei et al. 2020). There is a potential nil or even negative bias in studies of PFAS or any toxin and lipids in when end stage disease is part of the question). The EPA document should certainly link the well-known fact that cholesterol is made and metabolized in the liver to the strong evidence that PFAS disrupt lipid metabolism, and acknowledge that toxic disruptions of lipid metabolism by PFAS are indications of hepatotoxicity.

- Further, the uric acid findings associated to PFAS exposure also refer to clinical evidence of liver damage. This is a less well known but still fully consistent line of evidence that PFAS cause liver damage. Higher uric acid is seen in multiple populations with PFAS exposure and especially in

independent studies, reviewed briefly in (Fenton et al., 2020). Higher uric acid is seen consistently in NAFLD (Jensen et al. 2018, Wei et al. 2020) and has been understood to accompany both chronic liver disease and higher ALT (Afzali et al. 2010). The triad of higher transaminases, higher uric acid, and disruptions in lipid metabolism and bile acid handling, is seen across human populations with PFAS exposure and there is parallel data in animal studies. The consistency of the physiology in humans and in animals strongly supports a relationship between PFOA (and PFOS) exposure and liver toxicity, which is likely to be related to steatosis in humans just as in animals.

As discussed above, several offending sentence in the draft document dismiss rather than scientifically address what we care about, the predictable impact of PFOA (and please do not forget PFOS) on clinical outcomes related to hepatotoxicity. The problem appears to be based on an effort to support the choice of a different health endpoint. While the choice of a different endpoint is an EPA decision, the scientifically misleading and incorrect statements nevertheless need to be corrected. It may be that the draft document also intends to say that we do not yet have (and may never obtain) the same level of histopathologic evidence of liver disease outcomes in humans that is already richly documented across animal species. That would be an acceptable alternative wording in a more scientifically considered conclusion, so long as the important constraints on obtaining such histopathology data in human environmental studies are also mentioned. However, emerging human studies already show undesirable histopathology and corresponding biomarker data associated with PFOA and PFOS exposure in susceptible human populations (Sen et al. 2021), despite the many ethical limitations on such studies.

Additionally, on p. 148, the EPA draft documents recapitulates the industry concern that liver findings across animal species may not be adverse. While the document fortunately does not dwell on this speculative and unsupported concept, the EPA document should ultimately state that the panoply of enzymatic, pathway, histopathologic, gross pathologic, and transaminase enzyme findings in animals are in fact adverse, and are consistent with human biomarker findings.

In summary, the current ~~wording~~ discussion of human hepatic effects in the draft PFOA document is unacceptable and inconsistent with clinical understanding. Higher ALT is clearly evidence of clinically

relevant population harm, independent of the cause. Efforts to seek justify an exemption from that reality for PFAS ought not to extend to EPA authors.

## REFERENCES

- Afzali, A., N. S. Weiss, E. J. Boyko & G. N. Ioannou (2010) Association between serum uric acid level and chronic liver disease in the United States. *Hepatology*, 52, 578-89.
- Bassler, J., A. Ducatman, M. Elliott, S. Wen, B. Wahlang, J. Barnett & M. C. Cave (2019) Environmental perfluoroalkyl acid exposures are associated with liver disease characterized by apoptosis and altered serum adipocytokines. *Environ Pollut*, 247, 1055-1063.
- California Office of Environmental Health Hazard Assessment. Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonic Acid (PFOS) in Drinking Water. October 5, 2021. Available at <https://oehha.ca.gov/water/report/perfluorooctanoic-acid-pfoa-and-perfluorooctane-sulfonic-acid-pfos-drinking-water> Accessed December 26, 2021
- Darrow, L. A., A. C. Groth, A. Winkquist, H. M. Shin, S. M. Bartell & K. Steenland (2016) Modeled Perfluorooctanoic Acid (PFOA) Exposure and Liver Function in a Mid-Ohio Valley Community. *Environ Health Perspect*, 124, 1227-33.
- Fenton, S. E., A. Ducatman, A. Boobis, J. C. DeWitt, C. Lau, C. Ng, J. S. Smith & S. M. Roberts (2020) Per- and Polyfluoroalkyl Substance Toxicity and Human Health Review: Current State of Knowledge and Strategies for Informing Future Research. *Environ Toxicol Chem*.
- Gallo, V., G. Leonardi, B. Genser, M. J. Lopez-Espinosa, S. J. Frisbee, L. Karlsson, A. M. Ducatman & T. Fletcher (2012) Serum perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) concentrations and liver function biomarkers in a population with elevated PFOA exposure. *Environ Health Perspect*, 120, 655-60.
- Ghadir, M. R., A. A. Riahi, A. Havaspour, M. Nooranipour & A. A. Habibinejad (2010) The relationship between lipid profile and severity of liver damage in cirrhotic patients. *Hepat Mon*, 10, 285-8.
- Ioannou, G. N., E. J. Boyko & S. P. Lee (2006a) The prevalence and predictors of elevated serum aminotransferase activity in the United States in 1999-2002. *Am J Gastroenterol*, 101, 76-82.
- Ioannou, G. N., N. S. Weiss, E. J. Boyko, D. Mozaffarian & S. P. Lee (2006b) Elevated serum alanine aminotransferase activity and calculated risk of coronary heart disease in the United States. *Hepatology*, 43, 1145-51.
- Jain, R. B. & A. Ducatman (2019) Selective Associations of Recent Low Concentrations of Perfluoroalkyl Substances With Liver Function Biomarkers: NHANES 2011 to 2014 Data on US Adults Aged  $\geq 20$  Years. *J Occup Environ Med*, 61, 293-302.
- Jensen, T., K. Niwa, I. Hisatome, M. Kanbay, A. Andres-Hernando, C. A. Roncal-Jimenez, Y. Sato, G. Garcia, M. Ohno, M. A. Lanasa, R. J. Johnson & M. Kuwabara (2018) Increased Serum Uric Acid over five years is a Risk Factor for Developing Fatty Liver. *Sci Rep*, 8, 11735.
- Kwo, P. Y., S. M. Cohen & J. K. Lim (2017) ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol*, 112, 18-35.
- Malhotra, P., R. K. Gill, S. Saksena & W. A. Alrefai (2020) Disturbances in Cholesterol Homeostasis and Non-alcoholic Fatty Liver Diseases. *Front Med (Lausanne)*, 7, 467.
- Park, J. H., J. Choi, D. W. Jun, S. W. Han, Y. H. Yeo & M. H. Nguyen (2019) Low Alanine Aminotransferase Cut-Off for Predicting Liver Outcomes; A Nationwide Population-Based Longitudinal Cohort Study. *J Clin Med*, 8.

- Roth, K., Z. Yang, M. Agarwal, W. Liu, Z. Peng, Z. Long, J. Birbeck, J. Westrick, W. Liu & M. C. Petriello (2021) Exposure to a mixture of legacy, alternative, and replacement per- and polyfluoroalkyl substances (PFAS) results in sex-dependent modulation of cholesterol metabolism and liver injury. *Environ Int*, 157, 106843.
- Sen, P., S. Qadri, P. K. Luukkonen, O. Ragnarsdottir, A. McGlinchey, S. Jantti, A. Juuti, J. Arola, J. J. Schlezinger, T. F. Webster, M. Oresic, H. Yki-Jarvinen & T. Hyotylainen (2021) Exposure to environmental contaminants is associated with altered hepatic lipid metabolism in non-alcoholic fatty liver disease. *J Hepatol*.
- Sherman, K. E. (1991) Alanine aminotransferase in clinical practice. A review. *Arch Intern Med*, 151, 260-5.
- Wei, F., J. Li, C. Chen, K. Zhang, L. Cao, X. Wang, J. Ma, S. Feng & W. D. Li (2020) Higher Serum Uric Acid Level Predicts Non-alcoholic Fatty Liver Disease: A 4-Year Prospective Cohort Study. *Front Endocrinol (Lausanne)*, 11, 179.
- Yamaguchi, M., K. Arisawa, H. Uemura, S. Katsuura-Kamano, H. Takami, F. Sawachika, M. Nakamoto, T. Juta, E. Toda, K. Mori, M. Hasegawa, M. Tanto, M. Shima, Y. Sumiyoshi, K. Morinaga, K. Kodama, T. Suzuki, M. Nagai & H. Satoh (2013) Consumption of seafood, serum liver enzymes, and blood levels of PFOS and PFOA in the Japanese population. *J Occup Health*, 55, 184-94.