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Variability and epistemic uncertainty in water ingestion rates and pharmacokinetic parameters, and impact on the association between perfluorooctanoate and preeclampsia in the C8 Health Project population

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ABSTRACT

We recently utilized a suite of environmental fate and transport models and an integrated exposure and pharmacokinetic model to estimate individual perfluorooctanoate (PFOA) serum concentrations, and also assessed the association of those concentrations with preeclampsia for participants in the C8 Health Project (a cross-sectional study of over 69,000 people who were environmentally exposed to PFOA near a major U.S. fluoropolymer production facility located in West Virginia). However, the exposure estimates from this integrated model relied on default values for key independent exposure parameters including water ingestion rates, the serum PFOA half-life, and the volume of distribution for PFOA. The aim of the present study is to assess the impact of inter-individual variability and epistemic uncertainty in these parameters on the exposure estimates and subsequently, the epidemiological association between PFOA exposure and preeclampsia. We used Monte Carlo simulation to propagate inter-individual variability/epistemic uncertainty in the exposure assessment and reanalyzed the epidemiological association. Inter-individual variability in these parameters mildly impacted the serum PFOA concentration predictions (the lowest mean rank correlation between the estimated serum concentrations in our study and the original predicted serum concentrations was 0.95) and there was a negligible impact on the epidemiological association with preeclampsia (no change in the mean adjusted odds ratio (AOR) and the contribution of exposure uncertainty to the total uncertainty including sampling variability was 7%). However, when epistemic uncertainty was added along with the inter-individual variability, serum PFOA concentration predictions and their association with preeclampsia were moderately impacted (the mean AOR of preeclampsia occurrence was reduced from 1.12 to 1.09, and the contribution of exposure uncertainty to the total uncertainty was increased up to 33%). In conclusion, our study shows that the change of the rank exposure among the study participants due to variability and epistemic uncertainty in the independent exposure parameters was large enough to cause a 25% bias towards the null. This suggests that the true AOR of the association between PFOA and preeclampsia in this population might be higher than the originally reported AOR and has more uncertainty than indicated by the originally reported confidence interval.

1. Introduction

Many recent environmental epidemiology studies evaluating associations between perfluorooctanoate (PFOA) and various health effects including ulcerative colitis, kidney and testicular cancer, pregnancy outcomes, abnormal thyroid function, abnormal liver function, and abnormal kidney function have been based on participants from the C8 Health Project/C8 Science Panel Studies (Barry et al., 2013; C8 Science Panel, 2011; Gallo et al., 2012; Lopez-

Abbreviations: C8, PFOA Perfluorooctanoate; MC, Monte Carlo; AOR, Adjusted odds ratio; LN, Log-normal; PK, Pharmacokinetic; IQR, Inter Quartile Range; PI, Probability interval; eGFR, Estimated glomerular filtration rate

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Espinosa et al., 2012; Savitz et al., 2012a, 2012b; Steenland et al., 2013; Watkins et al., 2013). These individuals were environmentally exposed to PFOA from decades of emissions from DuPont's Washington Works facility in the Mid-Ohio valley (Frisbee et al., 2009). PFOA (in the form of ammonium perfluorooctanoate-APFO) was released by the facility from 1950s to early 2000s, and exposure to PFOA for participants in the surrounding communities occurred primarily via inhalation of contaminated air and ingestion of ground water (Paustenbach et al., 2007; Shin et al., 2011a, 2011b). For many of the epidemiological studies, individual exposure assignments were based on model predictions of yearly PFOA serum concentrations for consented C8 Health Project participants. The retrospective serum PFOA concentrations were reconstructed since 1951 using individual residential and water use histories, historical exposure concentrations, and a default elimination half-life. The predicted PFOA serum concentrations were well correlated with measured 2005–2006 serum concentrations (r_s=0.68), supporting the validity of the retrospective exposure estimates (Shin et al., 2011a, 2011b). The measured serum levels in the C8 Health population ranged over several orders of magnitude. The population mean (among the 48,998 consented participants) for serum PFOA concentration was 82.9 (with standard deviation of 240.8) ng/mL; the 2.5th to 97.5th percentile ranging from 4.3 to 530.4 ng/mL (Frisbee et al., 2009).

One of the C8 Science Panel studies analyzed the association between predicted PFOA serum concentration at the year of pregnancy and preeclampsia among the participants and found a moderate association, with an adjusted odds ratio (AOR) of 1.13 per interquartile range increase in ln serum PFOA (Savitz et al., 2012a). The interquartile range was 2.19 units on the log scale; thus there was a 13% increase in the odds of preeclampsia per exp (2.19) ≈ 9-fold increase in serum PFOA. The C8 Science Panel concluded that a probable link exists between PFOA exposure and the occurrence of pregnancy-induced hypertension/preeclampsia (C8 Science Panel, 2011). However, the validity of this study has been questioned by one group of researchers who excluded it from a meta-analysis of PFOA exposure and fetal growth due to the retrospectively modeled exposure assignments with limited validation by measured biomarkers (Johnson and Sutton, 2014; Koustas et al., 2014). Previous studies have shown that the use of modeled pollutant concentrations and self-reported activity patterns can introduce exposure measurement error (Sarnat et al., 2010; Wu et al., 2013), as can studies that rely only on a single biomarker measurement to characterize each individual's exposure (Bartell et al., 2004; Bradman et al., 2013; Prentice et al., 2013; Tsuchiya et al., 2012) For the Savitz et al. (2012a) study, uncertainties in spatiotemporal predictions of PFOA water/air concentrations and in individual-level variables (e.g., water ingestion rates, PFOA half-life, PFOA volume of distribution) used in the dose-reconstruction and pharmacokinetic models likely resulted in some exposure measurement error, potentially affecting the validity of the epidemiological findings.

In a recent uncertainty analysis (Avanasi et al., 2016), we used a Monte Carlo (MC) simulation methodology to characterize uncertainty in PFOA groundwater concentrations predicted from environmental fate and transport models, and determined its potential impacts on serum PFOA concentration predictions and the association between PFOA and preeclampsia (Avanasi et al., 2016). We found that shared water PFOA concentration uncertainty, which is correlated within individuals over time and between individuals with shared water sources, substantially impacts the PFOA serum concentration predictions but only mildly impacts the epidemiological association between PFOA and preeclampsia. This appears to be due to the fact that shared uncertainty, even at a high magnitude, does not perturb the rank order of exposure among the preeclampsia cases and controls of the study. However, preliminary analyses in that study suggested that uncertainty in independent exposure parameters such as the tap water ingestion rates might have a larger impact on epidemiological associations than that in shared PFOA water concentrations (Avanasi et al., 2016).

The objective of the present study is to determine the potential impacts of other input parameter uncertainties on the PFOA serum concentration predictions and the association between PFOA and preeclampsia. The input parameter uncertainties included in this study are realistic inter-individual variability and more subjective epistemic uncertainty in independent (non-shared) exposure factors such as water ingestion rates assigned using either self-reported (Frisbee et al., 2009) or population-level default values (U.S. EPA, 2011), PFOA elimination half-life, and PFOA volume of distribution. It has been previously identified that distinguishing these two types of uncertainty is important and commonly not addressed by researchers. Variability differs from epistemic uncertainty in a way that it represents heterogeneity in a parameter of interest, while epistemic uncertainty arises out of our lack of knowledge/understanding of the value of a parameter or its variability (Burmaster and Anderson, 1994; Cullen and Frey, 1999; Finley and Paustenbach, 1994; Morgan and Henrion, 1990). In this manuscript we obtained realistic variability distributions on these parameters from literature wherever possible. We then used Monte Carlo simulation to determine impacts on the predicted serum concentrations and the association between PFOA and preeclampsia.

2. Materials and methods

2.1. Environmental fate and transport modeling

The historical PFOA air and groundwater concentrations used in the exposure assessment were predicted by an integrated fate and transport model system (Shin et al., 2011a). This modeling system included a series of linked environmental fate and transport models to predict the yearly PFOA air and groundwater concentrations for the years 1951–2008, for the area that covers the communities that consented to the C8 Health Project (includes participants from the six public water districts-the City of Belpre, Little Hocking Water Association, Tuppers Plains Chester Water District, the Village of Pomeroy Water District, Lubeck Public Services District, and Mason County Public Service District). These models utilized information on historical release rates of PFOA, local meteorological and hydrogeological data, and PFOA physiochemical properties. More details on the modeling and the calibration methodology are described by Shin et al. (2011a).

2.2. Exposure-reconstruction and pharmacokinetic modeling

The predicted PFOA air and groundwater concentrations were then used in an exposure model to predict yearly PFOA exposure doses through inhalation and ingestion for each of the participants (Shin et al., 2011b). To predict yearly total exposure doses (combined inhalation and ingestion doses) for each of the participants, this exposure model utilized information on: self-reported participant demographics such as age, gender, body weight; residential/work histories; standard (recommended mean) inhalation rates (U.S. EPA, 2011); standard (self-reported, if available) water ingestion rates; and information on the historical pipe distribution systems of each of the six public water districts. Self-reported water ingestion rates (number of cups per day) were available for approximately 50% of the C8 Health Project participants (Shin et al., 2011b) and were used when available. This is