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Risk assessment for PFOA and kidney cancer based on a pooled analysis of two studies

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Abstract

Introduction.—Perfluorooctanoic acid (PFOA) has been associated with kidney cancer in human studies.

Methods.—We conducted a pooled analysis of two large studies of PFOA and renal cell carcinoma (RCC, the most common type of kidney cancer); one from the National Cancer Institute (NCI) (324 cases and controls), and a second from the C8 Science Panel (103 cases and 511 controls). Serum PFOA levels were estimated a median of 8 years before diagnosis. Analyses were conducted via conditional logistic regression. Lifetime risk of kidney cancer per unit serum PFOA concentration and per unit dose were calculated.

Results.—The 25th, 50th and 75th percentiles of serum PFOA levels were 4.8, 7.3, and 23.9 ng/ml for the pooled analysis. The preferred model for the pooled data was a two-piece linear spline model (knot at 12.5 ng/ml serum PFOA); the log odds of RCC increased 0.1349 per 1 ng/ml increase in serum PFOA up to the knot (eg, an OR of 2.02 (1.45–2.80) from the median to the knot), and was flat thereafter. The estimated lifetime excess risk (cancer slope factor) with an exposure of 1 ng/ml was 0.0018, similar to the excess risk of 0.0026 recently reported by CalEPA based on different methods. Assuming a serum half-life of 2.3 years and a distribution volume of 170 mL/kg for PFOA, our results are equivalent to 0.0128 per ng/kg/d of PFOA intake. To limit

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Disclosure

Scott M. Bartell serves as a compensated expert witness for PFOA medical monitoring lawsuits in New Hampshire. The terms of this arrangement were reviewed and approved by the University of California, Irvine in accordance with its conflict-of-interest policies.

excess lifetime kidney cancer risk to 1/1,000,000, our data suggest a limit of 0.0015 ng/L (0.0015 ppt) for PFOA in drinking water, similar to CalEPA's proposed Public Health Goal and the new US EPA Drinking Water Health Advisory.

Conclusions.—Our results correspond reasonably well with cancer slope factors developed by other investigators using published summary data, and suggest drinking water limits similar to new recommendations by the US EPA.

Keywords

kidney cancer; PFOA; pooled analysis; risk assessment

Introduction

Per- and polyfluoroalkyl substances (PFAS) are a diverse class of synthetic chemicals, many of which are highly persistent in the environment and are of major public health concern. Among the PFAS compounds, PFOA is one of the most studied for health effects.. Among studies of cancer, , perhaps the outcome with the most supporting evidence from epidemiologic studies is kidney cancer (Steenland et al. 2020, Steenland and Winquist 2021). The U.S. Environmental Protection Agency (US EPA, 2021) recently used inverse variance weighted regression to estimate the average increase in kidney cancer risk per unit exposure across reported exposure categories in the Shearer et al. (2021) study in the National Cancer Institute (NCI) Prostate Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, and the California Environmental Protection Agency performed a meta analysis using similar inverse variance weighted regression models for the NCI study and the for C8 Science Panel Study by Vieira et al. (2013) from the Ohio cancer registry (CalEPA, 2021). Both of these analyses were conducted to support new enforceable health limits on PFOA in drinking water, for which kidney cancer is one of e the primary health endpoints (CalEPA, 2021).

Bartell and Vieira (2020) previously combined four of the epidemiologic studies of kidney cancer in a random effects meta-analysis; using inverse variance weighted regression, they estimated an average relative increase in log risk of kidney cancer risk per 10 ng/mL increase in serum PFOA of 16% (95% CI: 3%, 30%) across the four studies. Two of the studies in this meta-analysis, with perhaps the best quantitation of serum PFOA concentrations, are Barry et al. (2013) from the C8 Science Panel population and the Shearer et al. (2021) NCI study.

Using Cox regression, Barry et al. analyzed 105 kidney cancer cases with complete data on serum level and covariates, and found a hazard ratio of 1.10 (95% CI: 0.98, 1.24, p for trend, 0.10) per 1 unit increase in log of cumulative serum PFOA. Categorical analyses showed increased trends in HRs with increasing exposure, with a 60% increased risk among those in the highest quartile vs. the lowest (OR = 1.58, 95% CI = 0.88 to 2.84). Analyses were adjusted for age (the time variable), time-varying smoking, time-varying alcohol consumption, gender, education, and stratified by 5-year period of birth year.

Shearer et al. observed a positive association for PFOA in relation to renal cell carcinoma (RCC); a doubling in serum PFOA concentrations was associated with an approximately 70% increased risk (odds ratio (OR) 1.71; 95% CI = 1.23 to 2.37; P = .002), and quartile analysis found a greater than two-fold increased risk among those in the highest quartile vs. the lowest (OR = 2.63, 95% CI = 1.33 to 5.20; P trend = .007). Covariates in the conditional logistic model included body mass index (BMI; missing, <18.5, 18.5-<25, 25-<30, or ≥30 kg/m^2), smoking status (never, former, current), history of hypertension (no, yes), estimated glomerular filtration rate (continuous), previous freeze-thaw cycle for serum samples, and calendar year of blood draw (1993–1995, 1996–1997, 1998–2002).

Here we conduct a pooled analysis of individual-level data from these two studies (Barry et al. 2013, Shearer et al. 2021). Pooled analyses have some advantages over meta-analyses, in that analysts can examine different models appropriate for the combined data, and are not constrained to point estimates of risk for selected exposure categories provided in the original publication. Although inverse weighted regression is an accepted approach for evaluating average dose-response trends across exposure categories in different studies (van Wijngaarden and Hertz-Picciotto, 2004), pooled individual-level data provide the best opportunity to examine the shape of the dose-response curve.

Methods

1. Study participants and designs

a. NCI Study.—The NCI study [Shearer et al (2021)] was a nested case-control study of 324 renal cell carcinoma (RCC) cases (ICD-02 C64.9) and 324 matched controls within the PLCO cohort. The case definition excluded cancer of the renal pelvis (code C65.9) and urothelial carcinoma (coded C64.9, but morphology codes 8120, 8130), as these cancers, which represent perhaps 10% of kidney cancer, may have a different etiology than the great majority of renal cell carcinomas

PLCO is a randomized screening trial that recruited ~150,000 adults ages 55–74 years from study centers in 10 U.S. cities between 1993–2001; participants in the screening arm provided non-fasting blood samples (Prorok et al. 2000). Controls were pair-matched to cases on age at enrollment (55–59, 60–64, 65–69, or ≥70 years), sex, race/ethnicity (non-Hispanic white, non-Hispanic Black, Hispanic, Asian, or Native American), study center, and study year of blood draw. Pre-diagnostic serum concentrations of PFOA were measured a median of 8.46 years prior to the diagnoses of the RCC cases. Serum levels were similar to general U.S. population levels, with 25th, 50th, and 75th percentiles of 4.0, 5.6, and 7.3 ng/ml respectively (with one extreme outlier of 306 ng/ml) in PLCO controls vs. 3.8, 5.1, and 6.8 ng/ml respectively in NHANES 1999–2000 (Calafat et al., 2007).

Participants in PLCO were actively followed for cancer incidence through mailed self-reported annual study update forms and medical record review by trained personnel at each of the 10 screening centers through at least 2011. Data collection transitioned to follow-up at a centralized data center in 2011 (Black et al, 2015). The present analysis included cancer diagnoses through 2014; all diagnoses of RCC were confirmed by medical record review.

b. C8 Science Panel study.—The C8 Science Panel study (Barry et al. 2013) was largely based on participants in the C8 Health Project, which was conducted in 2005/2006 and surveyed 69,030 people.. Participants were eligible for the C8 Health Project if they lived, worked or attended school for at least one year in one of six PFOA-contaminated water districts near the Dupont plant between 1950 and 2004, or had contaminated private water sources in those same geographic areas for ≥ 12 months during 1950–2004 at their residence, workplace or school. The Dupont plant used PFOA since the 1950s in the production of Teflon; plant emissions to surface water and air eventually migrated to local groundwater and public drinking water. Granular activated carbon filters installed in 2006–2007 effectively ended drinking water contamination by PFOA for these six public water supplies. Participants reported demographic and health characteristics and an extensive residential history. Serum was collected for measurement of PFAS and clinical biomarkers. The estimated C8 Health Project participation rate was high (81% among current residents 20 years and older) (Frisbee et al. 2009).

The C8 Science Panel sought to enroll adult C8 Health Project participants in subsequent surveys to study disease incidence; 74% of the participants 20 years and older consented to further contact by the C8 Science Panel. Of these, 82% participated in one or two surveys during 2008–2011, reporting demographic information, health-related behaviors, and medical histories. Additionally, the Science Panel obtained a list of DuPont workers, from a cohort that was originally constructed for a mortality study (Steenland and Woskie 2012); of these, 3713 had retrospective occupational exposure data and were interviewed by the C8 Science Panel, and were included in the final Science Panel cohort. The final cohort included 32,254 people 20 years or older who participated in at least one Science Panel interview and had PFOA exposure estimates. All participants gave informed consent to participate, to match personal information to state cancer registries, and to release medical records to study personnel (Winquist et al. 2013).

Cumulative PFOA serum concentrations were estimated retrospectively for each community participant for each year of their life from 1952 through 2011, based on an historical exposure reconstruction using regional data including the amount of PFOA emitted by the DuPont facility each year, wind and precipitation patterns, river flow, vadose zone transport, and groundwater flow to water supply wells (Shin et al., 2011a). Individual exposure estimates took into account each participant’s reported residential history, drinking water source(s), tap water consumption, workplace water consumption, inhalation of ambient air, and a one-compartment PFOA absorption, distribution, metabolism, and excretion model (Shin et al., 2011b).

For worker participants, additional information from occupational exposure was incorporated into the exposure estimation model, based on over 2,000 PFOA serum measurements taken over time from workers (Woskie et al. 2012). These estimates were used to create a job-exposure matrix to estimate serum levels for workers across time in different jobs and departments. After employment ended, serum estimates decayed at a rate of 18% per year based on a presumed half-life of 3.5 years (Olsen et al. 2007). These estimates were then combined with estimated serum levels from residential exposure to contaminated drinking water.

For the entire cohort (n=32,254), estimated serum levels in 2005/2006 were compared to measured levels; the Spearman correlation was 0.71 (Winquist et al. 2013). The mean of the measured serum levels in the cohort in 2005/2006 was 87 ng/ml (25^{th}, 50^{th}, 75^{th} percentiles, 13, 26, 68 ng/ml) (Winquist et al. 2013). These levels were much higher than those of the general population, which at the time had a mean of 4 ng/ml.

Participants were asked if they ever had cancer, and if they reported yes, were asked for permission to review their medical records. For all self-reported cancers, diagnosis validation was sought through medical chart review or Ohio/West Virginia state cancer registry matching; 70% were validated. Only validated cases were used in the cancer incidence analysis.

2. Methods for pooled analysis.

A number of adaptations were required to combine the NCI case-control data and the C8 Science Panel longitudinal data in a single analysis. First, we constructed nested case-control risk sets from the longitudinal C8 Science Panel data, to parallel the NCI study design. Up to five controls were selected for each case, matched on gender, race, year of birth (within 5 years), and were required to have survived past the age at which the case was diagnosed. Because the serum levels measured in matched cases and controls in the NCI study preceded case diagnosis by a median of approximately 8 years, we assigned exposure for C8 Science Panel cases and the controls in their risk sets as their estimated serum levels 8 years prior to diagnosis of the cases or prior to the case age at diagnosis for their matched controls. Second, in order to restrict cases to renal cell carcinoma as per the NCI study, we restricted C8 Science Panel cases to those with a kidney site code of C64.9 and excluded cancers of the renal pelvis (site code = C65.9). Among those with a site code of C64.9 (the vast majority of which are RCC), we also excluded those with urothelial carcinomas (e.g., morphology codes 8120, 8130). Overall this resulted in exclusion of two cases; 103 cases and 511 controls were included in the final data set for the C8 Science Panel. We also restricted covariates to those that were available in both populations and were the most important predictors of cancer in each data set, i.e., hypertension and BMI (kidney function was not available in Science Panel data). In the C8 Science Panel data, time-dependent hypertension and BMI were not available, and hence we used hypertension and BMI reported at time of interview in 2009–2011. Hypertension and BMI thus defined were statistically significant predictors of RCC risk ($p < 0.05$) in the C8 Science Panel data. In the NCI data, hypertension and BMI were also significant predictors of RCC risk. Omitting all confounders except hypertension and BMI from the NCI analysis did not change those results appreciably, with exposure coefficient for log PFOA reduced from 0.77 to 0.74 (a difference of less than 10%, a threshold used to determine whether to adjust for potential confounding (Greenland 1989). Cigarette smoking was not a significant predictor in either the NCI or Science Panel data, and was omitted from the pooled analysis. Hence the pooled analysis controlled for only hypertension and BMI.

3. Statistical analysis of pooled data.

We used conditional logistic regression to analyze the pooled data where each case-control set within either study was a stratum (case-control pairs within the NCI data, and up to

5 controls for each case within the C8 Science Panel data. We controlled for BMI and hypertension in all models. These variables were strong predictors or kidney cancer in our data, and were either significantly ly (p=0.0001) or marginally (p=0.15) associated with PFOA, respectively. Hence we considered them potential confounders, and based on our own prior work (Winquist et al. 2014, Barry et al. 2014), we did not think it likely these variables were mediators. Sensitivity analyses leaving them out of models led to a minor decrease of 5% in the exposure-response coefficient for log PFOA.

Controlling for BMI and hypertension, we then examined a variety of models, including linear, logistic, quadratic, categorical, 2 piece linear spline, and a 3-knot restricted cubic spline model (Harrell et al. 1988). We used both a natural log transformation of serum PFOA and untransformed serum PFOA as our continuous exposure value in the pooled analysis (the NCI study had used log base 2). All analyses were conducted in SAS (www.sas.com).

4. Risk Assessment.

For risk assessment, we used the results of the 2-piece spline model with untransformed PFOA, thereby avoiding the need to choose a non-zero referent. We obtained age-specific background rates (15–39, 40–64, 65–74, for kidney cancer (both sexes combined) from 2018 (https://seer.cancer.gov/statistics). We then calculated the background annual risk of kidney cancer for each year of age from age 20 to 80 (assuming negligible risk prior to age 20), by converting rates to yearly risks. We then calculated the increased rate of kidney cancer for each year of age due to an exposure of 1 ng/ml of PFOA in the serum vs. our counterfactual assumption of 0 exposure, by multiplying background kidney cancer rates by the odds ratio from our model (below the knot). We then converted these rates to annual risks under the 1 ng/ml exposure assumption, and subtracted off the age-specific background risk to obtain a yearly excess risk for each year of age. We then summed these yearly excess risks across age 20–80 to obtain lifetime excess risk Excess lifetime risks were calculated across all sexes and races. We adjusted for competing causes using all cause death rates (10 year age intervals) from CDC Wonder (https://wonder.cdc.gov/ucd-icd10.html). Yearly background risk, yearly risks at a given exposure level (serum PFOA level, per 1 ng/ml), and yearly excess risk (each year of age from age 20–80) were calculated, and then summed across ages to obtain lifetime excess risk (Gail 1975).

We also calculated the cancer slope factor per ng/kg/d intake of PFOA, as the quotient of the cancer slope factor per ng/ml increase in serum PFOA and the clearance rate for PFOA in ml/kg/d. The clearance rate is the product of the elimination rate coefficient and the volume of distribution for PFOA (CalEPA, 2021). Using a serum half-life of 2.3 years and a volume of distribution of 170 mL/kg (Lu and Bartell, 2020), we calculate a clearance rate of 0.14 ml/kg/d for PFOA in humans.

Following the approach of CalEPA (2021), we also calculated a health-protective concentration of PFOA in drinking water as $R \div (CSF_{intake} \times DWI)$, where R is the de minimus cancer risk threshold of 10^{-6}, CSF_{intake} is the cancer slope factor per ng/kg/d intake of PFOA, and DWI is the lifetime average daily water intake rate of 0.053 L/kg/d.

Results

1. Analyses of each data set and of pooled data..

There is a strong difference in exposure-response for the two different studies, with the NCI study showing a much steeper slope for both PFOA and log PFOA models, based on exposures which corresponded to the lower half of the exposure range of the C8 Science Panel study. In linear models the exposure-response coefficient using continuous PFOA for the NCI data was 0.089 (95% CI: 0.043, 0.136) for PFOA and 0.74 (95% CI: 0.38, 1.09, AIC 423.1) for log PFOA, whereas for the C8 Science Panel data it was 0.000079 (95% CI: 0.000480, 0.000635) for PFOA and 0.07 (95% CI: 0.02, 0.15, AIC 368.7) for log PFOA. If the data for the C8 Science Panel study were restricted to the range of the NCI study (approximately <=15 ng/ml PFOA after excluding one outlier), the coefficient for log PFOA in the C8 Science Panel study (38 cases) would increase to 0.22.

We also fit two-piece linear splines to each data set, using untransformed PFOA. For the NCI data, for which 13 ng/ml proved the best knot, the coefficient for the first piece was 0.126 (0.0640 0.1808) and for the 2nd piece was −0.110 (95% CI: −0.195 −0.025). For the C8 Science Panel data, 40 ng/ml proved to be the best knot; the coefficient was 0.012 (95% CI: −0.003, 0.028) for the first piece, and −0.012 (95% CI: −0.028, 0.003) for the 2nd piece.

We fit additional models with the pooled data, again using only hypertension, BMI, and PFOA or log PFOA in the model. See Table 1 for a list of the models tried and their respective model fits. Using the Akaike Information Criteria (AIC), the preferred model was a 2-piece spline model using log PFOA (Figure 1), while the 2nd best was a 2 piece spline model using untransformed PFOA (Figure 2). Restricted cubic splines with 4 knots produced a dose-response curve similar to the 2-piece linear model, providing further support. An interaction term between log PFOA (or untransformed PFOA) and study (NCI vs C8 Science Panel) was highly significant in all models, indicating substantially difference in effect sizes between the two studies, as expected, but we did not include interaction terms in our final model because we wished to determine the exposure-response relationship in the combined data.

2. Risk Assessment.

Using the coefficient from the slope below the knot in the untransformed 2-piece linear spline model (Figure 2), the lifetime excess risk for kidney cancer with an exposure of 1 ng/ml from age 20–80 was 0.00179, or 1.8 per thousand (95% CI 0.9, 2.7). This excess risk, also called the cancer slope factor, is similar to the cancer slope factor values reported by CalEPA of 0.00178 per ng/mL serum PFOA for the NCI study and 0.00029 per ng/mL serum PFOA for a C8 cancer registry-based case-control study with the highest exposure category excluded (Vieira et al., 2013), both based on inverse variance weighted regression and lifetime background risks of kidney cancer for males only (CalEPA, 2021). US EPA reports a cancer slope factor of $1.78*10^{-6}$ per ng/mL serum PFOA, based on the Shearer study and reportedly using the same inverse variance weighted regression method as CalEPA, but the difference is possibly due to an error in units in the US EPA draft report. We replicated the inverse variance weighted regression and lifetime background risk calculation

for the published NCI study results ourselves, and obtained 0.00178 (95% CI, 0.000929, 0.00273) per ng/mL serum PFOA.

Our cancer slope factor of 0.00179 per ng/mL serum PFOA is equivalent to 0.00179/0.14 = 0.0128 per ng/kg/day of PFOA intake, given our estimated clearance rate of 0.14. Our slope factor for intake is higher than the values reported by CalEPA (0.00637 and 0.00105 per ng/kg/day for the Shearer and Vieira studies, respectively, with a geometric mean of 0.0026 per ng/kg/day), which relied on a larger estimate of the clearance rate than we used. For an excess lifetime cancer risk level of 10^{-6} and a lifetime average daily water ingestion rate of 0.053 L/kg/day, our slope factor implies a health-protective concentration of 0.0015 ng/L (parts per trillion) for PFOA in drinking water. This value is similar but somewhat lower than CalEPA's result of 0.0073 ng/L based on kidney cancer, and the recent US EPAs recommendation of 0.004 ng/ml (ppt) based on decreased serum antibody concentrations (https://www.epa.gov/system/files/documents/2022-06/technical-factsheet-four-PFAS.pdf).

Discussion

The cancer slope factor for serum PFOA from our pooled data analysis is nearly identical to the cancer slope factor reported by CalEPA using inverse variance weighted regression across exposure categories for the NCI study alone. In both of our linear spline models (log and untransformed exposure), the optimal knot was found at about 10 to 13 ng/mL serum PFOA, with steeper slopes below the knot than above. There was no evidence in any of our models of any dose-response threshold for kidney cancer (i.e., a dose below which there was no increase in risk).

The relatively flat dose-response shape above the knot in each of our spline models is not uncommon in epidemiologic studies, and has been observed in many other settings (Stayner et al., 2003, Lanphear 2017). Such flattening of exposure-response curves at higher exposures can result from many things, including saturation of biological pathways at higher exposures, greater mismeasurement at higher exposures, and depletion of a group of susceptible subjects at higher exposures, among others. This flattening has been observed for other outcomes with PFOA, including cholesterol (Steenland et al. 2009, Li et al. 2020)

This flattening of the curve at higher exposures may also partly explain the marked difference in linear model slopes between the NCI and C8 Science Panel studies, as the majority of observations in the latter study occurred at PFOA concentrations above the knot, where the dose-response is essentially flat. Considering the slope change above these serum concentrations, it may be appropriate for kidney cancer risk assessments targeting lower exposures to exclude these higher dose groups when fitting linear models, as CalEPA did in one of its analyses (CalEPA, 2021).

There are several strengths to our approach. First we included the two largest studies of kidney cancer incidence with strong quantitative data on personal estimates of serum PFOA levels. Second, pooled analyses are able to flexibly model the combined data, compared to using published data, which use inverse-variance weighted regression lines through observed categorical point estimates. We were able to try a variety of models and found that the

best fitting ones were 2-piece linear spline models, which conform to the 'plateauing' of exposure-response curves at high exposure which, as noted, has been commonly observed. The fact that our own results for excess cancer risk closely match those derived from analyses using only published data with inverse-variance weighting is reassuring for those agencies tasked with setting recommended limits. We believe that the fact that one of our studies was mostly low exposure and one was mostly high, with overlapping ranges of exposure, can be viewed as a strength, rather than a weakness, as it enabled us to get a more complete picture of the exposure-response across all ranges of exposures.

Another strength is that we were able to assess the dose-response in the low dose region with the pooled data. Earlier estimates of a cancer slope factor by EPA and OEHHA, were done without evaluating the raw data. Some of the EPA and OEHHA risk assessment modelling assumptions and approaches were untestable (i.e., assuming dose-response linearity in the low dose range, estimating the slope by fitting inverse variance weighted models to the categorical data). This is the first time there's been a published analysis of the C8 data using lagged serum, compatible with the NCI study results, instead of cumulative serum.

Weaknesses to our approach include the limitation of our work to only two studies, although as noted these are perhaps the strongest and largest studies with quantitative data on kidney cancer and PFOA. There are two other studies of kidney cancer incidence in relation to PFOA; one is an occupational study with a small number of kidney cancers and potentially greater misclassification of PFOA exposure, without estimates of individual serum levels (Raleigh et al. 2014), and the other a study which overlaps to some degree with the population in Barry et al. (2014) that we used, the study by Vieira et al. 2013. The Vieira et al. study was limited by the lack of residential history for assigning historical estimated serum levels, and limited number of cases for which exposure could be estimated based on residence at the time of diagnosis (n=59). Vieira et al. also relied on cancer registry cases as controls (excluding kidney, pancreatic, testicular, and liver cancers, as well as the cancer type being analyzed), which may underestimate risks if some of the control cancers were also related to PFOA. A more recent study of a large population in Ronneby, Sweden, with high water contamination of several PFAS, has also implicated kidney cancer, but is not focused specifically on PFOA and does not quantify individual exposure estimates for any PFAS (Li et al. 2022).

Another limitation to our study is that estimates are based on a serum level at a specific point in time (approximately 8 years prior to diagnosis on average), and an assumption that excess lifetime risk can be estimated by an assumed constant serum level over time. It is possible that cumulative serum levels may have a more direct relation to kidney cancer; however, they were not available in the NCI study and hence not available for our pooled analysis. However, in the Science Panel data, cumulative serum levels 8 years prior to diagnosis did not fit the data better than current serum levels 8 years prior to diagnosis.

There is also some uncertainty regarding the average half-life of PFOA in human serum and its potential dependence on sex, age, kidney function, starting serum concentration, current exposure, and/or isomer, which could affect our estimates. Although a half-life of 3.5 years was used for the exposure reconstruction and serum estimates in the C8 Science

Panel study (Shin et al., 2011b), more recent evidence better supports a half-life in the range of 2 to 3 years (Steenland et al., 2020). Thus, here we used a half-life of 2.3 years to estimate a clearance rate of 0.14 ml/kg/d and a cancer slope factor of 0.0128 per ng/kg/d of PFOA intake. If we assume instead a half-life of 3.5 years, the clearance rate would be 0.0922 ml/kg/d, the cancer slope factor would be 0.0194 per ng/kg/d of PFOA intake, and the health-protective concentration for PFOA in drinking water would be 0.0010 ng/l. The slope factor and health-protective concentration in drinking water remain the same order of magnitude for any realistic value of the half-life.

The most appropriate value for the lifetime average daily water ingestion rate is also subject to debate, with the 0.053 l/kg/d estimate that we used being a relatively high value derived from the 95th percentile of 2-day average consumption in a national survey performed in the 1990s (CalEPA, 2021). The current recommended values for consumers only from the EPA Exposure Factors Handbook are 0.017 and 0.044 l/kg/d for the population mean and 95th percentile, respectively (US EPA, 2019). However, a recent study noted that long-term average water ingestion rates are likely to be much less variable across individuals than 2-day average water ingestion rates, producing shrinkage estimates of long-term average water ingestion rates (Cuvelier and Bartell, 2021). Using a mean lifetime average daily water ingestion rate of 0.17 l/kg/d, which may be more realistic for a typical lifetime average than 2-day upper percentile values, we compute a health-protection concentration of 0.0071 ng/L in drinking water. The health-protective concentration in drinking water remains the same order of magnitude for any realistic value of the daily water ingestion rate.

Finally, yet another limitation is that the evidence base remains somewhat sparse, and to date the link between PFOA and kidney cancer is probable but not definitive. Nonetheless the evidence in our view, and in the view of US and other regulatory agencies, is sufficiently strong to conclude that PFOA is a likely cause of kidney cancer, and as such it is prudent to develop health-based limits for levels of PFOA permissible in drinking water. Although EPA has a new Drinking Water Health Advisory of 0.004 ng/l (ppt), this health advisory is “non-enforceable and non-regulatory.”

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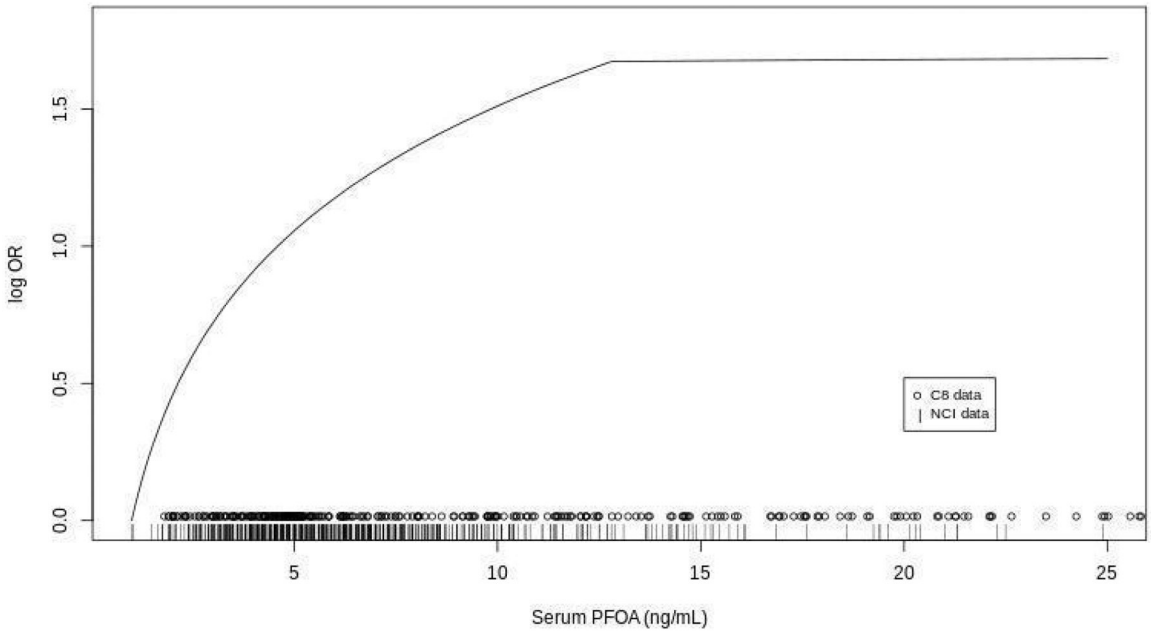

Figure 1.

below shows a graph of the log PFOA -piece linear spline model, with the best knot being at the 67th percentile of serum levels in the pooled data (and the 92.5% of the NCI distribution).

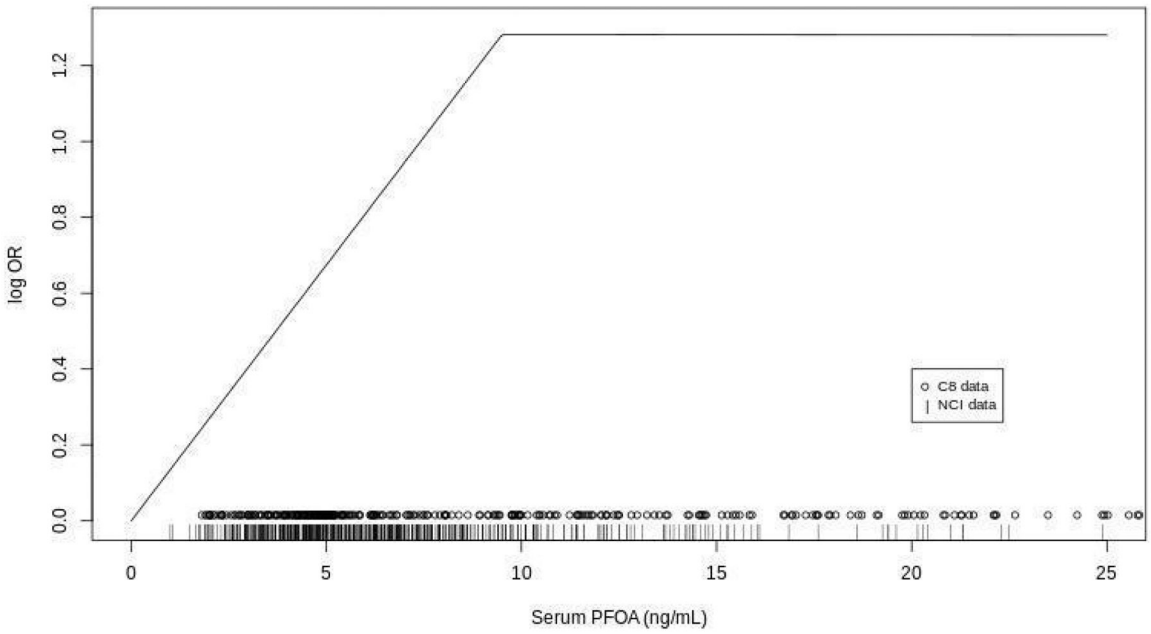

Figure 2.

shows a graph of the untransformed PFOA 2-piece linear spline model, with the best knot being at the 60th percentile of serum levels in the pooled data (and the 85th percentile of the NCI distribution).

Table 1.

Model fits for pooled analysis

Model*	**Coefficients, 95% CI**	**AIC**
linear PFOA	0.0001 (−0.0004, 0.0007)	807.8
log PFOA	0.189 (0.071, 0.307)	798.1
quintiles PFOA	0, 0.286 (−0.132, 0.705), 0.652 (0.273, 1.030), 0.905 (0.425, 1.385), 0.934 (0.370, 1.505)	793.6
cubic spline, 4 knots, PFOA	n.a.	793.2
cubic spline, 4 knots, log PFOA	n.a.**	792.3
quadratic, log PFOA	Linear 0.817 (0.358,1.28) Quadratic −0.087 (−0.148,−0.025)	791.8
2 piece linear spline in PFOA (knot, PFOA=9.5)	First slope, 0.135 (0.071, 0.198) Second slope, −0.0001 (−0.0007, 0.0005)	791.6
2 piece linear spline in log PFOA (knot, log PFOA=2.55)	First slope, 0.656 (0.333, 0.979) Second slope, 0.015 (−0.148, 0.178	790.3

*Conditional logistic regression model with exposure, BMI, and hypertension in the model; 324 cases and 324 controls from NCI study, 103 cases and 511 controls from the C8 Science Panel study.

**Cubic spline model coefficients have no straightforward interpretation.