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Review article

Review: Evolution of evidence on PFOA and health following the assessments of the C8 Science Panel

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ABSTRACT

Background: The C8 Science Panel was composed of three epidemiologists charged with studying the possible health effects of PFOA in a highly exposed population in the mid-Ohio Valley. The Panel determined in 2012 there was a 'probable link' (i.e., more probable than not based on the weight of the available scientific evidence) between PFOA and high cholesterol, thyroid disease, kidney and testicular cancer, pregnancy-induced hypertension, and ulcerative colitis.

Objective: Here, former C8 Science Panel members and collaborators comment on the PFOA literature regarding thyroid disorders, cancer, immune and auto-immune disorders, liver disease, hypercholesterolemia, reproductive outcomes, neurotoxicity, and kidney disease. We also discuss developments regarding fate and transport, and pharmacokinetic models, and discuss causality assessment in cross-sectional associations among low-exposed populations.

Discussion: For cancer, the epidemiologic evidence remains supportive but not definitive for kidney and testicular cancers. There is consistent evidence of a positive association between PFOA and cholesterol, but no evidence of an association with heart disease. There is evidence for an association with ulcerative colitis, but not for other auto-immune diseases. There is good evidence that PFOA is associated with immune response, but uneven evidence for an association with infectious disease. The evidence for an association between PFOA and thyroid and kidney disease is suggestive but uneven. There is evidence of an association with liver enzymes, but not with liver disease. There is little evidence of an association with neurotoxicity. Suggested reductions in birthweight may be due to reverse causality and/or confounding. Fate and transport models and pharmacokinetic models remain central to estimating past exposure for new cohorts, but are difficult to develop without good historical data on emissions of PFOA into the environment.

Conclusion: Overall, the epidemiologic evidence remains limited. For a few outcomes there has been some replication of our earlier findings. More longitudinal research is needed in large populations with large exposure contrasts. Additional cross-sectional studies of low exposed populations may be less informative.

1. Introduction

From 2004 to 2012, the 3-member C8 Science Panel, consisting of Tony Fletcher, David Savitz, and Kyle Steenland, was tasked by a West Virginia court with determining whether there was a 'probable link' between perfluorooctanoate (PFOA; referred to as C8 due to the 8-carbon structure) and any human disease (C8 Science Panel 2012, Steenland et al., 2014).

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The Science Panel's work was part of a legal settlement between community plaintiffs and DuPont, who had manufactured Teflon for 50 years near Parkersburg, West Virginia in the mid-Ohio Valley. Teflon production utilized PFOA during tetrafluoroethylene polymerization, and in the process of making Teflon, DuPont released PFOA into both the air and the adjacent Ohio River. PFOA eventually entered the groundwater and contaminated community drinking water supplies in the region (Shin et al. 2011a).

In the legal settlement (Leach et al. v. E.I. du Pont de Nemours & Co , 2005) 'probable link' was defined to mean that it was deemed more probable than not that the exposure had contributed to adverse disease outcomes (C8 Science Panel 2012). A disease was determined to have a 'probable link' with PFOA in the local community if the Science Panel (unanimously or by majority decision) considered that "based upon the weight of the available scientific evidence, it is more likely than not that there is a link between exposure to PFOA and a particular Human Disease among Class Members". In reaching their conclusions, the Science Panel considered epidemiological data published by other investigators, and data generated by the Panel in new studies of this population, with the latter given more weight.

The Science Panel conducted 11 different epidemiologic studies, most of which were dependent on estimating historical serum PFOA concentrations in Ohio Valley residents over time, via known plant emissions, a fate and transport model, and known residential history (C8 Science Panel 2012b). The exposure model predictions correlated well ($r = 0.69$) with observed measurements for 69,000 exposed residents in 2005/2006. Longitudinal studies were conducted, both retrospective and prospective, and self-reported disease was validated via medical records. Our population had both very high exposure and also low exposure, an advantage, although we could not explore effects using a non-exposed referent comparable to the general US population. After six years of study, probable links were declared for kidney and testicular cancer, pregnancy-induced hypertension, thyroid disease, high cholesterol, and ulcerative colitis (Table 1) (C8 Science Panel 2012a).

We compare more recent findings to our original findings not because we view our work as a gold standard, but because our probable link assessments provide a notable benchmark in the evolution of epidemiologic research on the health effects of PFOA exposure. The studies that we conducted remain important as the first large scale longitudinal study of a population with high exposure contrasts. Observations on the evolution of methods and findings since the C8 Science Panel's original assessment provides an informative way to organize the research that has followed.

Table 1
Diseases found by the C8 Science Panel to have a probable link with PFOA.

Disease with probable link[a]	Principal supporting publications from C8 Science Panel
Kidney cancer	Barry et al., 2013
Testicular cancer	Barry et al., 2013
Pregnancy-induced hypertension	Savitz et al. 2012a, Savitz et al. 2012b, Darrow et al. 2013
Thyroid disease	Winquist and Steenland 2014b
High cholesterol	Winquist and Steenland, 2014a; Fitz-Simon et al., 2013
Ulcerative colitis	Steenland et al. 2013

Note: A disease was determined to have a Probable Link with PFOA in the local mid-Ohio community studied by the Science Panel, if the Science Panel considered that "given the scientific evidence available, it is more likely than not that a connection exists between C8 exposure and a particular human disease among class members" (C8 Science Panel 2012).

[a] To see the probable link judgments in full, see C8 Science Panel 2012a, to see the list of the 11 studies conducted by the Science Panel, see C8 Science Panel 2012b.

2. Methods

We examined the studies included in three comprehensive recent reviews of the health effects of PFAS, by the International Agency for Research on Cancer (IARC 2018), Agency for Toxic Substances and Disease Registry (ATSDR 2018), and the European Food Safety Authority (EFSA) (EFSA Contamination Panel . 2018). We also examined other reviews devoted to specific aspects of PFOA health effects (Roth and Wilks 2014, Vrijheid et al. 2016, Ballesteros et al. 2017, Coperchini et al., 2017, Rappazzo et al. 2017, Liew et al., 2018a, Sunderland et al. 2019). We performed additional PubMed searches using keywords 'PFAS', and 'PFOA' for the period 2011 onward, after our Science Panel work concluded.

In this commentary we consider the overall strength of epidemiologic evidence for PFOA-disease associations now that some years have elapsed since the C8 Science Panel's work concluded in 2011–2012. We focus on thyroid disorders, cancer, immune and auto-immune disorders, liver disease, hypercholesterolemia, reproductive outcomes, neurotoxicity, and kidney disease. This re-assessment does not revisit the probable link decisions but re-states them, and then considers more recent evidence, including for some outcomes for which the Science Panel did not determine that there was a link to PFOA. We also discuss the Science Panel's exposure estimation, comment on study design issues, and suggest future epidemiologic research priorities for PFOA, and indirectly, other PFAS.

We reviewed the literature though March 1, 2020. Although we did not methodically search for new literature after March 1, 2020, we did come across an important new report on kidney cancer, which supports an association; hence we have included it here.

3. Results

3.1. Cancer

Overall, we found 19 epidemiologic studies of PFOA and cancer, six of which were of occupational cohorts (of which two were updates of the original cohorts) (see Table S1). In 2012, the Science Panel concluded that there was a probable link between PFOA and both testicular and kidney cancers (C8 Science Panel 2012c). The modest evidence that has accumulated since that time does not generally strengthen the conclusion that PFOA is carcinogenic for any given site, also there is somewhat stronger evidence for kidney cancer.

Despite these caveats, we believe the evidence for an association of PFOA with testicular cancer is suggestive overall, with two Science Panel studies, one cohort (Barry et al. 2013), one ecological/case-control (Viera et al. 2013), having found a relatively strong positive exposure–response for this cancer, supported by animal studies (ATSDR 2018). Testicular cancer is rare and generally not fatal (American Cancer Society 2020), and only Science Panel studies have reported on its relation to PFOA, limiting conclusions (Leonard et al. 2008 also reported on testicular cancer mortality but had only 1 death). The evidence for kidney cancer, also implicated by the Science Panel in their community (Barry et al., 2013) and worker (Steenland and Woskie 2012) cohorts, also remains suggestive although not consistent in newer studies. Kidney cancer was not found in a high-exposure occupational cohort of 3 M workers (Raleigh et al. 2014) based on mortality or incidence, although the number of kidney cancers was small (16 exposed incident cases). Mastrantonio et al. (2017), in an ecologic study in the Veneto region of Italy, comparing areas with PFOA-contaminated drinking water (as well as some other PFAS) with areas with non-contaminated water, did not find an excess of kidney cancer overall, although some excess among women (SMR 1.32(95% CI 1.06–1.65)). Finally a recent population-based case-control study by US National Cancer Institute investigators, with 324 renal cancer cases and 324 individually matched controls, found a positive exposure–response trend with renal cancer for several PFAS including PFOA, perfluorooctane sulfonic acid, and

perfluorohexane sulfonic acid. Only the association with PFOA remained apparent after adjustment for all three chemicals (Shearer et al. 2020). It should be noted that this general population study had much lower exposure contrasts than other studies.

There is little evidence for a relationship of PFOA with either liver or pancreatic cancer, tumors of which are associated with PFOA in animal studies (ATSDR 2018), with the exception of an increased risk for liver cancer , recently seen in Italian workers exposed occupationally to PFOA (Girardi and Merler, 2019). In our view there is some suggestive evidence for prostate cancer (positive Lundin et al. 2009; some suggestion Vieira et al. 2013, Hardell et al. 2014 , Steenland et al. 2015; largely negative Ericksen et al. 2009, Steenland and Woskie 2012, Barry et al., 2013), but results are inconsistent. This inconsistent evidence has led other reviewing bodies such as IARC (IARC, 2018), ATSDR (ATSDR 2018), and EFSA (EFSA Contamination Panel 2018), to similarly conclude the evidence for PFOA carcinogenicity remains suggestive but not conclusive.

To our knowledge there have been no studies of childhood cancer, but the effects of PFOA on the immune system (see below) might suggest these would be appropriate.

3.2. PFOA in relation to cholesterol and heart disease

The Science Panel concluded in 2012 that there was a probable link between PFOA and serum cholesterol (C8 Science Panel, 2012a). In 2018, the EFSA Panel on Contaminants in the Food Chain concluded that human epidemiological studies provide strong support for causal associations between exposure to PFOS and PFOA and increased serum levels of cholesterol (EFSA Contamination Panel 2018).

There have been numerous cross-sectional studies of associations between PFOA and lipid markers, most finding a clear positive association between serum PFOA and total cholesterol (TC) or low-density (LDL) cholesterol and a minority with positive associations with high-density lipoprotein (HDL) and triglycerides (ATSDR 2018). The few studies reporting the TC/HDL ratio do not show a clear pattern (one positive in a community population (Steenland et al. 2009), another study with workers and community (Wang et al. 2012), being negative or null, respectively). Most studies have focused on total cholesterol, LDL and HDL, though one recent study highlighted a possible association with lipoprotein subfractions, apoC-III in particular (Liu et al. 2020), and more work on such subfractions may help in elucidating the mechanisms of action of PFAS on cholesterol.

The cross-sectional studies have been carried out in three contexts, with positive results in all of them: general population samples with mean PFOA less than 5 ng/mL (for example Nelson et al. 2010), occupational studies with most serum levels above 1000 ng/mL (for example Sakr et al. 2007), and polluted community samples such as the C8 studies, with mean serum PFOA approximately 80 ng/mL (eg., Steenland et al. 2009, Frisbee et al. 2010). The lower the range of PFOA that was studied, the greater the change in cholesterol per unit change in PFOA (Steenland et al. 2010). This observation might reflect a non-linear dose–response relationship, with a stronger effect per unit of exposure in the lower exposure range

The positive association could reflect confounding, if for example regulation of serum level of both PFOA and cholesterol was correlated. Inter-individual variation in enterohepatic cycling of both PFAS and bile acids, the latter affecting serum cholesterol levels, has been postulated as a mechanism for such a correlation between PFAS and cholesterol (EFSA Contamination Panel 2018). Some observations lend support to this view. Correlation between PFAS and cholesterol excretion has been shown in patients with high levels of PFOS, another long chain PFAS, who were given cholestyramine, a drug known to reduce cholesterol, and which led to a sharp decrease in PFOS (Genuis et al., 2014).

If cross sectional studies were the only available evidence, major doubts would remain about the association. However, the same association has been seen in other designs. In a study in Sweden with high mixed exposure to several PFAS, principally PFOS, PFHxS and PFOA, associations with cholesterol were evident in both cross sectional analyses and ecological analysis comparing high and low exposure communities (Li et al. 2020). A longitudinal Science Panel study of 560 adults with repeated serum PFOA, PFOS and cholesterol measurements demonstrated an association between the magnitude of the decline in PFOA or PFOS and fall in cholesterol or LDL, suggesting a reversible effect of PFOA on cholesterol levels (Fitz-Simon et al., 2013). In a different design investigating a diagnosis of raised cholesterol in a large, highly exposed cohort, there was a positive association between modeled cumulative serum PFOA concentrations prior to diagnosis and cholesterol levels. The modeled level was based on estimated intake so there was no concern of correlated excretion (similar to other cohort analyses in this population) (Winquist and Steenland, 2014). A longitudinal study over 15 years of hypercholesterolemia and hypertriglyceridemia in relation to baseline PFAS found positive associations of both with PFOA (Lin et al. 2019).

The increase in LDL cholesterol in relation to PFOA might have been expected to manifest with a concomitant increase in cardiovascular disease risk. The only longitudinal study of cardiovascular disease incidence in relation to prior PFAS exposure is the C8 study of (modeled) PFOA and the results were null (Winquist and Steenland, 2014a). The explanation for this apparent anomaly may be explained by the other associations observed. There is some although inconsistent evidence for a positive association of PFOA (Steenland et al, 2009, see Table 4) with HDL, and also for PFOS (Chateau-Degat et al, 2010, Frisbee et al. 2010) and HDL, in certain populations; an increase of HDL has in turn been associated with a reduced risk of cardiovascular disease. Analysis of data from the C8 Health Project indicated a negative association between PFOA and C-reactive protein (Genser et al. 2015), lower levels of which are also associated with reduced risk of heart disease. Thus, it is plausible that there is a positive association of PFOA with raised cholesterol, yet no impact on the risk of cardiovascular disease.

3.3. Non-malignant thyroid disease and thyroid hormones

3.3.1. Thyroid disease

The Science Panel concluded in 2012 that there was a probable link between PFOA and thyroid disease (C8 Science Panel 2012d), primarily based on its own study of 32,000 participants in the mid-Ohio Valley (Winquist and Steenland, 2014b, published after the probable link judgment but used in the decision). Combining hypo- and hyper-thyroid diseases, a significant trend of increasing risk was observed among adult females in relation to both cumulative and serum level at diagnosis. The clearest trend was for female hyperthyroidism in relation to serum PFOA at the time of diagnosis. A parallel study focused on Dupont Plant workers (n = 3713; 80% male), published a few years after the probable link judgment), reported a trend of increasing thyroid disease risk across quartiles of modeled serum PFOA (with a 10 year lag) for males, but no evidence of trends with the log of cumulative exposure for either males or females (Steenland et al. 2015). Another study by the Science Panel found that measured PFOA child serum levels were associated with a higher risk of thyroid disease (mostly hypothyroidism, n = 61). However, serum PFOA was not associated with subclinical hypo- or hyperthyroidism based on cross-sectional analyses of individual hormone levels (Lopez-Espinosa et al. 2012).

Subsequent to the C8 Science Panel studies, thyroid disease was studied in a community in Sweden, with PFAS exposure from firefighting foam contamination of drinking water (Andersson et al 2019). Community members in the contaminated area had median serum levels of 257 ng/mL (PFHxS), 280 ng/mL (PFOS) and 15 ng/mL (PFOA), being approximately 300, 60 and 10 times higher respectively, than general population levels in unexposed areas. Individuals were linked to registers providing diagnoses and prescriptions for hypo- and hyperthyroidism. The study period was divided into three periods of increasing PFAS exposure and cases were assigned to the exposure period at time of

diagnosis. Neither hypo- nor hyper-thyroidism exhibited evidence of a trend of increasing risk across exposure categories.

Three recent reviews noted that the literature is scarce, and the type of thyroid disease-related outcome assessment varied considerably across studies, with few studies of pregnant women or children (Ballesteros et al. 2017, Coperchini et al. 2017, EFSA, 2018). Two of these judged that there was insufficient evidence to draw a conclusion on PFOA and thyroid disease (Ballesteros et al. 2017, EFSA Contamination Panel 2018), while the third one (Coperchini et al. 2017) reported hypothyroidism as the most consistent finding across studies. Overall, since the original Science Panel findings, our view is that the evidence of an association of PFOA with thyroid disease has gotten weaker.

3.3.2. Thyroid hormones

There were two key studies regarding thyroid hormones that were considered in the original Science Panel probable link judgment (C8 Science Panel 2012d), which concluded there was no consistent evidence of an association between PFOA and thyroid function (Knox et al. 2011, Lopez-Espinosa et al. 2012).

According to a systematic review (Ballesteros et al. 2017), three out of seven studies on the association between prenatal PFOA exposure, and either maternal or child hormones, found positive associations (note, Knox et al. (2011) was omitted from this review). The timing of the studies varied (at birth, first days of life, childhood) as did the type of hormones (one study found an association with TSH; two studies with TT4), so there were no consistent patterns across studies. A *meta*-analysis of 11 thyroid hormone studies in adults (including pregnant women) reported a modest inverse association between PFOA and TT4 but not TSH, free T4 (FT4) or total triiodothyronine (TT3) (Kim et al. 2018). EFSA (2018) concluded there was insufficient support for causal associations between exposure to PFOA and changes in thyroid hormones in adults based on 20 epidemiological studies. A similar conclusion of insufficient evidence was also reported in a prior (Coperchini et al. 2017).

Overall, while a number of studies have suggested associations between thyroid hormones and PFOA in cross-sectional analyses, in our view there is little consistency across studies so evidence for a causal impact on thyroid hormones remains weak.

3.4. Immunotoxicity

In 2012, the Science Panel concluded that there was not a probable link between PFOA exposure and common infections in children or adults (C8 Science Panel 2012e, Looker et al., 2014). Despite some evidence from the C8 Health Study (2005/2006) that higher PFOA exposure was associated with lower influenza vaccine efficacy and lower clinical markers of the immune system, there were also indications that higher PFOA exposure was associated with fewer infections in children and adults (Looker et al., 2014). At the time of the probable link report there was insufficient evidence from either Science Panel or other epidemiological studies (Fei et al. 2010, Grandjean et al. 2012, Okada et al., 2012) to infer a probable link between PFOA exposure and immune function.

Since 2012, however, toxicological, animal, and human epidemiological studies have continued to examine links between PFOA exposure and immunotoxicity related to both immunosuppression (e.g., vaccine response, infection) and hypersensitivity (e.g., asthma, allergy). In 2016, the U.S. National Toxicology Program (NTP) concluded "PFOA is presumed to be an immune hazard to humans based on a high level of evidence that PFOA suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans… there is additional, although weaker, evidence that is primarily from epidemiological studies that PFOA reduced infectious disease resistance [and] increased hypersensitivity-related outcomes" (NTP 2016). The U.S. ATSDR's 2018 public comment draft Toxicological Profile for Perfluoroalkyls listed decreased antibody response to vaccines and increased risk of asthma diagnosis among PFOA's suggested human health effects (ATSDR, 2018). Also in 2018, the EFSA Panel on Contaminants in the Food Chain concluded that associations between PFOA exposure and reduced serum antibody vaccine response were likely to be causal, although there was little evidence to suggest that PFOA was associated with asthma and allergies in children or adults (EFSA Contamination Panel 2018). In contrast, a 2016 review determined that there was insufficient evidence of a causal association between PFOA and immune function in humans (Chang et al. 2016). The most recent reviews, however, support the conclusions of the NTP, ATSDR, and EFSA that PFOA has immunosuppressive potential (Rappazzo et al. 2017, Liew et al., 2018a, DeWitt et al. 2019).

Studies published in recent years primarily focus on outcomes related to asthma (Zhou et al. 2017, Zhou et al. 2017, Impinen et al. 2018, Impinen et al. 2019) and atopic dermatitis (Chen et al. 2018, Impinen et al. 2018, Impinen et al. 2019, Wen et al. 2019) with only two studies examining PFOA exposure in relation to infection (Impinen et al. 2018, Impinen, Longnecker et al. 2019) and one study in relation to Rubella antibody titers (Pilkerton et al. 2018). We believe these recent studies provide little support for an association between PFOA exposure and asthma or atopic dermatitis among children. Results of associations between PFOA exposure and childhood infection are mixed, with studies reporting both increased and decreased associations with parent report of infections in their children (Impinen et al. 2018, Impinen et al. 2019). We believe these newest studies do little to alter the conclusions on PFOA and immunotoxicity previously made by several federal agencies.

In summary, a relatively large number of studies consistently report that PFOA impairs immune function; evidence that PFOA increases risk of human infectious disease or asthma is inconsistent.

3.5. Reproductive outcomes

In 2012 the Science Panel concluded that there was not a probable link between PFOA and birth defects, miscarriage, stillbirth, preterm birth or low birth weight, while there was a probable link to pregnancy-induced hypertension (C8 Science Panel, 2012a). Below we review the cumulative evidence for these outcomes, some of which have received substantial attention with respect to potential impact of PFOA (e.g., birthweight) and others very little (e.g., miscarriage).

There were initial suggestions of higher PFOA levels being associated with a slightly prolonged time to pregnancy (Fei et al. 2009, Velez et al. 2015) as well as reports of decreased sperm count and quality with higher PFOA exposure (Joensen et al. 2009, Vested et al. 2013), but subsequent studies did not support an adverse effect on fecundability (Jorgensen et al. 2014, Bach et al. 2015). In our view, cumulatively the evidence on PFOA provides little support for a consistent or substantial effect on fecundability.

Miscarriage has been considered in few studies, including several from the C8 Health Project (Stein et al. 2009, Savitz et al 2012a, Darrow et al, 2014) as well as in other populations (Jensen et al., 2015, Buck-Louis et al. 2016). With minor exceptions, the associations have been consistently null, indicating the absence of a discernible impact of PFOA on risk of miscarriage.

Hypertensive disorders of pregnancy were judged to have a probable link by the C8 Science Panel based solely on a series of analyses conducted in that population that showed modest but reasonably consistent increases in risk with elevated PFOA exposure (Savitz et al. 2012a, Savitz et al. 2012b, Darrow et al. 2013). Subsequent analyses found that those conclusions were relatively insensitive to potential errors in our exposure and toxicokinetic models (Avanasi et al. 2016a, Avanasi et al. 2016b, Avanasi et al. 2016c). We identified two studies since the C8 Science Panel study (Huang et al. 2019, Wikstrom et al., 2019). Wikstrom et al. (2019) provided supportive evidence of an association between PFOA and preeclampsia (adjusted OR per log unit increase = 1.3 (0.9–1.8) whereas Huang et al. (2019) did not identify an association.

The most extensive body of research pertains to PFOA exposure

during pregnancy and birthweight, with the most recent *meta*-analysis identifying 24 pertinent studies (Steenland et al. 2018), and with 12 additional studies in the short interval that has followed (see Table S2). Most earlier *meta*-analyses (Johnson et al. 2014, Negri et al, 2017), as well as Steenland et al. (2018), identified an association between level of PFOA in maternal serum or cord blood and a modest reduction in infant birthweight, generally on the order of 10 g per ng/mL. While the absolute magnitude of reductions identified would not be of direct clinical significance for an individual neonate, there would likely be an impact at the population level from reduced infant size at birth. However, this association may be in part a reflection of reverse causality (the outcome itself alters the measured exposure, rather than the other way around) or confounding, related to plasma volume expansion which is associated with birthweight and likely with reduced serum PFOA. Reverse causality or confounding would be most likely to affect studies with low exposure contrasts. Including studies with the widest range of exposure from the C8 Health Project (Stein et al. 2009, Savitz et al. 2012a,b, Darrow et al. 2014) would have effectively reduced the prior pooled estimate of effect to the null (Steenland et al. 2018). Furthermore, studies with PFOA measurement later in pregnancy show stronger associations with birth weight than those with measurements earlier in pregnancy, consistent with the possibility that the overall association is distorted by the magnitude of plasma blood volume expansion and glomerular filtration rate (Steenland et al. 2018, Verner et al. 2015).

More recent studies continue to generate mixed findings, some suggesting a reduced birthweight associated with elevated PFOA and others not finding evidence for such an effect.

Preterm birth has not been the focus of as much research. The studies from the C8 Health Project generated null findings (Stein et al. 2009, Savitz et al. 2012a, b, Darrow et al. 2014). A recent report from the Danish National Birth Cohort did identify elevated risk of preterm birth in the highest PFOA exposure ranges (Meng et al., 2018), but with little corroborative support. Similarly, congenital defects have received little attention and the studies that have been done (Stein et al. 2014a, Vesterholm et al. 2014) generated null findings.

In summary, with the exception of reduced birthweight, discussed in detail above, there have been few studies on other reproductive endpoints (subfecundity, miscarriage, preterm birth, and birth defects). What studies do exist provide little indication of an adverse effect of PFOA. For the one outcome for which the Science Panel did find a probable link, pregnancy-induced hypertension, there are few subsequent studies with mixed results.

3.6. Auto-immune disease

The Science Panel concluded that there was a probable link between PFOA and ulcerative colitis, but not with any other auto-immune disease, including Crohn's disease, the other principal inflammatory bowel disease (C8 Science Panel 2012f). The conclusion of the Science Panel was based on their own community cohort study of 32,000 adults (Steenland et al. 2013). The evidence of an association between PFOA and ulcerative colitis in that cohort in internal exposure–response analyses was among the strongest seen in Science Panel studies, and was consistent between the retrospective (extending back to first exposure, prior to original cohort enrollment in 2005/2006) and prospective (beginning in 2005/2006 at time of original cohort enrollment) components of the cohort study. The Science Panel study of PFOA-exposed workers at DuPont also found an association with ulcerative colitis; the workers in that study represented 12% of the larger community cohort (Steenland et al. 2015). There was a positive finding for rheumatoid arthritis in this worker cohort, but this was contradicted by a null finding in the large community cohort. Since the Science Panel studies, there have been two other studies of the PFOA/ulcerative colitis association. One was a case-control study (Steenland et al. 2018a) in which investigators found higher serum PFOA among cases compared to controls, but findings were limited because PFOA was measured after diagnosis. A recent study of inflammatory bowel disease (Xu et al. 2019), including specifically ulcerative colitis and Crohn's disease, was conducted in an area of Sweden where public water had been contaminated from fire-fighting foam). The main contamination was from PFHxS and PFOS, although there was also an increase in PFOA compared to non-exposed areas. Community members in the contaminated area had median serum levels in 2014, shortly after exposure ended, of 257 ng/mL (PFHxS), 280 ng/mL (PFOS) and 15 ng/mL (PFOA) (Andersson et al 2019). Inflammatory bowel disease was ascertained by linking the registered residential population to registries of diagnoses and prescriptions. No increase in ulcerative colitis, Crohn's disease, or any inflammatory bowel disease was seen comparing the exposed population (n = 60,000) to an adjacent non-exposed population, nor was there any trend in increased risk over exposure period (reflecting increasing cumulative PFAS emissions).

Overall, based on the four published studies to date, we believe the evidence still supports an association of PFOA with ulcerative colitis. Both Science Panel studies of PFOA found strong exposure–response trends. On the other hand, the latest study from Sweden did not find a positive association. However, the Swedish study had a different exposure profile: the population was highly exposed to PFHxS and PFOS, while PFOA was moderately elevated, lower on average than in the mid-Ohio valley. Furthermore, exposure was assigned ecologically based on residential location, and exposure response analyses were conducted based only across decade of increasing exposure. Given the sparse literature, more studies are clearly needed to reach more definitive conclusions.

3.7. Non-malignant liver disease and biomarkers of liver function

3.7.1. Liver disease

In 2012, the Science Panel concluded there was not a probable link between PFOA and liver disease (CS Science Panel 2012h), primarily based on its own study in the mid-Ohio Valley (Darrow et al. 2016). Overall in the literature, there have been five epidemiologic studies of PFOA and incident liver disease, liver disease mortality, or biopsy-determined prevalent fatty liver disease conducted to date. Three studies were conducted among DuPont or 3 M workers with small numbers of cases (<=35) (Lundin et al. 2009, Steenland and Woskie 2012, Steenland et al. 2015); one study was conducted in the community living near the DuPont Washington Works plant (Darrow et al, 2016); and one cross-sectional study based on liver biopsies was conducted among gastric bypass patients (n = 105) in Finland (Rantakokko et al. 2015). Outcomes included all chronic liver diseases (Steenland and Woskie 2012, Darrow et al. 2016), non-hepatitis liver diseases (fatty liver disease, enlarged liver and cirrhosis combined) (Darrow et al. 2016, Steenland et al, 2015), cirrhosis (Lundin et al, 2009) and steatosis or non-alcoholic steatohepatitis (NASH) (Rantakokko et al. 2015). The Steenland et al. (2015) study was a study of disease incidence among a cohort of DuPont workers exposed to PFOA (a subset of the community cohort studied in Darrow et al. 2016), and found a suggestion of a positive association between PFOA and non-hepatitis liver disease, but only when using a 10-year lag of PFOA exposure, and estimated rate ratios were highly imprecise because of the small numbers of cases among workers. There was no evidence of an association in the larger community study, which included 427 cases of fatty liver, enlarged liver, and cirrhosis grouped together for analysis. In the cross-sectional study of gastric bypass patients, Rantakokko et al. (2015) examined serum levels of PFAS in relation to prevalence of simple steatosis (fatty liver with inflammation, n = 24) or non-alcoholic steatohepatitis (NASH, n = 35), measured via liver biopsies of obese patients with background levels of exposure; no association was observed (specific estimates not provided). The Rantakokko et al. study (2015) is the only study data that was unavailable to the Science Panel in 2012. In our view, the limited available data continues to support a conclusion of no probable link between PFOA and liver disease.

3.7.2. Biomarkers of liver function

In 2012, the Panel concluded there was sufficient support for a causal association between PFOA and increased serum levels of the liver enzyme alanine transferase (ALT), a marker of hepatocellular damage, based largely on its own findings (Gallo et al. 2012). This association has been observed in populations with high occupational exposures (Sakr et al. 2007), in populations experiencing background level exposures such as NHANES (Jain and Ducatman 2019, Gleason et al. 2015, Lin et al., 2010), and in the community living near the DuPont Washington Works plant who experienced a wide range of exposures (Gallo et al. 2012, Darrow et al, 2016). Importantly this positive association is still evident when entirely based on external measures of PFOA exposure (i.e., modeled as opposed to measured serum levels), ruling out the possibility that the positive association is attributable to reverse causality or confounding (e.g., poor liver function causing poor PFOA elimination or sharing a pathway affecting PFOA storage or excretion) (Darrow et al. 2016). In the Gallo et al. (2012) and Darrow et al. (2016) studies, PFOA was positively associated with ALT levels above the reference range, although the clinical relevance of this elevation in enzyme levels is not clear. Adding to the evidence that PFOA causes liver cell injury, a recent study of 200 C8 Health Study adult participants showed that PFOA exposure was associated with cytokeratin 18 M30, a marker of hepatocyte apoptosis (Bassler et al. 2019), and a mechanism of disease progression in nonalcoholic fatty liver disease. There is also evidence that effects on ALT are more pronounced among obese subjects, who are at higher risk of nonalcoholic fatty liver disease (Lin et al. 2010, Jain and Ducatman 2019). Two other markers of liver function commonly assessed, γ-glutamyltransferase (GGT, an early marker of cholestatic liver disorders) and bilirubin have shown inconsistent patterns of association with PFOA (Sakr et al. 2007, Lin et al. 2010, Gallo et al. 2012, Gleason et al. 2015, Darrow et al. 2016,).

The EFSA Panel on Contaminants in the Food Chain March 2018 report (EFSA Contamination Panel 2018) provides a thorough overview of the studies of liver function biomarkers in relation to PFOA and PFOS (see Table 24).

Overall, in our view, the limited existing evidence does not support a link between PFOA and diagnosed liver disease. However, the dearth of adequately powered epidemiologic studies of liver disease, the established liver toxicity of PFOA in experimental animal studies (EFSA Contamination Panel 2018), the storage of PFOA in liver tissue in humans, and extensive evidence that PFOA exposure is associated with markers of hepatocyte cell death, warrants additional research on PFAS and liver disease, particularly nonalcoholic fatty liver disease.

3.8. Neurotoxicity

At the time of the Science Panel's probable link findings in 2012 (C8 Science Panel 2012g), there were four published epidemiologic studies examining associations between developmental exposure to PFOA and neurobehavioral outcomes in children (Fei et al. 2008, Hoffman et al. 2010, Fei and Olsen 2011, Gumpet al. 2011), plus three studies conducted in the C8 Health Project (Stein et al. 2011, Stein et al. 2013, Stein et al. 2014b). The Science Panel concluded that there was no probable link between exposure to PFOA and neurodevelopmental disorders in children, including attention deficit disorders and learning disabilities.

Since that time, numerous studies as well as seven reviews (Bellinger 2013, Roth and Wilks 2014, Vrijheid et al. 2016, Rappazzo et al. 2017, EFSA Contamination Panel 2018, Liew et al., 2018a, Sunderland et al. 2019) have reported on associations between prenatal and/or early childhood exposure to PFOA and various markers and measures of neurotoxicity, such as developmental milestones, attention-deficit/hyperactivity disorder (ADHD), Autism Spectrum Disorder and other behaviors in childhood, and neuropsychological functioning. Despite some compelling data from toxicological and animal studies (summarized in EFSA Contamination Panel 2018), these seven reviews concluded that existing human studies provide no consistent evidence for an association between prenatal and/or early childhood PFOA exposure and adverse neurodevelopmental outcomes in children.

To date, there are an additional nine published studies that were not included in at least one of the seven reviews. Four studies were based in populations previously unexamined for PFOA and neurodevelopment (Jeddy et al. 2017, Ghassabian et al. 2018, Harris et al. 2018, Lyall et al. 2018). Five studies reported on previously examined populations in the Health Outcomes and Measures of the Environment (HOME) Study (Vuong et al. 2018a,b, Zhang et al. 2018), Danish National Birth Cohort (Liew et al., 2018b), and HUMIS Norwegian Human Milk Study (Lenters et al. 2019).

We believe the findings from these nine newest investigations continue to support the conclusion that there is no consistent evidence of an association between prenatal and/or early childhood PFOA exposure and neurobehavioral development. PFOA exposure is variably associated with both better and worse neurodevelopmental outcomes, as well as null findings. The magnitude and direction of the associations vary by timing and dose of exposure, as well as by timing and type of endpoint. Analyses conducted within the same cohort can highlight consistency across the course of development, such as the Danish National Birth Cohort's null findings when examining prenatal PFOA exposure in relation to developmental milestones in infancy (Fei et al. 2008), IQ at age 5 (Liew et al., 2018b), behavioral and motor coordination problems at age 7 (Fei and Olsen 2011), and ADHD or autism by approximately age 11 (Liew et al. 2015). Repeated investigations in the same cohort also underscore the need for discussion of results within the context of existing literature. In the HOME study, for example, cross-sectional analyses at mid-childhood indicated that higher PFOA exposure is associated with increased likelihood of impaired executive function (Vuong et al. 2018a,b); however longitudinal analyses of prenatal and early childhood PFOA exposure and mid-childhood executive function in the same population yielded null findings (Vuong et al. 2016, Vuong et al. 2018a,b).

Overall, a relatively large number of studies examining PFOA and neurotoxicity provide no consistent evidence of increased risk.

3.9. Kidney disease

In 2012, the Science Panel concluded there was insufficient evidence to find a probable link with kidney disease, largely based on its own studies (C8 Science Panel, 2012a). Overall in the literature, there are few studies of kidney disease and PFOA, especially longitudinal studies of populations with above-background exposure. In two occupational cohort mortality studies (one of DuPont workers in the mid-Ohio Valley (Steenland et al. 2012), the other of 3 M workers (Raleigh et al., 2014)), one found a positive trend with estimated PFOA and death from kidney disease (based on serum levels, 13 deaths) and the other did not (based on air levels, 27 cases).

A study of disease incidence among the DuPont occupational cohorts, which showed a mortality positive trend, found no association between estimated cumulative PFOA serum levels and chronic kidney disease incidence (43 cases, verified via medical records) (Steenland et al. 2015).

In a large longitudinal study of a highly-exposed community in the mid-Ohio Valley (of which the workers in the incidence study were a subset), estimated cumulative serum levels were not associated with chronic kidney disease incidence, whether the cohort was studied retrospectively or prospectively (397 cases, verified by medical records) (Dhingra et al. 2016). The remaining studies were cross-sectional studies of glomerular function. In two cross-sectional studies of highly exposed children and adults from the mid-Ohio Valley, there were inverse associations between *measured* serum PFOA and estimated glomerular filtration rate (eGFR), but no association when using *modeled* serum levels; the authors suspected reverse causality or confounding was responsible for the inverse association using a biomarker of PFOA (Watkins et al. 2013, Dhingra et al. 2017). Three other cross-sectional

studies of measured serum PFOA and glomerular function were conducted in low-exposed general populations. In one cross-sectional study in China the authors found no trend of decreased eGFR with increased serum PFOA (Wang et al. 2019), and in two studies of the US NHANES population, the authors found either an inverse association with eGFR (children: Kataria et al. 2015), or an inverted U-shaped relationship (adults: Jain and Ducatman 2019).

In summary, consistent with the C8 Science Panel conclusion, we believe there is little evidence of an association between PFOA and chronic kidney disease, with the most informative study still being the large cohort study conducted by the C8 Science Panel in the mid-Ohio Valley (Dhingra et al. 2016).

3.10. Methodologic considerations

3.10.1. Cross sectional studies of serum PFOA and biomarkers

There have been a large number of studies of serum PFOA and other exposure biomarkers in low-exposed general populations in relation to biomarkers of disease (eg., kidney function), most notably in NHANES. PubMed, for example, lists 70 such NHANES studies addressing PFOA. Many studies with this design find associations between PFOA and clinical biomarkers or prevalent disease. However, we believe that caution should be exercised about such studies because of the potential for reverse causality or uncontrolled confounding, which can be particularly important at low exposure levels where the exposure contrasts are modest, and more strongly influenced by complex behaviors such as diet. In our own work we have observed instances when an association was found using measured serum PFOA, but not found with modeled PFOA (Dhingra et al. 2017, Watkins et al. 2013, Steenland et al. 2018). While one might argue that the modeled exposure is less accurate than measured biomarkers, we believe in fact the reverse may sometimes occur, that modelled exposure may sometimes provide less biased epidemiological effect estimation than measured biomarkers, as has been argued elsewhere (Weisskopf and Webster, 2017, Savitz and Wellenius 2018).

For example, as noted above, both Watkins et al. (2013) and Dhingra et al. (2017) observed an inverse association between measured serum PFOA and glomerular function, but no association using modeled PFOA, perhaps reflecting decreased glomerular function leading to increased serum PFOA. The inverse association between the PFOA in maternal serum and birthweight found for late but not early pregnancy assessment may reflect maternal blood volume expansion decreasing serum PFOA levels, with several studies showing a decrease in serum PFOA during pregnancy (Fromme et al. 2010, Kato et al. 2014). Furthermore, greater maternal blood volume expansion is associated with increased fetal growth (Vricella 2017), hence the possibility that larger babies would have lower maternal (and therefore newborn) serum PFOA. As a final example from our own work, Dhingra et al. (2016) have shown that the association between early menopause and higher PFOA in several cross sectional studies may also be due to reverse causality, whereby decreased excretion of PFOA at menopause leads to higher serum levels, creating a spurious association of early menopause and higher serum PFOA. Dhingra et al. analyzed measured and model-estimated PFOA in relation to self-reported menopause (controlling for age). Being postmenopausal was associated with higher measured (trend tests: $p = 0.013$), but not modeled ($p = 0.50$) serum PFOA. Modeled PFOA is not affected by excretion dynamics.

Another issue with general population studies, with low background exposure, is that serum PFOA is often highly correlated with other PFAS, eg, PFOS, PFNA, and PFHxS. It is difficult to separate the effects of these chemicals on purported effects. This can also at times occur even in high-exposure settings (e.g., Consonni et al. 2013, Li et al. 2018)

We recognize that cross-sectional studies of biomarkers of disease and serum PFOA levels can provide valuable information, particularly when the variation in exposure biomarkers is driven to a significant degree by exogenous exposure. For example, cross-sectional studies associating PFOA with higher cholesterol provided evidence later confirmed in longitudinal studies. However, caution should be exercised regarding positive associations between biomarkers of disease and PFOA in cross-sectional studies of populations with low background exposure, due to the potential for confounding and reverse causality.

3.10.1. Fate and transport models

Fate and transport models (built with adequate data and accompanied by toxicocokinetic models, see next section) are key to any valid reconstruction of past exposures, needed for longitudinal epidemiologic studies.

For the C8 Science Panel studies in West Virginia and Ohio, we built upon the work of Paustenbach et al. (2007) and others, using a combination of several modeling systems to develop a multimedia model of the transport process. Airborne emissions result in particle-bound PFOA/PFOS/PFAS being distributed into the surrounding community in a pattern dependent upon the prevailing winds, followed by deposition on soil surfaces, penetrations through the soil vadose zone, and subsequent impact upon local groundwater sources (Shin et al. 2011a, Shin et al. 2011b, Shin et al. 2012). Additionally, direct release into water supplies has also been noted (Shin et al. 2011a, Shin et al. 2011b, Shin et al. 2012) and was included in our modeling efforts.

To our knowledge, since our work in 2011–2012, there have been no further instances of comprehensive modeling of the fate and transport of PFOA and PFAS through the environment, coupled to health outcomes. However, incremental advances have been made in several areas focusing on improving physicochemical properties of PFOA and related compounds (Brusseau 2018, Hong and Purucker 2018, Brusseau et al. 2019, Lyu et al. 2018, Silva et al. 2019). From an empirical standpoint, several groups have carried out field investigations to validate laboratory and modeling assessments of physical phenomena associated with PFAS environmental transport (Xiao et al. 2020, Shan, et al. (2014), Zhu and Kannan (2019), Ferrey, et al. 2012, Webster and Ellis 2011). Further, new modeling efforts are now underway to estimate PFAS serum levels in Ronneby, Sweden, where large scale contamination took place (Li et al. 2018). Other large-scale efforts are beginning in the PFOA-contaminated Veneto region of Italy (Pitter et al. 2020), at various U.S. sites as part of the CDC/ATSDR Multi-Site PFAS Study (https://www.atsdr.cdc.gov/pfas/Multi-Site-Health-Study.html), and near Wilmington, North Carolina due to water contamination with several PFAS, including GenX, a shorter-chain fluorinated PFOA substitute (https://cleanaircarolina.org/wp-content/uploads/2019/04/4-Hoppin-NC-Breathe-Final.pdf). In our view, while such work is critical in the development of fate and transport modeling systems, a more comprehensive program is needed whereby modelers, laboratory scientists, exposure scientists, and epidemiologists work together to establish a coherent understanding of the efficacy of using source to human receptor/health effects models to address the impact of these compounds on human health. Such work requires transdisciplinary cooperation similar to that accomplished in the C8 Study and should be expanded to evaluate differential fate and transport, as well as health outcomes, associated with the broader PFAS class of toxicants.

3.10.2. Exposure and toxicokinetic modeling

For the C8 Science Panel studies in the mid-Ohio valley, we relied on individual residential and work histories, reconstructed water PFAS concentrations, water use questionnaires, and (in the absence of self-reported water consumption rates) default EPA exposure factors to develop individual year-by-year estimates of the amount of PFOA ingested through water consumption, and inhaled at the residence and workplace since birth for each study participant (Shin et al. 2011b). However, toxicological effects are believed to be a function of internal target tissue dose (Müller et al. 2004a,b), rather than ingested dose, and other exposure pathways for PFOA are common, including diet (IARC, 2016). We therefore applied a one compartment toxicokinetic model to convert ingested doses to year-by-year serum concentrations, which

serve as surrogates for target tissue doses (Shin et al. 2011b). Our model accounted for likely contributions of other pathways using a time-dependent background serum contribution that was assigned to all participants in common, based on US median serum PFAS concentrations over time obtained from NHANES (Centers for Disease Control, 2019), and added to serum concentration expected from local water consumption and air inhalation according to the superposition principle. Water concentrations changed dramatically over time (Shin et al. 2011a) and few participants remained in the same water district throughout an entire lifetime, making steady-state assumptions unreliable. Instead, we used a time-dependent closed-form forward solution for standard one compartment toxicokinetic models with piecewise constant exposure rates (i.e., we assumed that PFOA ingestion rates were roughly constant within any one calendar year) (Flesch-Janys et al. 1998).

Our toxicokinetic model assumed a serum half-life of 3.5 years (Olsen et al. 2007), a volume of distribution of 0.181 L/kg for males and 0.198 L/kg for females (Butenhoff et al., 2004), and infant:maternal serum PFOA concentration ratios of 0.785 and 1.27 at birth and age 1 year, respectively (Shin et al. 2011b). Towards validation, we evaluated the Spearman's rank correlation between modelled and measured serum PFOA concentrations, finding a coefficient of 0.67 among all participants and 0.82 among those with the highest quality exposure data (residence in one of the six qualifying water districts at the time of blood sample, and had a self-reported water consumption rate) (Shin et al. 2011b).

Since our original toxicokinetic modeling was performed, evidence has emerged that better supports an average human half-life for PFOA in the range of 2 to 3 years (Bartell et al. 2010, Bartell et al. 2012, Zhang et al. 2013, Russell et al. 2015, Gomis et al. 2016, Li et al. 2018,). A simplified version of our one compartment toxicokinetic model for PFOA, using constant values for the dose rate and background contribution and an updated half-life value of 2.3 years, is available in the form of an online calculator (Bartell 2017), recently updated to incorporate several other PFAS chemicals and the effects of menstruation (Lu and Bartell 2019, Wong et al. 2014).

Our modelled serum PFOA values were used in multiple epidemiologic investigations in the C8 Science Panel Studies, and later sensitivity analysis indicated that epidemiological effect estimates for preeclampsia per interquartile range of modelled serum PFOA were not substantively changed by simulated measurement error in the exposure assignments (Avanasi et al. 2016a, Avanasi et al. 2016b). These results using modelled serum PFOA have also been very useful for triangulating epidemiological effects by comparison to epidemiological associations using measured serum PFOA, due to their distinctly different threats to validity (Watkins et al. 2013, Weisskopf and Webster, 2017).

4. Discussion

Clearly, the volume of epidemiologic research on PFOA and health outcomes has grown since the work of the C8 Science Panel was completed, quite considerably for outcomes such as birthweight, neurodevelopment, thyroid function, and immunology, often supported by toxicological evidence. Much of the research has been opportunistic, extending studies conceived for other purposes to take advantage of the relative ease of measuring biomarkers of PFAS and then assessing their relationship to various health outcomes, illustrated most clearly by the use of NHANES data (e.g., Lin et al. 2010, Gleason et al. 2015, Jain and Ducatman 2019), but also in many established cohort or registry populations (e.g., Fei et al. 2008, 2009, 2010, 2011). Exploiting readily available data from general population studies is efficient but when focused on background exposures as reflected in biomarkers, differences may be strongly influenced by variability in uptake and excretion (rendering them vulnerable to confounding and reverse causation) and precluding historical exposure reconstruction which is feasible only if there is historical information on specific dominant exposure sources.

The strengths of the C8 Science Panel studies remain the examination of a large population with a well-defined source of elevated exposure, an ability to reconstruct historical exposure, a wide range of exposure from background to very high levels, and thorough assessment of clinical health endpoints. However, we studied only a single population. Newer studies for specific outcomes would be expected to vary from our findings due to different sample sizes, lower exposures to PFOA, co-exposures to other PFAS, and varying patterns of confounders such as diet and age.

There are now examples of comparable circumstances in the recent literature including Swedish studies at Ronneby (Andersson et al. 2019, and Xu et al. 2019), and Italian studies from Veneto (Mastrantonio et al. 2018, Girardi and Merler 2019, Manea et al. 2020). A multi-site community study of populations with elevated exposure due to contaminated drinking water is in progress in the US through the Agency for Toxic Substances and Disease Registries (https://www.atsdr.cdc.gov/pfas/index.html). With the discovery of multiple locations around the world with well-defined environmental sources of elevated exposure, more opportunities are likely to arise that individually or collectively offer great promise for extending knowledge of the health effects of PFOA. Occupational studies are also of interest because of their high exposure contrasts, but they generally involve relatively small populations.

The charge to the C8 Science Panel required making dichotomous judgments regarding probable links, which had to be based on the available evidence even recognizing that it was (and remains) incomplete. Those assessments were influential in focusing research attention and it is not surprising that for some of outcomes for which probable links were found, the evidence from research has become weaker with the accumulation of additional studies, e.g., thyroid disorders, and ulcerative colities. For other outcomes that were not found to have probable links to PFOA, the evidence continues to corroborate that assessment, e.g., neurodevelopment. Some of the most important rare diseases for which probable links were identified have had little additional research to confirm or refute the original assessment, notably testicular cancer, pregnancy-inducted hypertension, and ulcerative colitis. For kidney cancer the evidence has been somewhat strengthened by a recent positive case-control study. As noted above, the evidence associating PFOA to some clinical biomarkers is increasingly persuasive, e.g., cholesterol, liver enzymes, and immunologic response to vaccines, yet in our view the evidence on increased risk of heart disease, chronic liver disease, and infectious disease related to PFOA is not evident. As the literature matures, the needs for advancing research on the specific different health endpoints becomes more clear, building on past efforts. While it is disappointing that we do not have greater clarity on adverse human health effects associated with PFOA, this still remains a relatively new area of investigation. With ongoing efforts to minimize exposure to PFOA, however, the opportunities for informative new studies may well diminish.

Declaration of Competing Interest

Three authors (Drs. Savitz, Ryan, Fletcher) have served in the past as paid consultants to law firms conducting litigation involving PFAS. Drs. Savitz and Ryan have worked for plaintiffs, while Dr. Fletcher has worked for both plaintiffs and defendants. Dr. Bartell serves as an expert witness for plaintiffs in two PFAS medical monitoring lawsuits, and receives compensation for those services; the terms of this arrangement were reviewed and approved by the University of California Irvine in accordance with its conflict of interest policies. Dr. Savitz is doing current consulting, in one case for plaintiffs and in the other for defendants.

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Appendix A. Supplementary data

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