UNIVERSITY OF CALIFORNIA,
IRVINE

The Impacts of Uncertainty/Variability in the C8 Exposure Assessment on Serum PFOA Concentration Predictions and the Epidemiological Association with Preeclampsia

DISSERTATION

submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in Environmental Toxicology

by

Raghavendhran Avanasi Narasimhan

Dissertation Committee:
Associate Professor Scott M. Bartell, Ph.D., Chair
Professor Ulrike Luderer, Ph.D.
Associate Professor Verónica Vieira, Ph.D.

2016

DEDICATION

To

My family and friends

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGMENTS

I would like to express the deepest appreciation to my mentor and research advisor, Dr. Scott Bartell, who guided me through this challenging research project. I am grateful to him for pushing me in the right direction when I went astray and the constant encouragement and positive support. Without his guidance and persistent help this dissertation would not have been possible.

I would then like to thank my other dissertation committee members, Dr. Luderer and Dr. Vieira, for all the support through this process and for their valuable time. In addition, a thank you to Dr. Baker and Dr. Detwiler for being a part of my advancement committee and Dr. Savitz for kindly providing the data for this study. I also thank Dr. Shin for the constant support and help with the dissertation research project. I acknowledge the funding from the National Institute of Environmental Health Science for this project. I then thank the faculty and students of the Environmental Health Science graduate program and the Public Health graduate program at UCI for being excellent colleagues and for all their support.

Finally, I thank my parents and my brother for the constant support through this endeavor. Without them I wouldn't have been able to pass the ups and downs of graduate school life. I also thank all my friends and family members for their support and encouragement.

CURRICULUM VITAE

Raga Avanasi

ragaavanasi@gmail.com, Ph: 806-224-6848

https://www.linkedin.com/in/ragaavanasi

Education

Ph.D. Environmental Toxicology, University of California, Irvine *June 2016*

Specialty Track: *Exposure Science and Risk Assessment*

- ***Dissertation project***: Impact of exposure uncertainty on the association between perfluorooctanoate (PFOA) and preeclampsia in the C8 Health Project population (2012-2016)

M.S. Environmental Toxicology, Texas Tech University, Lubbock *August 2010*

- ***Thesis project:*** The environmental fate of C_{60} nanomaterial: sorption, desorption, plant uptake and biodegradation (2008-2010)

B.Tech Biotechnology, VIT University, Vellore, India *May 2008*

Research Interests

Exposure science, human health/ ecological risk assessment, uncertainty analysis, environmental health science

Research Experience

Graduate Student Researcher *September 2011 – June 2016*

Exposure Science and Risk Assessment, University of California, Irvine

- Conducted PFOA exposure assessment and statistical methods of data analysis, environmental epidemiology analyses, managed large data sets, conducted uncertainty analysis, evaluated the literature in PFOA toxicology, mechanisms of action, epidemiology and the exposure measurement error literature, contributed to a successful NIH R21 grant proposal, communicated key findings in conferences, published peer-reviewed manuscripts
- *Softwares: R, MATLAB, Microsoft office suite, BMDS, familiar with ArcGIS, AERMOD*
- *Projects:*
  - Impact of correlated uncertainty in PFOA water concentrations on the association between PFOA and preeclampsia in the C8 Health Project population
  - Impact of variability and epistemic uncertainty in water ingestion rates and pharmacokinetic parameters on the association between PFOA and preeclampsia in the C8 Health Project population
  - Impact of geocoding uncertainty on the association between PFOA and preeclampsia in the C8 Health Project Population

Co-instructor of Environmental Modeling and Risk Assessment course *Spring 2015*

- Guest lecture, helped students understand the concepts of environmental modeling and risk assessment

Technical Consulting-Health Scientist Intern *April – September 2013*
Cardno ChemRisk, LLC

- Summarized literature on CNT exposure assessment from nanocomposite applications, critically evaluated the toxicological literature of Nickel nanomaterials, reviewed and summarized the current state of nanomaterial regulations, identified data gaps, assisted with client consulting work (litigation support), co-authored a conference publication, wrote toxicology reports
- *Projects:* Release-ability of CNT from nanocomposite materials, nanomaterial risk ranking framework

Environmental Chemist *September 2010 – April 2011*
ERMI Environmental Services, Allen, Texas

- Executed EPA's standard chemical analyses on industrial samples for regulatory purposes, followed SOP's, reported and maintained data in the LIMS system, helped with achieving the client turnaround time

Graduate Research Assistant *August 2008 – August 2010*
Department of Environmental Toxicology, TTU

- Reviewed environmental toxicology literature, studied the environmental fate of C60 fullerene nanomaterial, contributed to analytical toxicology projects, communicated key results in conferences and published a peer-reviewed manuscript

- *Projects:*
  - The environmental fate of C_{60} nanomaterial: sorption, desorption, plant uptake and biodegradation (2008-2010)
  - Ecological risk assessment: Modeling diazinon fate from a field to a playa lake- estimating risks to Daphnia *magna* and bluegill fish
  - Field work: Air sampling in a superfund site for PAHs, Dioxins and PCBs

Publications

- **R.Avanasi**, HM. Shin, V.M. Vieira, S.M. Bartell. Impact of geocoding uncertainty on the association between perfluorooctanoate and preeclampsia in the C8 Health Project Population (manuscript under review)
- **R.Avanasi**, HM. Shin, V.M. Vieira, S.M. Bartell. 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 (Environmental Research, April 2016)
- **R. Avanasi**, HM. Shin, V. M. Vieira, D. A. Savitz, S. M. Bartell. Potential impact of exposure uncertainty on the association between perfluorooctanoate and preeclampsia in the C8 Health Project population (Environmental Health Perspectives, January 2016)

- **Avanasi R,** Jackson WA, Sherwin B, Mudge J, Anderson TA. C60 fullerene soil sorption, biodegradation, and plant uptake. *Environ. Sci. Technol.*, *48* (5): 2792–2797 (2014)
- Kovochich M, **Avanasi R**, Madl AK. Analysis of factors associated with the releasability of Carbon Nanotubes (CNTs) from materials containing nanocomposites. *Nanotech,* 3(5):485-488 (2013)

Awards and Affiliations

- Student Merit Award (Exposure Assessment Specialty Group)- Society of Risk Analysis national conference, 2013
- The Bob and LaRae Parry Environmental Scholarship, 2013
- SETAC Foundation for Environmental Education student award, 2009
- VIT University Merit Scholarship for the academic years 2005-06 and 2006-07
- Member of SOT (current), ISES (past), SRA (past), SETAC (past), MENSA INDIA (life)

Technical Presentations and Conferences

- Oral Presentations
    - The ISES International conference in Cincinnati, OH, October 2014
    - The SETAC National meeting in New Orleans, LA, November 2009
- Poster presentations
    - The ISES International conference in Henderson, NV, October 2015
    - The SRA annual conference in Baltimore, MD, December 2013
    - The South Central SETAC regional meeting in San Marcos, TX, May 2009

Manuscript Referee

- Volunteer referee for the journal *Biological Trace Element Analysis*

Other interests

- ***Science communication***: Blogging about chemical exposures and health risks in a non-technical language https://ragaavanasi.wordpress.com/category/chemicals-exposure-risk/
- ***Leadership***: Past Graduate Student Representative of the Environmental Health Science graduate program at UCI- acting as a liaison between students and the program committee, mentoring of students
- ***Extracurricular***: Racquetball, badminton, yoga, art, juggling

ABSTRACT OF THE DISSERTATION

The impacts of uncertainty/variability in the C8 exposure assessment on serum PFOA concentration predictions and the epidemiological association with preeclampsia

By

Raghavendhran Avanasi Narasimhan

Doctor of Philosophy in Environmental Toxicology

University of California, Irvine, 2016

Scott M. Bartell, Chair

Previous studies produced the C8 exposure assessment which included PFOA release assessment, integrated fate and transport modeling, and dose reconstruction to predict the serum PFOA concentration of each individual in the C8 Health Project population from 1951 to 2008. The serum concentration predictions were used in various C8 Science Panel epidemiological studies to evaluate whether there is a 'probable link' between PFOA exposure and health effects. One such study analyzed the association with preeclampsia among the participants and found a moderate association (Savitz et al., 2012a). For this study, uncertainties in spatiotemporal predictions of PFOA water/air concentrations and in individual-level variables used in the dose-reconstruction and pharmacokinetic models likely resulted in some exposure measurement error, potentially affecting the validity of the epidemiological findings.

The main objective of this dissertation was to analyze the impacts of different sources of input parameter uncertainty/variability in the C8 exposure assessment and study the impacts on the serum PFOA concentration predictions and the epidemiological association with

preeclampsia. Monte Carlo (MC) simulation techniques were used to conduct these uncertainty analyses in this exposure assessment-environmental epidemiology model system.

I found that autocorrelated and shared uncertainty in the PFOA water concentration estimates produced a highly variable set of plausible serum PFOA concentrations for study participants; however, it had less impact on the AOR of preeclampsia occurrence. Together, inter-individual variability and epistemic uncertainty in independent individual-level exposure parameters including water ingestion rates, the serum PFOA half-life, and the volume of distribution for PFOA impacted the serum PFOA concentration predictions and their association with preeclampsia moderately, with a 25% bias towards the null in the AOR of preeclampisa occurrence. Geocoding based uncertainty in residential addresses and work history together moderately impacted the rank exposure among the participants and caused a 41% bias away from the null in the AOR of preeclampsia occurrence.

Future studies with complex exposure scenarios and multiple sources of variability/uncertainty might benefit from our approach of separating out the different kinds of uncertainty to better understand their individual impacts on the validity of epidemiological associations

CHAPTER 1: INTRODUCTION

1.1 Background

1.1.1 The C8 exposure assessment

Perfluorooctanoic acid (PFOA)

Ammonium Perfluoroocatanoate (APFO) is a surfactant that was used in the manufacture of perfluorinated compounds with multiple applications including non-stick cook ware, stain-free carpets and clothing, food contact paper etc. Once in the environment, APFO dissociates into the Perfluorooctanoate anion (PFOA) and ammonia. PFOA is also known as 'C8', owing to the fact that the structure has a per-fluorinated eight carbon backbone with a carboxylate group. This unique chemical structure gives the molecule high stability and surfactant properties which makes it very useful in consumer and industrial applications (Paustenbach et al., 2007; Post et al., 2012). Unfortunately, the stability also makes the chemical highly persistent in the environment (Lau et al., 2007). The major sources of PFOA to the environment include direct and indirect emissions from manufacturing facilities around the world. As a result, PFOA is ubiquitous in various environmental media including surface water, soil, sediment, ground water, as well as in biological media including blood samples from wildlife and human beings (Lau et al., 2007; Paustenbach et al., 2007; Post et al., 2012). Exposure sources to humans include occupational exposure, contaminated drinking water, air, and food, non-stick cookware, and household dust (Lau et al., 2007; Paustenbach et al., 2007). The median blood level of PFOA in the non-institutionalized U.S. population (in the NHANES study) was reported to be 5 ppb (Calafat et al., 2007).

PFOA is amphiphilic in nature and is absorbed through oral, inhalational and dermal routes of exposure. The distribution of PFOA is highest in the liver, followed by serum proteins (primarily albumin), kidneys, lungs and other tissues (Hundley et al., 2006). Once inside the

human body, PFOA is not metabolized and the excretion half-life has been estimated at 2.3-3.8 years (Bartell et al., 2010; Olsen et al., 2007). Renal and fecal elimination are primary routes of excretion of PFOA from the human body (Han et al., 2012). In animal models, PFOA has been shown to cause benign tumors of the liver, pancreas and the testes through the PPAR-α agonist mechanism. PFOA has been shown to cause weight loss, hepatic hypertrophy and necrosis, immune suppression, neurobehavioral effects, reproductive effects, and developmental effects (Kennedy et al., 2004; Lau et al., 2007; Post et al., 2012). Epidemiological studies have been based on occupational and community exposures, and mostly cross-sectional study designs; some with modest associations between PFOA exposure and cholesterol, hyperuricemia, and elevated liver enzymes, colitis, thyroid disease, kidney and testicular cancer, pregnancy induced hypertension/preeclampsia (Steenland et al., 2010; Lau et al., 2007; Post et al., 2012; C8 Science Panel, 2011; Steenland et al., 2013; Barry et al., 2013; Savitz et al., 2012a, Savitz et al., 2012b, Lopez-Espinosa et al., 2012; Gallo et al., 2012; Watkins et al., 2013; C8 Science Panel, 2011).

The C8 Health Project

The C8 Health Project is a cross-sectional epidemiologic study of 69,030 people who lived near a primary U.S. PFOA production facility, located in the Mid-Ohio Valley near Parkersburg, West Virginia. Formed in 2005, the study is a result of a settlement between DuPont and local residents who may have suffered adverse health consequences due to their PFOA exposures. C8 Health Project participants constitute the most highly exposed sentinel population in the world, with serum PFOA concentrations up to thousands of times larger than typically found in the US general population (Frisbee et al., 2009). APFO was used in the manufacture of fluoropolymers at the Mid-Ohio Valley production facility since the 1950s. For decades, large amounts of PFOA were released into the atmosphere through emissions from air

stacks as well as effluent discharge into the Ohio River. The surrounding air, surface soil, surface water and subsurface water had been contaminated with PFOA through wet/dry deposition onto the surface, leaching through the vadose zone, and transport in the ground water aquifers. As a part of the C8 Health Project, a retrospective PFOA exposure assessment was conducted at UCI (Shin et al., 2011a, Shin et al., 2011b).

The C8 exposure assessment included PFOA release assessment, integrated fate and transport modeling, and dose reconstruction to predict the exposure dose to each individual in the C8 Health Project from 1951 to 2008. First, historic PFOA emission rate estimates for the DuPont facility were obtained from a previous study conducted by Paustenbach et al. in 2007. Using these estimates with the physiochemical properties of PFOA and the historic local meteorological and geologic characteristics, a suite of environmental fate and transport models including AERMOD, PRZM-3, BreZo, MODFLOW, and MT3DMS were applied to generate predicted concentrations of PFOA in the air, surface water and ground water around the facility (Shin et al., 2011a). The predicted air and water concentrations were utilized along with individual residential/work histories, demographics (age, gender, body weight), standard exposure factors (air inhalation rate, drinking water ingestion rate), historical pipe installation information of public water supply and a single compartment pharmacokinetic model to reconstruct the PFOA exposures of the study population and predict their yearly serum PFOA concentrations (Shin et al., 2011b). Among all participants (N = 43,449), the Spearman's rank correlation coefficient between the estimated and the 2005-2006 observed serum PFOA concentration (measured as a part of the C8 Health Project) was 0.67 (Shin et al, 2011b). Median estimated and observed serum concentrations in 2005-2006 were 13.7 and 23.5 ng/mL, respectively.

The serum concentration predictions were/are being used in various epidemiological studies to evaluate whether there is a 'probable link' between PFOA exposure and health effects. The C8 Science Panel concluded that the following outcomes may be linked to PFOA exposure in the C8 Health Project study population: cholesterol, colitis, uric acid, kidney and testicular cancer, thyroid disease, pregnancy induced hypertension/ preeclampsia (Steenland et al., 2013; Barry et al., 2013; Savitz et al., 2012a, Savitz et al., 2012b, Lopez-Espinosa et al., 2012; Gallo et al., 2012; Watkins et al., 2013; C8 Science Panel, 2011).

1.1.2 Perfluorooctanoate exposure and preeclampsia occurrence

The validity of the C8 Science Panel PFOA-preeclampsia epidemiology study

One of the C8 Science Panel studies analyzed the association between PFOA serum concentrations at the year of pregnancy and preeclampsia among the participants and found a moderate association (Savitz et al., 2012a). Using the estimated historical PFOA serum concentrations, Savitz et al. (2012a) evaluated the associations between estimated PFOA serum concentrations at pregnancy and self-reported pregnancy related health outcomes, including preeclampsia among the C8 Health Project participants from 1990-2006 using generalized estimating equation regression models. There are 730 self-reported preeclampsia outcomes among the total 10,189 pregnancies. To address potential confounding, they adjusted for maternal age, parity, education and maternal smoking status. The adjusted odds ratio (AOR) for the continuous exposure variable was 1.13 (95% confidence interval (CI) = 1.00-1.28) for an interquartile range (25th to 75th percentile) of log PFOA serum concentration (units of nanograms per milliliter).

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). Also, 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; Tsuchiya et al., 2012; Bradman et al., 2013; Prentice et al., 2013). 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, residential/work addresses) used in the dose-reconstruction and pharmacokinetic models likely resulted in some exposure measurement error, potentially affecting the validity of the epidemiological findings.

Possible mechanisms of preeclampsia development due to PFOA exposure

Hypertensive disorder is one of the most common complications of pregnancy with 6-8% prevalence. Pregnancy induced hypertension, preeclampsia, chronic hypertension, and preeclampsia super-imposed with chronic hypertension are the four categories of hypertensive disorders of pregnancy; gestational hypertension/pregnancy induced hypertension is described as a provisional diagnosis for women with new-onset, non-proteinuric hypertension after 20 weeks of gestation, and preeclampsia is described as the development of new-onset gestational hypertension with proteinuria after 20 weeks of gestation (The National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000). Adverse health effects of preeclampsia include pre-term birth, decreased fetal weight; with severe forms leading to Hemolysis Elevated Liver enzymes Low Platelet count syndrome (HELLP), eclamptic seizure, maternal and neonatal morbidity or mortality (Leeman and Fontaine, 2008; The National

High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000; Zamorski and Green, 2001). The mechanism by which preeclampsia is caused is still unclear (The National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000; Wagner, 2004). Multiple mechanisms of action have been proposed (Granger et al., 2001; Leeman and Fontaine, 2008). Risk factors for preeclampsia include high Body Mass Index (BMI), first pregnancy, multiple birth, family history of PIH, age (<20, >40), race, smoking, high blood pressure, kidney disease, gestational diabetes (Sibai et al., 1997; Zamorski and Green, 2001).

Epidemiological studies associating PFOA exposure and preeclampsia/pregnancy induced hypertension have been very limited and have mostly been results of the C8 Health Project. Four studies (Nolan et al., 2010; Savitz et al., 2012a; Savitz et al., 2012b; Stein et al., 2009) were cross-sectional in nature with only one study being a cohort follow-up study (Darrow et al., 2013). Three studies used the measured serum PFOA concentration (Nolan et al., 2010; Stein et al., 2009; and Darrow et al., 2013), while two studies (Savitz et al., 2012a; Savitz et al., 2012b) utilized the predicted serum concentrations based on the UCI exposure assessment model (Shin et al., 2011b). A recent study by Starling et al., 2014 did not find any increased risk of preeclampsia occurrence with increasing exposure to perfluoroalkyl compounds including PFOA using data from the Norwegian Mother and Child Cohort study. It should be noted that most of the studies are cross-sectional and the resulting association doesn't necessarily imply causation. Also, it is possible that confounders including co-exposures might have been missed in the studies. Nevertheless, these are the only published studies looking at the association between PFOA exposure and preeclampsia development. It should also be noted that the strength of association increased with increased accuracy of the exposure estimates and the results of the

only cohort follow-up study (Darrow et al., 2013) showed a stronger positive association with adjusted odds ratio (OR) per log unit increase in PFOA of 1.27 (95% CI: 1.05, 1.55). This study followed a sub-set of the population after 2005 and utilized the measured serum concentrations, corrected for decay over time as the exposure variable. This study is particularly important given that there was little ongoing PFOA exposure for study participants after serum measurements were obtained in 2005-2006, so the uncertainty stemming from exposure measurement error is relatively low compared with the other studies that utilize retrospectively predicted serum PFOA concentrations.

The C8 Science Panel reviewed the existing studies and based on the weight-of-evidence, concluded that there is a probable link between PFOA exposure and preeclampsia/pregnancy induced hypertension (C8 Science Panel, 2011). The C8 Science Panel review concluded that there is a weak to moderate association between PFOA exposure and the occurrence of preeclampsia, with an irregular dose-response pattern. It also noted that the association strengthened with increased confidence/accuracy in the exposure estimates (C8 Science Panel, 2011). However, there is currently little toxicological evidence regarding preeclampsia induction following exposure to PFOA.

In general, the possible independent mechanisms through which preeclampsia is caused are not clearly elucidated (The National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000; Wagner et al., 2004; Granger et al., 2001; Leeman and Fontaine, 2008). Some of the theories of preeclampsia pathogenesis include abnormal placental implantation, abnormal angiogenic factors, cardiovascular maladaptation, genetic predisposition, immunologic intolerance between fetoplacental and maternal tissue, platelet activation, and vascular endothelial dysfunction or damage (Leeman and Fontaine,

2008). The possible mechanism through which PFOA exposure can lead to preeclampsia has not been studied. One possible mechanism by which PFOA can lead to PIHP is through the induction of hyperuricemia. Based on the C8 Health Project, exposure to PFOA has been modestly associated to elevated uric acid levels (Steenland et al., 2010). Shankar et al., 2011 showed that, at background exposure levels in a different study population, PFOA is positively associated with elevated uric acid levels. Currently, there are no mechanistic studies looking at this association, but, one proposed mechanism of action is the competition between PFOA and uric acid for tubular secretion via OAT 1/ OAT 3 transporters. In general, substrates for renal OATs include chemically heterogeneous weak acids with a carbon backbone and a net negative charge at physiological pH (Anzai et al., 2006). *In vitro* studies have shown that PFOA can lead to the production of ROS in liver cells (Panaretakis et al., 2001; Yao and Zhong, 2005) and potentially lead to elevated uric acid levels, given that uric acid is a known antioxidant (Shankar et al., 2011a). Hyperuricemia can lead to preeclampsia indirectly through the induction of renal micro vascular disease. Strong toxicological evidence suggests that elevated uric acid levels can lead to renal micro vascular disease through fibrosis, interstitial collagen deposition, and macrophage infiltration; leading to tubulointerstitial injury and renal vasoconstriction. The vasoconstriction and ischemic injury has been shown to stimulate the renin-angiotensin system and also inhibit the NOS in the macula densa of the kidney and cause hypertension (Mazzali et al., 2001). Hyperuricemia has also been shown to cause arteriolopathy and vascular smooth muscle cell proliferation *in vitro* (Mazzali et al., 2002). In humans, hyperuricemia has been well established to be an independent risk factor for hypertension (Heinig and Johnson, 2006) and also been shown to be strongly associated with endothelial dysfunction; suggested mechanisms include inflammation-dependent/ independent pathways (Zoccali et al., 2006).

Hyperuricemia has long been used as a marker to diagnose preeclampsia (mostly thought to be a secondary effect of preeclampsia through impaired kidney function), but recently, it has been proposed to play a direct role in the pathogenesis of the disorder. The proposed mechanism includes the promotion of inflammation, oxidative stress and endothelial dysfunction of the placental and maternal vasculature (Kang et al., 2004; Bainbridge et al., 2009). It has been suggested that vasospasm can occur as a secondary effect of endothelial dysfunction caused by elevated uric acid levels and this can lead to ischemic injury. Uric acid has also been suggested to impede trophoblast invasion leading to reduced placental perfusion, placental ischemia and oxidative stress; eventually promoting a feed-forward loop of increased uric acid production and reduced excretion (Bainbridge and Roberts, 2008; Bainbridge et al., 2009). Epidemiological studies have shown a strong correlation between hyperuricemia and preeclampsia (Kang et al., 2004; Laughon et al., 2011). Hence, it is plausible that elevated uric acid levels could be responsible for the induction of preeclampsia in pregnant women.

There could be other mechanisms through which PFOA exposure can lead to preeclampsia. PFOA exposure has been epidemiologically associated with kidney disease (Shankar et al., 2011b), although the possibility of reverse causation cannot be ruled out (Watkins et al., 2013b). Perfluorooctane sulfonate (PFOS) has been shown to induce the production of ROS in human microvascular endothelial cells and lead to increased endothelial cell permeability (Qian et al., 2010). Increased endothelial cell permeability has been suggested to play role in the induction of ischemic acute kidney injury and this can lead to chronic kidney disease (Sutton et al., 2010). Kidney disease has been shown to be a risk factor for increased uric acid levels and pregnancy-related hypertension (Bainbridge and Roberts, 2008; Darrow et al., 2013). Although this has not been shown mechanistically with PFOA exposure, it is still

biologically plausible. Other unknown mechanisms that explain the association between PFOA exposure and the induction of preeclampsia might exist and are yet to be hypothesized/ discussed.

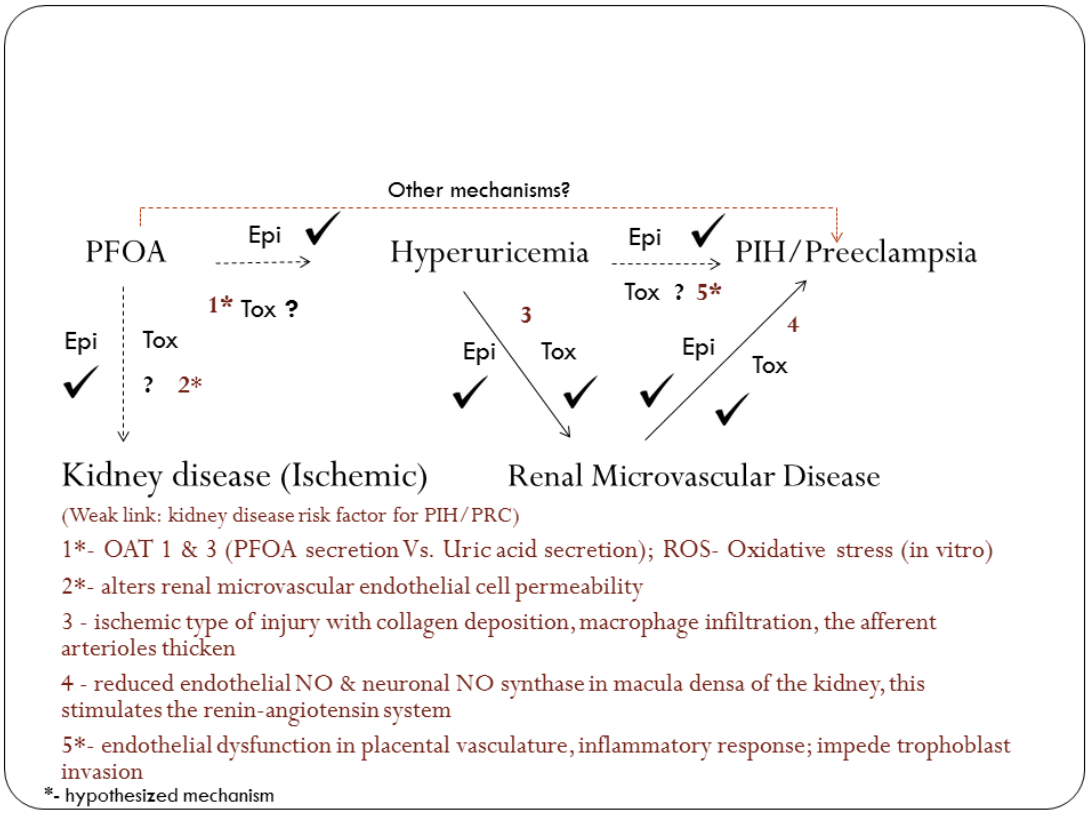

Figure 1.1: Possible mechanisms of preeclampsia development due to PFOA exposure

To summarize, the current literature seems to suggest a possible causal link between PFOA exposure and the induction of preeclampsia, but there are some critical data gaps that need to be addressed. Although epidemiological studies suggest an association between PFOA exposure and preeclampsia induction, there is a need for mechanistic studies to support the association. One possible mechanism is through the induction of hyperuricemia which can directly or indirectly lead to preeclampsia. There is sufficient epidemiological evidence linking

PFOA exposure to elevated uric acid levels among the population, however, there are no mechanistic studies supporting the association and this is a critical data gap that needs to be addressed. Strong toxicological and epidemiological evidence support the link between hyperuricemia and the induction of preeclampsia through the development of RMVD. Direct role of hyperuricemia in the development of preeclampsia has also been proposed, but needs mechanistic evidence to support the hypothesis. Another possible mechanism is through the induction of ischemic acute kidney disease, but toxicological evidence is lacking. Other mechanisms through which PFOA exposure leads to preeclampsia might exist. Given the ubiquitous nature of PFOA distribution and the prominent role of preeclampsia in maternal and fetal morbidity/mortality; future studies that aim to fill these data gaps are needed.

1.1.3 Exposure measurement error

Input parameter uncertainty in exposure estimates contributes to exposure measurement error, which can be described as the difference between an individual's true exposure and the assigned exposure estimate (Armstrong, 1998). The difference between true and assigned exposure can result from inaccuracies in measurement or model-based estimation of environmental chemical concentrations, biomarkers, time-activity patterns, and/or pharmacokinetics. Retrospective fate and transport model estimates may be particularly prone to inaccuracies, and integrating multiple models in the process of an exposure assessment can result in structural uncertainty, whereby uncertainty in one model gets propagated through the following models and can contribute more to the overall uncertainty than all of the individual uncertainties combined (Özkaynak et al. 2008). The use of surrogates for pollutant and participant-level spatiotemporal input data, such as modeled pollutant concentrations, self-reported activity patterns or independent (non-shared) exposure factors, pharmacokinetic

parameters, or single geographic imputation /geocoding at a coarse spatial resolution, can be viewed as a type of exposure measurement error in the assessment (Bartell et al. 2004; Sarnat et al. 2010; Shin et al. 2014; Tsuchiya et al. 2012; Henry and Boscoe, 2008; Zandbergen, 2009).

Exposure measurement error has been shown to introduce bias and random error in environmental epidemiological studies (Thomas et al., 1993) and the quality of exposure data has been identified as a major determinant of the validity of environmental epidemiology studies (Baker and Niewenhuijsen 2008; Rothman et al. 2008). Random exposure measurement error can bias the odds ratio and other epidemiological effect estimates, and also diminish the precision and power of the epidemiologic studies. As a result, it typically hampers the ability to detect an association between the exposure and adverse health effects (Armstrong 1998). Although there is a substantial literature on the potential impacts of exposure measurement error on epidemiologic studies, much of the literature relies on theoretical examples and/or simplified assumptions such as statistically independent measurement errors across participants (Carroll et al. 2006; Gustafson 2003; Zeger et al., 2000). Therefore, there is a need to characterize uncertainty in exposure estimates and in turn, to evaluate its potential impacts on reported epidemiological associations.

1.2 Rationale for the study

The C8 Health Project retrospective exposure assessment model is prone to potential exposure measurement error due to 1) the presence of uncertainty in various physiochemical, hydrogeological parameters utilized in the environmental models to predict the PFOA air and water concentrations, 2) potential variability and epistemic uncertainty in individual-level exposure parameters such as self-reported or population-level drinking water ingestion rates, the

PFOA elimination half-life, the PFOA volume of distribution, and 3) positional error due to the use of ZIP code centroid geocodes for residential addresses that could not be geocoded to exact locations. The uncertainty and variability in these input parameters can impact the accuracy of the exposure model predictions and subsequently, the epidemiological study results. This can potentially lead to questions on the validity of such epidemiological studies and there is a need to study such sources of uncertainty in the C8 exposure assessment.

1.3 Research objectives

The main objective of this dissertation was to analyze the impacts of different sources of input parameter uncertainty/variability in the C8 exposure assessment and study the impacts on the serum PFOA concentration predictions and the epidemiological association with preeclampsia (Savitz et al., 2012a). Specific research objectives are outlined below:

1) To evaluate the potential impact of systematic and random uncertainty in the shared water sources (estimated PFOA drinking water) of the study participants on the predicted serum PFOA concentrations and the epidemiological association between PFOA exposure and preeclampsia.

2) To evaluate the potential impacts of 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 or population-level default values, PFOA half-life, and PFOA volume of distribution, on the predicted serum PFOA concentrations and the epidemiological association between PFOA exposure and preeclampsia.

3) To evaluate potential impacts of geocoding uncertainty due to single geographic imputation (which may have resulted in mischaracterized water PFOA concentrations experienced by those

participants geocoded to ZIP code centroids) on the predicted serum PFOA concentrations and the epidemiological association between PFOA exposure and preeclampsia.

1.4 Overview of the dissertation

In the following three chapters, I present my research work to address the above listed specific objectives respectively. In chapter 2, I used Monte Carlo simulation as a screening-level uncertainty analysis to study the impact of the shared uncertainty (correlated uncertainty across individuals and years) in PFOA water concentration as a surrogate for the uncertainty in various fate and transport parameters used in the environmental modeling system. I present the results and discussion of this analysis comparing the MC simulation based serum PFOA concentration distribution, the rank exposure of participants and the adjusted odds ratio of preeclampsia occurrence with the original results of the Savitz et al. (2012a) study.

In Chapter 3, I studied realistic inter-individual variability and more subjective epistemic uncertainty in independent (non-shared) exposure factors such as water ingestion rates, PFOA half-life, and PFOA volume of distribution by obtaining realistic variability distributions on these parameters from literature. I then used Monte Carlo simulation to determine impacts on the predicted serum concentrations and the epidemiological association between PFOA and preeclampsia. I present the results of this analysis similar to the chapter two and discuss the implications of the results.

In chapter 4, I studied the impact of geocoding uncertainty in the PFOA exposure assessment by using Monte Carlo (MC) simulation to assign alternate geographic locations within the reported ZIP code for all residential addresses that were geocoded to a ZIP code centroid and the reported work addresses. I present the resulting distributions of serum PFOA

concentrations and epidemiological association with preeclampsia and discuss the results in detail.

In the last chapter (chapter 5), I summarize what I learnt from my uncertainty analyses, discuss possible directions for future studies and describe the conclusions of my dissertation.

CHAPTER 2: IMPACT OF EXPOSURE UNCERTAINTY ON THE ASSOCIATION BETWEEN PERFLUOROOCTANOATE AND PREECLAMPSIA IN THE C8 HEALTH PROJECT POPULATION

Raghavendhran Avanasi

Hyeong-Moo Shin

Verónica M. Vieira

David A. Savitz

Scott M. Bartell

Chapter 2 is reproduced with permission from Environmental Health Perspectives. R. Avanasi, HM. Shin, V. M. Vieira, D. A. Savitz, S. M. Bartell. Potential impact of exposure uncertainty on the association between perfluorooctanoate and preeclampsia in the C8 Health Project population. Environmental Health Perspective., Copyright 2016 National Institute of Environmental Health Science)

2.1 Introduction

The C8 retrospective exposure assessment included uncertainty in input parameters utilized in our PFOA fate and transport models. Out of many input parameters, the soil adsorption coefficient (K_d) of PFOA, annual emission rates from the production facility, fraction of organic carbon (f_{oc}) in the surface soil and unsaturated soil zones, and historical pumping rates of public water wells were previously identified as being influential and uncertain due to incomplete data (Shin et al. 2011a; Shin et al. 2012). Uncertainty in these and other parameters can impact the accuracy of exposure estimates and subsequently, the validity of epidemiological study results. However, it is unclear to what extent uncertainties in the exposure estimates threaten the validity of those study results and other epidemiologic findings in this study population. Critical features of our exposure model include a common exposure pathway for people using the same public water source, and linkage of personal residential histories with specific public water sources over time. These model features are important not only as drivers of PFOA exposure, since contaminated drinking water is thought to be the predominant exposure route for most participants (Shin et al. 2011b), but also as indications that exposure uncertainty is unlikely to be statistically independent across participants with the same water source, or across years for the same participant.

In this Chapter, we evaluate the potential impact of systematic and random uncertainty in the estimated PFOA drinking water and serum concentrations on the epidemiological association between PFOA exposure and preeclampsia. For each of the six public water districts (PWD) in the C8 Health Project, we generated multiple plausible year-by-year PFOA drinking water concentrations via Monte Carlo simulation (for a range of 2, 5 and 10-fold uncertainty) and used these new water concentrations to estimate serum PFOA concentrations using the integrated

exposure and pharmacokinetic model. This manuscript evaluates the impact of uncertainty in the fate and transport models by specifying probability distributions directly for PFOA drinking water concentrations instead of specifying distributions for each of the many input parameters in the models; hence it can be considered a screening-level uncertainty analysis. This analysis focuses solely on uncertainty in PFOA drinking water concentrations and does not consider uncertainty in individual-level parameters (drinking water intake and pharmacokinetics).

2.2 Methods

2.2.1 Retrospective exposure assessment

To estimate historical PFOA serum concentrations for participants in the C8 Health Project, we previously conducted a retrospective exposure assessment (Shin et al. 2011a, Shin et al. 2011b) which includes PFOA release assessment, integrated fate and transport modeling, dose reconstruction, and estimation of historical serum PFOA concentrations for each participant. The major steps in that exposure assessment are summarized in the following paragraph.

First, historical PFOA emission rate estimates from the DuPont facility were obtained from a previous study conducted by Paustenbach et al. (2007). Second, we applied a suite of established environmental fate and transport models to estimate the concentrations of PFOA in the air, groundwater and six municipal water supply wells around the facility for the years of 1951-2008. Input parameters of these environmental models include historical emission rate estimates, physicochemical properties of PFOA, and local meteorological and hydrologic data. The six PWDs that are involved in the C8 Health Project included 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.

Figure 2.1 shows the model estimated PFOA water concentrations in the six PWDs over time from 1951 to 2008. Third, the estimated yearly air and water concentrations from environmental modeling were utilized to estimate historical PFOA exposures along with individual residential/work histories, demographic information (age, gender, body weight), standard exposure factors (air inhalation rate, drinking water ingestion rate), and historical pipe installation information of public water supply. Last, a single-compartment pharmacokinetic model was used to estimate year-by-year serum PFOA concentrations for each individual. Among all participants (N = 43,449), the Spearman's rank correlation coefficient between the estimated and the 2005-2006 observed serum PFOA concentration (measured as a part of the C8 Health Project) was 0.67 (Shin et al, 2011b). Median estimated and observed serum concentrations in 2005-2006 were 13.7 and 23.5 ng/mL, respectively.

In the present manuscript we did not change the first or second steps of the exposure assessment, but repeated the third and lasts steps many times using alternative water concentration estimates in order to gauge the potential impacts of uncertainties in PFOA drinking water concentrations (uncertainties in the exposure assessment/pharmacokinetic models were not considered) on estimated serum concentrations and epidemiologic results.

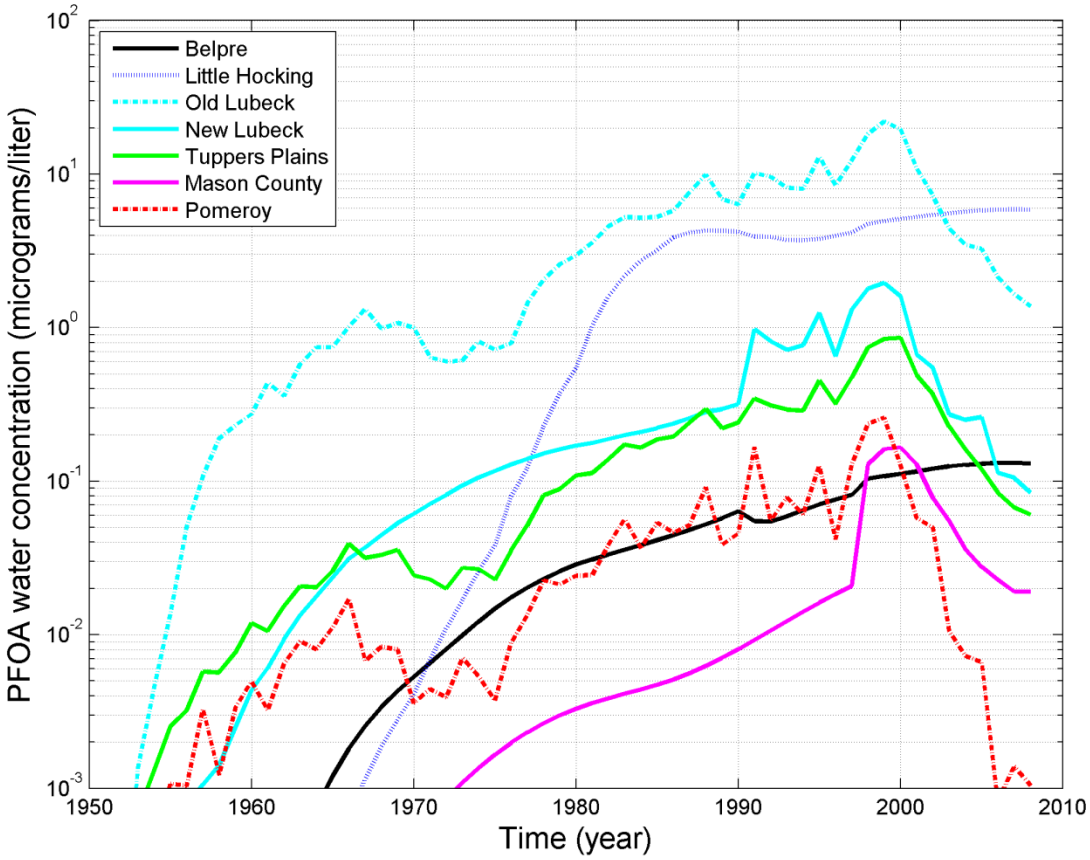

Figure 2.1 Estimated annual average PFOA water concentrations in the six public water districts (adapted from Shin et al., 2011a). Concentrations are shown in log (base 10) micrograms/liter

2.2.2 Previous epidemiological analysis

Using the estimated historical PFOA serum concentrations, Savitz et al. (2012a) evaluated the associations between estimated PFOA serum concentrations at pregnancy and self-reported pregnancy related health outcomes, including preeclampsia among the C8 Health Project participants from 1990-2006 using generalized estimating equation regression models. There are 730 self-reported preeclampsia outcomes among the total 10,189 pregnancies. To

address potential confounding, they adjusted for maternal age, parity, education and maternal smoking status. The adjusted odds ratio (AOR) for the continuous exposure variable was 1.13 (95% confidence interval (CI) = 1.00-1.28) for an interquartile range (25th to 75th percentile) of log PFOA serum concentration (units of nanograms per milliliter).

We obtained approval (HS#2013-9421) from the Institutional Review Board at the University of California, Irvine, to work with the human subject data in this current study. We modified the original analysis by excluding 40 pregnancies of 25 mothers who had work histories in the DuPont PFOA production facilities. These participants might have additional occupational exposure to PFOA before and during pregnancy, which sometimes exceeds the contribution from residential drinking water ingestion. Excluding these pregnancies changes the AOR (95% CI) to 1.11 (0.99-1.24) with 725 preeclampsia outcomes among 10,149 pregnancies.

2.2.3 Monte Carlo simulation

In the Monte Carlo uncertainty analysis, because public well water was a primary exposure route for our study population (Shin et al. 2011b), we selected year-by-year PFOA drinking water concentrations for each of the six PWDs (output from the retrospective fate and transport model) as primary uncertain input parameters and AOR for preeclampsia (output from the epidemiological model) as the output of Monte Carlo simulations. We assumed that PFOA drinking water concentrations are log-normally distributed, because contaminant concentrations are non-negative (Limpert et al., 2001; Morgan et al. 1990).

For each of the six PWDs, we used the following equation to generate multiple simulated drinking water concentrations (n = 500, using Monte Carlo simulation) by multiplying the originally estimated average PFOA drinking water concentrations (Shin et al. 2011a) by three multiplicative uncertainty factors, U1, U2, and U3:

$$C_{i,j,k} = C_{0,i,j} \times U1_{i,j,k} \times U2_{i,k} \times U3_{k}$$

[1]

where $C_{i,j,k}$ is the simulated PFOA drinking water concentration for a PWD *i* for a year *j* for the *k'*th iteration. $C_{0,i,j}$ is the previously estimated average PFOA drinking water concentration for a PWD *i* for a year *j*.$U1_{i,j,k}$ is the random uncertainty factor for a PWD *i* for a year *j* for the *k*'th iteration not specific to any source and it varies the PFOA concentration by PWD by year by iteration. Log $U1_{i,j,k}$ follows a multivariate normal (MVN) distribution (corresponding to each year of exposure) with a mean of 0 for every year, a correlation matrix of Σ, and a constant variance across years, σ^2, i.e., log $U1_{i,j,k} \sim$ MVN ($\underline{\mathbf{0}}$, $\boldsymbol{\Sigma}\ \sigma^2$). We chose off-diagonals of the correlation matrix to stipulate first order autocorrelation of uncertainties across years, with an auto-correlation factor φ. Thus, sampled uncertainty factors for closer years are similar compared to those that are far apart. For example, the sampled PFOA concentrations that are 3 years apart will be correlated by a factor of φ^3.

$U2_{i,k}$ is the systematic uncertainty factor for a PWD *i* for the *k*'th iteration due to mis-characterized PFOA transport in the unsaturated soil zone and groundwater aquifers within the groundwater catchment area of each PWD and thus the PWD-specific uncertainty factor is applied during the time period public water was a primary drinking water source. Log $U2_{i,k}$ follows a normal distribution with a mean of 0 and variance of σ^2, i.e., log $U2_{i,k} \sim N(0, \sigma^2)$. An example to describe U2 is the role of a parameter like the wind direction/speed. Any uncertainty in the wind direction/speed will impact the atmospheric transport and the deposition location of PFOA, systematically influencing each estimated PWD PFOA concentration for all years but with a different magnitude and/or direction for each PWD. For example, mischaracterization of the wind speed and direction due to reliance on off-site meteorological data might be expected to

systematically increase the PFOA deposition in some water districts for all years, and to decrease the PFOA deposition in other water districts for all years because a different prevailing wind direction would increase PFOA deposition rates for downwind water catchment basins but decrease deposition rates for other catchment basins. .

$U3_k$ is the global uncertainty factor for the *k*'th iteration and includes systematic error that affects all PWDs and all years in the same way, such as systematic under- or over-estimation of the PFOA emission rates. Log $U3_k$ follows a normal distribution with a mean of 0 and variance of σ^2, i.e., $\log U3_k \sim N(0, \sigma^2)$.

Because U1, U2, and U3 are generated independently of the original water concentration assignments $C_{0,i,j}$, this model simulates additional classical (as opposed to Berkson) measurement error in the drinking water concentrations.

We repeated the analysis for four different hypothetical values of φ (which applies only to U1): 0, 0.5, 0.9, and 0.95 (chosen in order to represent a range starting with no correlation between adjacent years to a high correlation between adjacent years). The medians of U1, U2 and U3 are each set to 1 (giving equal probability for any randomly selected value to be higher or lower than 1), which corresponds to a log mean of $\mu = 0$. A range of log variances (σ^2): 0.13, 0.67, and 1.38, which corresponds to 95% probability intervals of 2-, 5- and 10-fold uncertainties respectively (chosen to represent low, medium, and high levels of uncertainty) are simulated with the same value of σ^2 used to specify the distributions of U1, U2, and U3. Thus, a total of 12 different Monte Carlo simulations were conducted corresponding to the various combinations of the log variance parameter σ^2 (0.13, 0.67, and 1.38, each applied to U1, U2, and U3) and φ (0, 0.5, 0.9, and 0.95, applied to U1 only).

MATLAB (The Mathworks Inc., Natick, MA, 2000) and R (http://www.r-project.org/) programming languages were used to run Monte Carlo analyses. For each of the 500 Monte Carlo iterations, we applied simulated drinking water concentrations to our integrated exposure and pharmacokinetic model to estimate serum concentrations and reanalyzed the association between newly simulated PFOA serum concentrations and the odds of preeclampsia occurrence. The AOR was computed per inter-quartile range (IQR) of serum PFOA concentrations using multiple logistic regression, with recalculation of the IQR and a new regression for each Monte Carlo iteration.

We charactered overall uncertainty in the epidemiologic association using the Law of Total Variance: $var(b) = E(var(b|X)) + var(E(b|X))$, where b is the log odds parameter estimate, E refers to the expectation and X is the collection of personal exposure estimates. The first term in the summation is the contribution of participant sampling uncertainty, and is estimated by the mean value of the log odds parameter variance across 500 iterations of the logistic regression. The second term in the summation is the contribution of exposure uncertainty, and is estimated by the variance of the log odds point estimate across 500 iterations. The standard error of the log odds is the square root of the total variance, and is used to produce 95% probability intervals summarizing the Monte Carlo simulation results. The percent contribution of exposure uncertainty to total uncertainty is given by $var(E(b|X)) / var(b)$.

2.3 Results

2.3.1 Illustrative examples

We begin by showing plots with results from individual iterations, using 5 Monte Carlo iterates as an illustrative example. Although 5 iterations are insufficient to generate a reliable sample for propagation of uncertainty, we find the plots helpful for visualizing the complex exposure patterns produced by our three-level uncertainty factors (U1, U2, and U3). In order to illustrate the combined effect of the three uncertainty factors, we randomly selected five sets of values ("iterations") for U1, U2, and U3 from the appropriate probability distributions, and then computed PWD water concentrations for each iteration using Equation 1. Figure 2.2 shows PFOA concentrations in Pomeroy PWD (micrograms/liter) in log 10 scale over time for five iterations, with the upper panel representing the Monte Carlo simulation using uncertainty factors U1, U2, and U3, ($\varphi = 0.95$, $\sigma^2 = 0.13$) and the lower panel representing the Monte Carlo simulation using uncertainty factors U1, U2, and U3, ($\varphi = 0$, $\sigma^2 = 0.13$). The black line corresponds to the original estimated PFOA drinking water concentrations and the other five colored lines correspond to each of the Monte Carlo iteration obtained by multiplying the original PFOA concentration by the uncertainty factors. This example was chosen to visually show how the Monte Carlo simulation looks for the scenario when there is a low level of uncertainty in PWD concentration and high correlation versus no correlation between sampled uncertainty factors for adjacent years (U1). The Monte Carlo simulated PWD PFOA concentration curves are smoother over time with $\varphi = 0.95$, as expected. $\varphi = 0$ corresponds to no correlation between the random values sampled (from the multivariate lognormal distribution U1) for adjacent years; for those simulations, the Monte Carlo simulation curves are more jagged. Adjacent year PFOA drinking water concentrations are expected to be correlated and the

PFOA concentration curves are smooth over time, since changes in PFOA flux to the surface soil will tend to be smoothed over time as PFOA travels through the subsurface into the groundwater table.

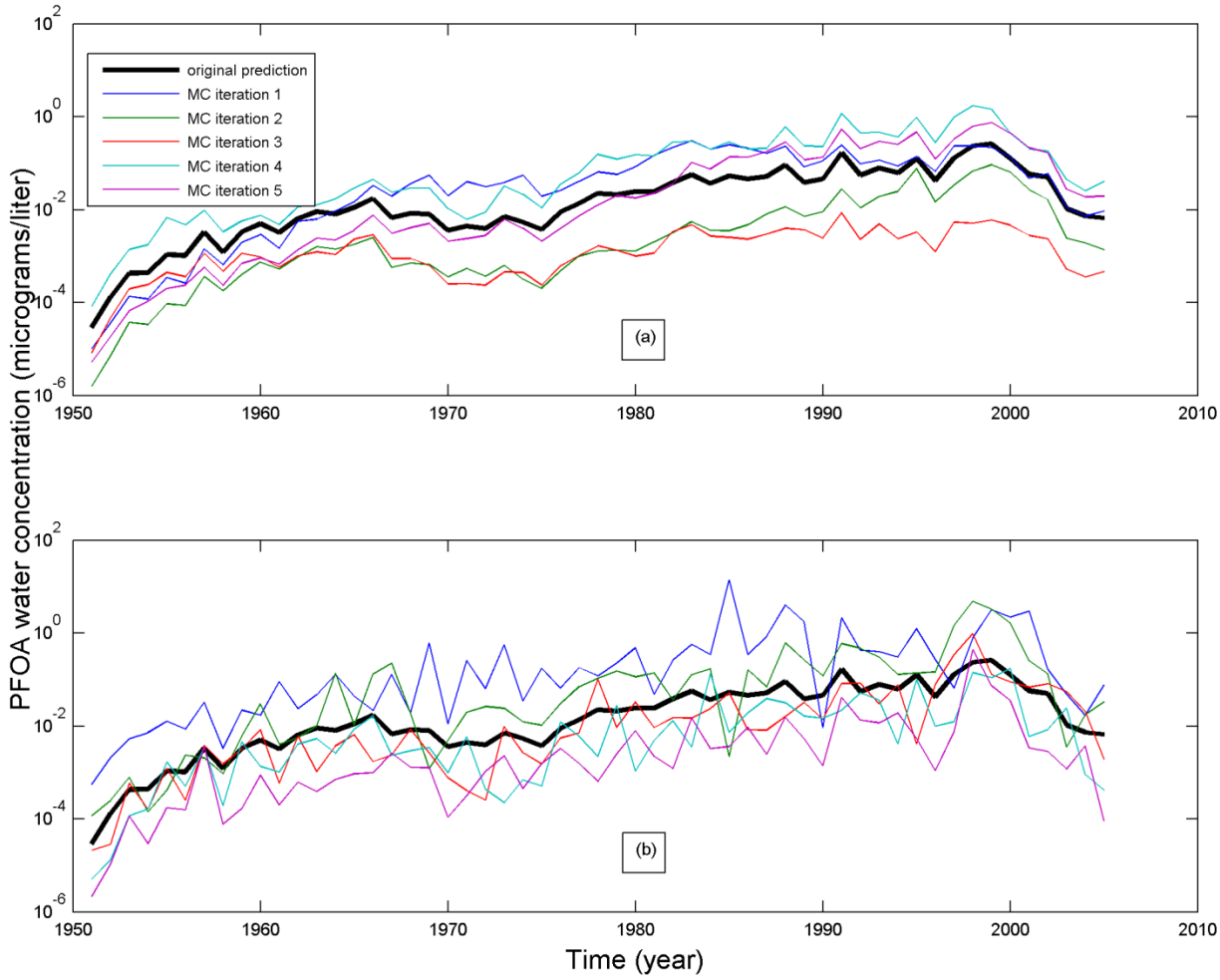

Figure 2.2 PFOA drinking water concentrations in Pomeroy PWD over time- comparing original estimates with Monte Carlo iterations using uncertainty factors with parameter values of $\sigma^2 = 0.13$ and either (a) $\varphi = 0.95$ for high autocorrelation or (b) $\varphi = 0$ for no autocorrelation. Concentrations are shown in log (base 10) micrograms/liter

2.3.2 Full Monte Carlo simulation

Next we present results for Monte Carlo simulation with 500 iterations for each of the 12 simulations (Table 2.1) using the full uncertainty model with U1, U2, and U3 (with $\sigma^2 = 0.13$, 0.67, or 1.38, and $\varphi = 0$, 0.5, 0.9, or 0.95). Figure 2.3 is a plot of mean and 95% probability interval (the 2.5^{th} and 97.5^{th} percentiles) over 500 iterations of rank correlation between the simulated and original serum PFOA concentration estimates for all the Savitz et al. (2012a) study participants between the years 1990 and 2006, for the Monte Carlo simulation using uncertainty factors U1, U2, and U3 ($\varphi = 0.95$, $\sigma^2 = 1.38$). Although only one simulation is plotted here, it is the simulation with the highest impact of uncertainty on the serum prediction estimates (i.e., the other 11 simulations produce higher rank correlations).

Table 2.1 The mean and the 95% probability interval of the mean, median, 25th and 75th percentile serum concentrations at birth (ng/mL), across 10,149 participants for each of the 12 Monte Carlo simulations

Simulation	Mean	Median	25th percentile	75th percentile
Original	51.06	9.42	5.09	32.45
(σ^2=0.13, φ=0)	60.20 (27.07-132.37)	9.73 (7.69-13.15)	5.09 (4.94-5.27)	36.35 (19.72-71.53)
(σ^2=0.13, φ=0.50)	60.57 (25.80-121.72)	9.73 (7.52-12.56)	5.09 (4.91-5.26)	36.74 (18.98-64.36)
(σ^2=0.13, φ=0.90)	57.58 (27.27-120.46)	9.56 (7.75-12.17)	5.08 (4.95-5.20)	34.67 (20.26-62.98)
(σ^2=0.13, φ=0.95)	61.38 (26.65-135.05)	9.66 (7.65-12.67)	5.09 (4.91-5.25)	36.11 (19.99-68.27)
(σ^2=0.67, φ=0)	124.43 (17.73-477.59)	11.27 (6.66-23.65)	5.14 (4.88-5.75)	55.16 (14.52-181.99)
(σ^2=0.67, φ=0.50)	118.07 (15.19-490.83)	10.89 (6.67-26.49)	5.12 (4.81-5.80)	54.57 (13.93-209.57)
(σ^2=0.67, φ=0.90)	124.00 (16.82-578.14)	10.61 (6.43-21.34)	5.10 (4.78-5.61)	53.73 (12.96-218.77)
(σ^2=0.67, φ=0.95)	128.44 (12.85-641.07)	10.77 (6.38-26.59)	5.11 (4.80-5.77)	55.79 (12.69-222.65)
(σ^2=1.38,φ=0)	267.18 (14.73-1595.08)	13.84 (6.14-39.71)	5.19 (4.77-5.92)	95.98 (11.42-451.10)
(σ^2=1.38, φ=0.50)	455.98 (13.90-2600.70)	14.27 (6.18-57.83)	5.16 (4.78-6.10)	102.68 (11.82-620.82)
(σ^2=1.38, φ=0.90)	390.51 (11.50-3075.62)	13.67 (5.86-51.01)	5.14 (4.72-6.11)	102.90 (11.19-565.64)
(σ^2=1.38, φ=0.95)	396.66 (10.03-2686.75)	12.47 (5.72-35.71)	5.12 (4.69-6.03)	83.63 (10.48-433.71)

σ^2 = Log variance of the uncertainty distributions U1, U2, and U3

φ = autocorrelation factor of uncertainty distribution U1

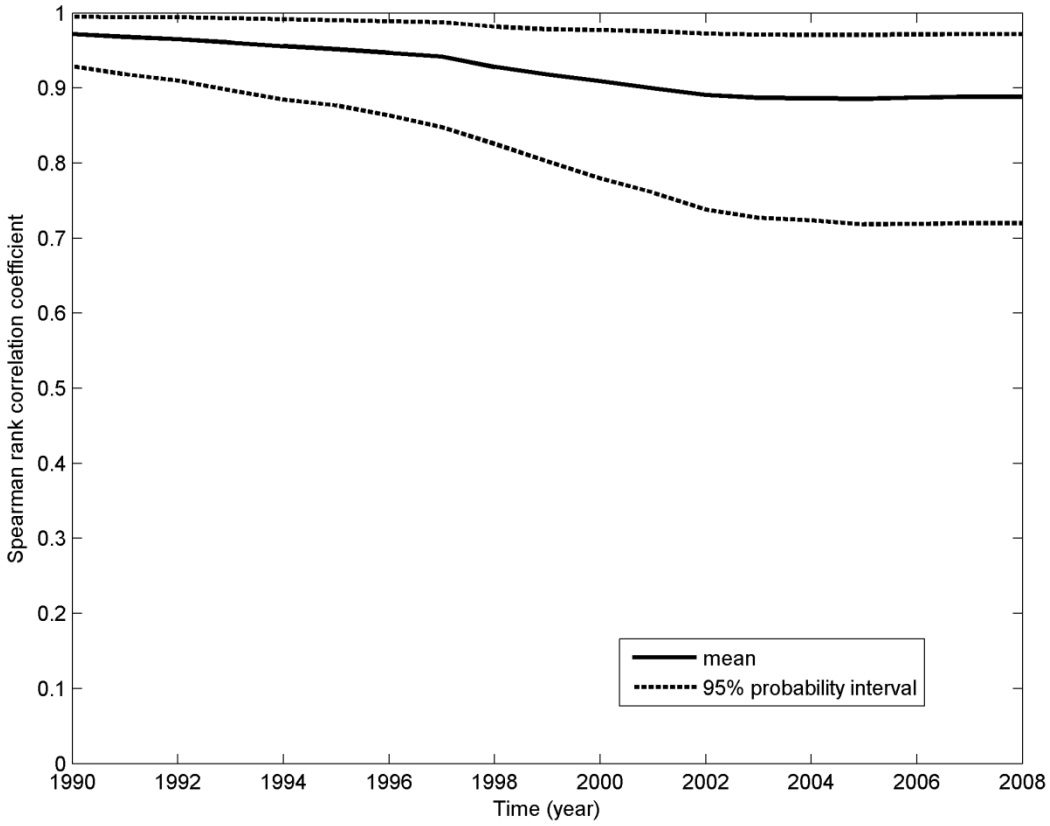

Figure 2.3 An example plot of the mean and the 95% probability interval of the correlation coefficient between the estimated serum concentrations for each Monte Carlo iterate and the original estimated serum concentrations, for all the participants, over time (U1, U2, and U3 with $\varphi = 0.95$, $\sigma^2 = 1.38$)

The mean, median, 25-75 percentile serum concentrations at birth (ng/mL), across 10149 participants were calculated and their mean and 95% probability interval among 500 iterations are shown in the Table 2.1, along with those of the original epidemiology analysis. The mean and 95% probability interval for the AOR associating serum PFOA concentrations and preeclampsia for each simulation are shown in Table 2.2. The percent contribution of exposure

uncertainty to total uncertainty is tabulated in Table 2.3. Exposure uncertainty contributed anywhere between 5 and 31 % to the total uncertainty in this analysis.

Table 2.2 The AOR (and 95% probability interval computed from the total standard error which includes participant sampling variability and exposure uncertainty) when applying all uncertainty factors (U1, U2, and U3) simultaneously in Monte Carlo simulations. The AOR (and 95% confidence interval computed from participant sampling variability only) using the original exposure assignments is 1.11 (0.99, 1.24)

φ \ σ^2	0.13	0.67	1.38
0	1.11(0.99, 1.25)	1.11 (0.98, 1.26)	1.12 (0.97, 1.28)
0.5	1.11 (0.99, 1.25)	1.11(0.98, 1.26)	1.11 (0.97, 1.27)
0.9	1.11 (0.99, 1.24)	1.11 (0.98, 1.25)	1.10 (0.96, 1.27)
0.95	1.11 (0.99, 1.25)	1.11 (0.97, 1.26)	1.10 (0.96, 1.26)

σ^2 = Log variance of the uncertainty distributions U1, U2, and U3

φ = autocorrelation factor of uncertainty distribution U1

Table 2.3 Percent contribution of participant exposure uncertainty to the total uncertainty for the combined effect of participant sampling variability and exposure uncertainty

φ \ σ^2	0.13	0.67	1.38
0	5 %	18 %	29 %
0.5	5 %	19 %	30 %
0.9	5 %	19 %	31 %
0.95	5 %	21 %	30 %

σ^2 = Log variance of the uncertainty distributions U1, U2, and U3

φ = autocorrelation factor of uncertainty distribution U1; not applicable to uncertainty factors U2 or U3.

2.4 Discussion

Although incorporating autocorrelated and shared uncertainty in our water concentration estimates produced a highly variable set of plausible serum PFOA concentrations, it had less impact on the rank order of estimated serum PFOA concentrations during pregnancy. Moreover, these changes in estimated serum PFOA had a negligible impact on the mean AOR for preeclampsia and only modestly increased its total standard error, likely because the regression is more sensitive to the rank order of participant exposures than it is to absolute exposure assignments. The existing epidemiological literature suggests that adding independent, non-differential classical exposure measurement error will tend to bias the effect estimate towards the null hypothesis (Armstrong 1998). However, we observed no substantial bias in our Monte Carlo simulations. This may be due to our focus on potential errors in characterizing PWD water

concentrations, which are shared exposure sources, rather than simulating independent exposure measurement errors. As a brief test of that explanation, we ran two additional simulations without U1, U2, or U3, but now adding a new lognormal uncertainty factor for individual drinking water ingestion rates, with 10-fold and 100-fold uncertainty (100 iterations each). Mean AORs in these simulations were 1.09 and 1.07, respectively, indicating greater sensitivity of the epidemiologic results to independent exposure errors than to shared exposure errors. The weak association between PFOA and preeclampsia may also make it appear less sensitive to both shared and independent exposure uncertainties (e.g., a change of the AOR from 1.11 to 1.07 appears small but actually constitutes a 35% decrease in the log odds parameter). PFOA water concentrations in the contaminated region differed by several orders of magnitude across PWDs and across years (Shin et al. 2011a), which may explain why perturbing the exposure estimates with as much as 10-fold uncertainty contributed only modestly to the total standard error and negligibly to bias. Indeed, using regression calibration (Rosner, 2010) treating the Monte Carlo simulation as a simulated reproducibility study and assuming independent measurement errors across participants, we compute for the simulation with $\varphi = 0.95$ and $\sigma^2 = 1.38$ an intra-class correlation coefficient of $r_1 = 0.25$ and a corrected AOR of 1.72 (95% confidence interval: 1.04, 2.87). The independence assumption is clearly unwarranted here, but this exercise illustrates that potential inaccuracies in our historical water concentration estimates may pose a far lesser threat to the validity of previously published epidemiologic associations between PFOA and preeclampsia in the C8 Health Study than suggested by traditional models for exposure measurement error.

At the selected exposure uncertainty variances (σ^2), varying the autocorrelation parameter (φ) had little impact on the output AOR distribution, only slightly increasing the total standard

error. Although the direction of the effect is reasonable because a multi-year increase or multi-year decrease in water concentrations is more likely with higher autocorrelation and produces a larger change in serum concentration than a mix of yearly increases and decreases, we expected the total standard error to be more strongly affected by this parameter than it was. This is somewhat reassuring considering that it is more difficult to interpret and choose a reasonable value of φ than σ^2.

The contribution of correlated exposure uncertainty to the overall uncertainty in an epidemiologic analysis of PFOA exposure and preeclampsia is estimated here. Traditional confidence intervals only account for participant sampling variance, not the effects of exposure uncertainty. In this specific PFOA exposure assessment-environmental epidemiology analysis, fate and transport model uncertainty seems to contribute only modestly to the overall uncertainty in the relationship between PFOA exposure and preeclampsia. Although these results cannot be generalized to other settings, the methods could be applied to other epidemiological analyses including studies of PFOA and other health effects in this population. This may be particularly important in weighing disparate findings from studies that utilize different methods of exposure assessment (e.g., fate and transport models, questionnaires, and/or biomarkers). Although meta-analysis provides a method for combining disparate study findings, it traditionally weighs studies only by their estimated parameter variances (i.e., sampling variability) and does not address the quality of exposure assessment or other study design characteristics.

Drinking water ingestion is a major exposure route (versus inhalation or dermal exposure) for our study population in all years, except for the participants who consumed water from Little Hocking before 1974 and those who consumed water from Belpre before 1990 (Shin et al. 2011b). Given this, and the fact that the epidemiological analysis included pregnancies

occurring only between 1990 and 2006, we chose to model uncertainty only for the drinking water concentrations in this analysis, not perturbing the original inhalation exposure estimates for each Monte Carlo iteration. Private well water has been used by participants in the study over their residential history in the area and can be a potential source of uncertain PFOA exposure to the participants. However, only 9.6% of the Savitz et al. (2012a) study participants had at least one source of private water consumption between the years 1985 and 2006. Therefore, we did not consider the uncertainty in the private well PFOA concentrations in our analysis as we deemed it to be negligible compared to the PWD PFOA contribution to the total exposure. Another relatively minor source of PFOA exposure is through the consumption of vegetables that were either grown locally or home grown; however due to the sparseness of data specific to the individual participant vegetable consumption, the original model did not consider this route of exposure (Shin et al. 2011a). We also did not assess independent sources of error such as individual variations/uncertainty in ingestion rates and pharmacokinetics of PFOA. These uncertainties are likely to produce Berkson-like error structures in the individual exposure assignments (Berkson 1950; Heid et al. 2004), because group-level pharmacokinetic and water ingestion rates were assigned in the absence of individual-level data. Incorporation of these components into the uncertainty analysis would likely cause an increase in the apparent contribution of exposure uncertainty to uncertainty in the epidemiologic findings.

Our uncertainty analysis explores the impact of changing the original PFOA exposure assignments by simulating additional measurement error, but it does not "correct" or "adjust" for errors in exposure assignment. Regression calibration (Rosner 2010) can be used to correct AORs to account for a simple exposure measurement error structure, but would have to be adapted for use with complex simulations such as our setting. Regression calibration includes

three important assumptions that are not valid in our study: 1) the measurement errors are normally distributed, 2) the errors are statistically independent of the surrogate exposure and independent across individuals, and 3) the other covariates in the regression model are measured without error. In our study the measurement error components are lognormally distributed and strongly correlated among individuals with the same water source, and covariates such as smoking status were likely measured imperfectly due to the use of self-reports.

2.5 Conclusions

The Monte Carlo uncertainty analysis described here can be considered a screening-level uncertainty analysis, since we are characterizing uncertainty in the environmental model estimated PWD PFOA concentrations as a surrogate for hundreds of parameters in the suite of fate and transport models used to estimate the PWD PFOA concentrations. Using separate U1, U2, and U3 uncertainty components allows for specification of correlations in exposure measurement errors across years and across individuals with shared exposure sources, in contrast to standard epidemiologic models that assume independence of the measurement errors (Armstrong 1998; Rosner 2010). Due to the complexity of this particular suite of fate and transport models, which take days to weeks to run for a single set of input parameters, a parameter-based Monte Carlo uncertainty analysis would require a prohibitive amount of computer time. Our screening-level assessment suggests that correlated exposure measurement error may produce dramatic changes in PFOA serum estimates yet contribute only modestly to overall uncertainty regarding the epidemiologic association between PFOA and preeclampsia. As a next step, exploring the impact of individual-level uncertainties in the exposure assessment and pharmacokinetic model will provide more insight regarding the effects of exposure uncertainty on this epidemiological association. Future epidemiologic analyses might benefit

from simulation studies or other techniques for evaluating the impacts of uncertainties in complex exposure models.

CHAPTER 3: 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

Raghavendhran Avanasi

Hyeong-Moo Shin

Verónica M. Vieira

Scott M. Bartell

Chapter 3 is reproduced with permission from Environmental Research. R.Avanasi, HM. Shin, V.M. Vieira, S.M. Bartell. 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. Copyright 2016 Environmental Research.

3.1 Introduction

In this Chapter, we determine the potential impacts of individual-level 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 half-life, and PFOA volume of distribution. It has been previously identified that distinguishing these two types of uncertainty is important and commonly missed.

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 (Morgan et al., 1990; Finley and Paustenbach, 1994; Burmaster and Anderson, 1994). 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 epidemiological association between PFOA and preeclampsia.

3.2 Materials and methods

3.2.1 Environmental fate and transport model

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 contaminant 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).

3.2.2 Exposure-reconstruction and pharmacokinetic model

The predicted PFOA air and groundwater concentrations were then used in a dosimetry model to predict yearly PFOA exposure doses through inhalation and ingestion for each of the participants (Shin et al., 2011b). This exposure-reconstruction 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, 2009); standard (self-reported, if available) water ingestion rates; and information on the historical pipe distribution systems of each of the six public water districts, to predict yearly total exposure doses (combined inhalation and ingestion doses) for each of the participant. Self-reported water ingestion rates (number of cups per day) were available for ~50 % of the C8 Health Study participants (Shin et al., 2011b) and were used when available. For the self-reported participants, the model also assumed a constant water consumption rate for each individual over the entire exposure period.

A one-compartment pharmacokinetic model (PK) was used to predict yearly PFOA serum concentrations in the study participants, based on their individual yearly total PFOA dose estimates and assuming 100% absorption by both exposure routes (Shin et al., 2011b). The total PFOA serum concentration was computed as the sum of PFOA serum concentration due to emissions from the Washington Works plant and PFOA serum concentration due to background

exposure from other exposure sources (Shin et al., 2011b). By default, the model used age- and gender-specific PFOA volume of distribution (based on previously recommended volume of distribution per unit body weight derived from a monkey model by Butenhoff et al. (2004). The PFOA excretion half-life in the PK model was fixed at 3.5 years for all participants based on follow-up of retired workers by Olsen et al., 2007.

3.2.3 Epidemiological analysis

The Savitz et al. (2012a) epidemiological analysis of self-reported preeclampsia in association with PFOA utilized the retrospective predicted PFOA serum concentrations at the year of birth among 10,189 pregnancies occurring between 1990 and 2006 in the C8 Health Project population. Among these pregnancies, 730 occurrences of preeclampsia were reported and the analysis adjusted for confounding by parity, maternal age, education level and smoking status. The original reported adjusted odds ratio (AOR) for the occurrence of preeclampsia was 1.13 (1.00-1.28) per interquartile range (IQR) of PFOA serum concentration in log (natural logarithm) scale (nanograms per milliliter-ng/mL). We restrict our analysis to 10,149 pregnancies (725 preeclampsia cases) by removing those mothers with previous work history in the Washington Works facility, thereby focusing only on PFOA contribution from non-occupational sources of exposure. The modified analysis yielded an AOR of 1.12 (1.00-1.26). We received approval from the Institutional Review Board at the University of California, Irvine (HS#2013-9421) to conduct our analyses.

3.2.4 Methodology: Monte Carlo simulation I

In the first MC simulation, we study the impact of variability in the individual-level input parameters introduced in section 1.1. We used the outputs from the fate and transport models- the PFOA air and water concentrations and ran multiple iterations of the dosimetry and the pharmacokinetic models. For each iteration, individual-level independent exposure parameters including the standard tap water ingestion rates or the self-reported water ingestion rates, the PFOA half-life, and the PFOA volume of distribution were varied by randomly sampling from variability distributions developed based on our literature survey described below.

Variability in standard/self-reported water ingestion rates

In the original exposure model, for the participants who did not provide a self-reported tap water ingestion rate (~30 % of the Savitz et al., 2012a study participants), default water ingestion rates recommended by the EPA Exposure Factors Handbook (Shin et al., 2011b; U.S. EPA, 2009) were used. These were mean survey-based community water ingestion rates for different age categories (for the U.S. population) and included estimates of water ingested directly as a beverage and water used in preparing various food/beverages. Percentile estimates of these water ingestion rate distributions are also available for each age category in the Exposure Factors Handbook. In order to account for inter-individual variability in the MC analysis, we assumed the water ingestion rate to be log-normally (LN) distributed and calculated the log-normal parameters (the log mean, μ_a and the log standard deviation, σ_a) based on the mean and 95th percentile values for each age category (Table 3.1).

Table 3.1 The parameters μ_a and σ_a of the log-normal distribution for all age categories of standard water ingestion rates (mL/day) recommended by the U.S. Environmental Protection Agency in the Exposure Factors Handbook (U.S. EPA, 2009)

Age category (years)	Mean	95th Percentile	μ_a	σ_a
1 to < 2	308	893	-1.5697	0.8855
2 to < 3	356	912	-1.3044	0.7370
3 to < 6	417	1099	-1.1702	0.7688
6 to < 11	480	1251	-1.0199	0.7562
11 to < 16	652	1744	-0.7365	0.7859
16 to < 18	792	2002	-0.4941	0.7224
18 to < 21	895	2565	-0.4897	0.8704
> 21	1183	2848	-0.0571	0.6709
> 65	1242	2604	0.0719	0.5381

In the MC analysis, for each iteration, the percentile of the water ingestion rate for any specific individual was randomly sampled from a uniform distribution and used throughout the individual's lifetime to compute the water ingestion rate from the age-specific log-normal variability distributions as shown.

$p \sim U(0,1)$ [1]

$IR_i = F^{-1}(p)$

Where,

p is the sampled percentile for individual i,

F^{-1} is the inverse distribution function (or "quantile function") for LN (μ_a, σ_a),

IR_i is the computed water ingestion rate for individual i,

μ_a is the log mean specific to individual i's age category and,

σ_a is the log standard deviation specific to individual i's age category.

Holding the water ingestion rate constant throughout the lifetime for any iteration simulated the effect of consistently high or low water consumption, e.g., an individual assigned to the 92nd percentile of water consumption would remain at that percentile within each age group, throughout his or her lifetime, for that MC iteration.

For the participants who had self-reported tap water ingestion rates (~ 70 % of the participants), in the form of choosing one of six categories of the number of cups of water consumed in a day: 0-1, 1-2, 3-4, 5-6, 7-8, > 8 cups, the original exposure model had used the median of each category (except for the > 8 cups category, 9 cups was used as representative of range) as the water ingestion rate. These rates were held constant throughout the individual's lifetime.

In the MC analysis, to account for the variability within each category, for any individual, we randomly sampled a value of water ingestion rate based on a uniform distribution shown below, instead of the median value (as used in the original model) and used it throughout all years of the individual's lifetime.

$$m_i \sim U(L_i, U_i) \qquad [2]$$

Where,

m_i is the sampled self-reported water ingestion rate for individual i,

L_i and U_i are the lower and upper bounds of the uniform distribution.

For example, mi ~ U (1.183, 1.4196) L/d for an individual who reported 5-6 cups per day of tap water ingestion.

Variability in the PFOA elimination half-life

In the original model, the PFOA half-life used in the pharmacokinetic model was fixed at 3.5 years for all individuals based on a study by Olsen et al. (2007). This study followed 26 retired fluorochemical production workers, over five years and estimated individual PFOA elimination half-lives. In order to account for inter-individual variability in PFOA half-life, we assumed it to be log-normally distributed and calculated the log-normal parameters (μ_h = 1.247 and σ_h = 0.399) based on the reported arithmetic mean and standard deviation of the PFOA half-life among the 26 subjects in the Olsen et al. (2007) study.

In the MC analysis, for each iteration, the PFOA half-life for any specific individual was randomly sampled from the log-normal variability distributions as shown below and used throughout each year of the individual's lifetime.

$T_{½\,i} \sim LN(\mu_h, \sigma_h)$ [3]

Where,

$T_{½\,i}$ is the PFOA half-life for individual i,

μ_h is the log mean of the PFOA half-life and,

σ_h is the log standard deviation of the PFOA half-life.

Variability in the PFOA volume of distribution

The PFOA volume of distribution per weight used in the original model (female = 0.198 L/Kg) was based on a study in cynomolgus monkeys by Butenhoff et al., 2004. This volume of distribution was held constant for all the participants in the original model (Shin et al., 2011b). To account for inter-individual variability in the volume of distribution, we assumed it to be log-

normally distributed and calculated the parameters (μ_v = 5.2453 and σ_v = 0.3540) based on the reported arithmetic mean and standard deviation of the PFOA volume of distribution among the 3 female monkey subjects in the study.

In the MC analysis, for each iteration, the PFOA volume of distribution for any specific individual was randomly sampled from the log-normal variability distributions shown below and used throughout the individual's entire lifetime.

$$VD_i \sim LN(\mu_v, \sigma_v) \quad [4]$$

Where,

VD_i is the PFOA volume of distribution for individual i,

μ_v is the log mean of the PFOA volume of distribution and,

σ_v is the log standard deviation of the PFOA volume of distribution.

3.2.5 Monte Carlo simulation II: Epistemic uncertainty in self-reported water ingestion rates, PFOA half-life and PFOA volume of distribution

In addition to studying the impact of variability in the self-reported water ingestion rates as described in section 2.4.1., in a separate MC simulation (II), we studied the impact of epistemic uncertainty in the three individual-level parameters. For uncertainty regarding the validity of each self-reported water ingestion rate, we use a log-normal distribution shown below.

$$IR_i \sim LN(\mu_i, \sigma_i) \quad [5]$$

$$\mu_i = \log(m_i) \quad [6]$$

Where,

IR_i is the sampled water ingestion rate for individual i,

μ_i is the individual specific log mean and,

σ_i is the log standard deviation reflecting potential inaccuracy in the self-reported water ingestion rates.

This was a two-level analysis evaluating both uncertainty in the self-reported water ingestion rate category and, as described in section 2.4.1, variability within each selected category. The median of the log-normal distribution was sampled randomly from a uniform distribution as described in equation 2. The standard deviation (σ_i = 0.446) was computed from the confidence interval of the mean difference between a questionnaire (self-reports) and 3-day diary based on water ingestion rates studied by Shimokura et al., (1998). This standard deviation represents the uncertainty in self-reported water ingestion rates as a surrogate for true rates. We also included the epistemic uncertainty in PFOA half-life and PFOA volume of distribution in the MC simulation II. The PFOA half-life used in the study was based on a study (Olsen et al., 2007) of mainly older (ranged between 55-75 years) males (24 males and 2 females) and may not be representative of the participants in the Savitz et al., 2012a study, which were mainly women of child-bearing age (ranged between 14-45 years). Therefore, we included epistemic uncertainty by increasing the log standard deviation of the log-normal distribution in equation 3 to 0.798 (2-times the original value in the half-life estimate used in the MC simulation I). Because only three monkeys were used in the Butenhoff et al., 2004 study to calculate the PFOA volume of distribution for females, and monkeys were used as a surrogate for humans in our analysis (Shin et al., 2011b), there could be additional uncertainty in the parameter. To address these sources of uncertainty we added epistemic uncertainty in the volume of distribution by multiplying the log standard deviation by a factor of 5 (1.77). In MC simulations II, the same variability

distributions from MC simulation I and these three epistemic uncertainties (self-reported water ingestion rates, PFOA half-life and PFOA volume of distribution) were all included in the model.

The MC simulations (300 iterations each) were run using MATLAB (The Mathworks Inc., Natick, MA, 2000) programming language and R (http://www.r-project.org/) programming language was used to reanalyze the epidemiological association between the estimated serum PFOA concentrations and preeclampsia. For each MC iteration of the exposure model, the serum PFOA concentrations were estimated and multiple logistic regression was used to compute the AOR per IQR of the estimated serum concentrations. The yearly rank exposure of the participants (among all 300 iterations) was also compared with the original model predicted rank exposure for each MC simulation. The contribution of inter-individual variability/epistemic uncertainty to the total uncertainty in the epidemiological association (including participant sampling uncertainty) was calculated for each MC simulation using the law of total variance as described in our previous study (Avanasi et al., 2016a). Briefly, if b is the log odds parameter estimate and X is a collection of individual exposure estimates, the total variance (as a measure of uncertainty) in b is given by $var(b) = E(var(b|X)) + var(E(b|X))$. The first and the second terms in the summation correspond to the participant sampling variability and the inter-individual variability/epistemic uncertainty respectively. The formula $var(E(b|X)) / var(b)$ gives the relative contribution of the inter-individual variability/epistemic uncertainty to the total uncertainty.

3.3 Results

3.3.1 Impact on predicted serum concentrations

The summary statistics (mean, median 25-75 percentile across 10149 participants) of the predicted serum concentrations (ng/mL) were calculated for each iteration and their mean and 95% probability interval among 300 iterations for each MC simulation were calculated (Table 3.2), along with the corresponding values for the modified original data. Across the 300 iterations of the two MC simulations, the IQR of the log serum PFOA concentrations varied minimally with the 95% probability interval of the IQR ranging between 1.32 and 2.29 for MC simulation I and between 0.96 and 2.86 for MC simulation II. The mean and the 95% probability interval for the IQR for the two simulations (including the original IQR) are given in Table 3.3.

Table 3.2 The mean and the 95% probability interval (PI) of the mean, median, 25th and 75th percentile serum concentrations at birth (ng/mL), across 10149 participants for each of the 2 Monte Carlo simulations (300 iterations per simulation)

Simulation	Median (95% PI)	Mean (95% PI)	25^{th} percentile (95% PI)	75^{th} percentile (95% PI)
Modified original	9.42	51.06	5.09	32.45
MC simulation I	9.4 (6.8, 12.5)	58.4 (32.6, 93.0)	5.1 (4.9-5.2)	33.2 (18.3, 51.3)
MC simulation II	8.7 (5.3, 13.3)	267.6 (63.5, 578.8)	4.9 (4.6-5.1)	44.8 (12.0, 89.3)

Table 3.3 The mean and 95% probability interval (PI) of the IQR of the log serum PFOA concentration (ng/mL) across the 300 iterations for each of the 2 MC simulations

Simulation	Mean IQR (95% PI)
Modified original	1.85
MC simulation I	1.85 (1.32, 2.29)
MC simulation II	2.09 (0.96, 2.86)

The rank correlation between the simulated and original serum PFOA concentration estimates for the 10,149 participants between the years 1990 and 2006 was calculated. The plot of the mean and 95% probability interval over 300 iterations of the rank correlation for the Monte Carlo simulation I is presented in Figure 3.1. A similar plot for MC simulation II is shown in Figure 3.2. For the MC simulation II, as seen in Figure 3.2, we find that the estimated and the original predicted serum concentrations are well correlated, around 0.92 (in the year 1990), but over time, this reduces (due to the addition of variability/uncertainty) and the lowest mean rank correlation was 0.77 (for the years 2003, 2004 and 2005). This represents the simulation with the maximum impact of variability/epistemic uncertainty on the rank exposure, with the other simulation (the Monte Carlo simulation I) producing higher rank correlations (as shown in Figure 3.1) with the original serum PFOA concentrations.

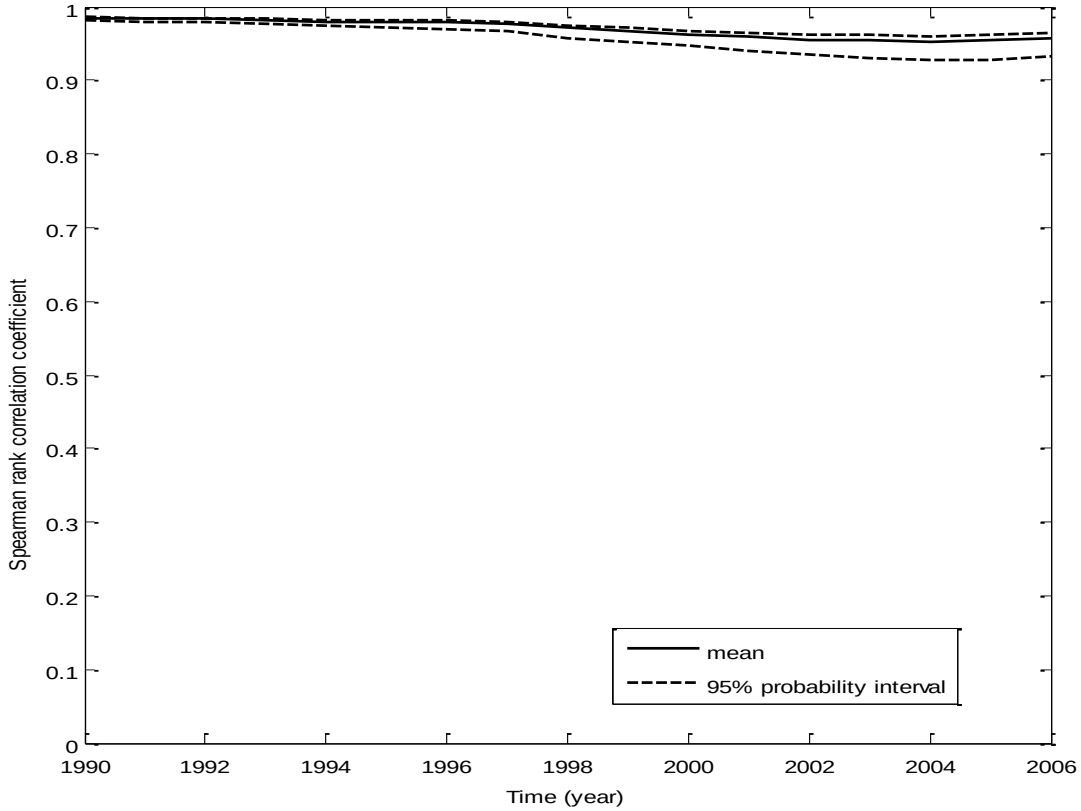

Figure 3.1 A plot of the mean and the 95% probability interval of the correlation coefficient between the estimated serum concentrations for each Monte Carlo iterate and the original estimated serum concentrations, for all the participants, over time- MC simulation I (analysis of the impact of variability in independent input parameters)

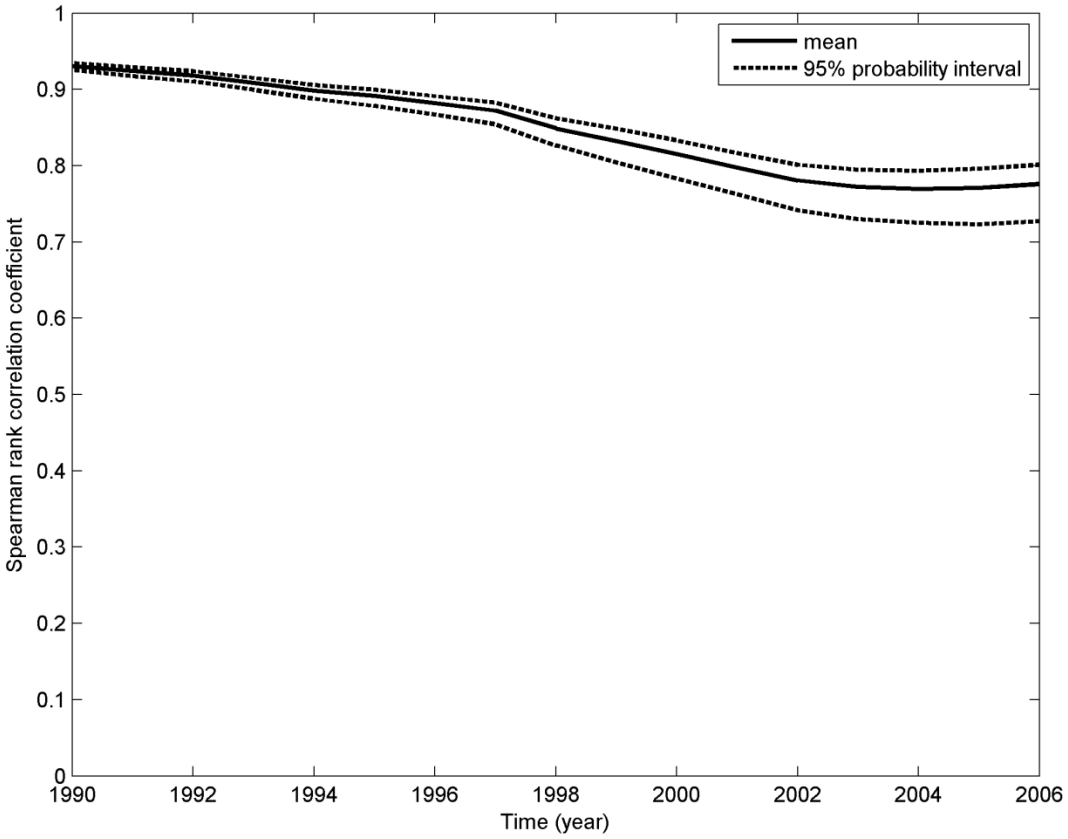

Figure 3.2 A plot of the mean and the 95% probability interval of the correlation coefficient between the estimated serum concentrations for each Monte Carlo iterate and the original estimated serum concentrations, for all the participants, over time -MC simulation II (analysis of the impact of variability as well as epistemic uncertainty in independent input parameters)

3.3.2 Impact on the epidemiological association

The mean (95% probability interval) AOR for each simulation was calculated and is presented in Table 3.3. The percent contribution of the variability/epistemic uncertainty to the overall uncertainty is also presented in Table 3.4. We find that the addition of epistemic uncertainty to variability increases the contribution of exposure uncertainty to the total uncertainty (including sampling variability) in the epidemiological association by 21%. The impact of variability/epistemic uncertainty on the AOR of preeclampsia occurrence is also reduced from 1.11 to 1.09. As previously reported in the literature (Armstrong, 1998), the increasing variability/epistemic uncertainty in independent exposure factors resulted in increasing bias of the AOR towards the null and increased the contribution of exposure uncertainty to overall uncertainty.

Table 3.4 The mean and the 95% probability interval (PI) of the AOR and the percent contribution of exposure uncertainty to total uncertainty for each of the three MC simulations. The AOR (and 95% confidence interval computed from participant sampling variability only) using the original exposure assignments is 1.12 (1.00, 1.26)

Simulation	Mean AOR (95% PI)	Percent contribution of exposure uncertainty
MC simulation I	1.12 (1.00, 1.25)	6.9%
MC simulation II	1.09 (0.97, 1.23)	32.7%

3.4 Discussion

From the results of MC simulation I, we found that realistic inter-individual variability (determined based on our literature review) in independent exposure parameters such as the water ingestion rates, PFOA half-life, and PFOA volume of distribution impacted the absolute serum PFOA concentration predictions (Table 3.2) and the rank order of estimated serum PFOA concentrations only mildly (the lowest mean rank correlation between the estimated and the original predicted serum concentrations was 0.95 for the years 2003, 2004 and 2005 as seen in Figure 3.1), without causing any change to the mean AOR of preeclampsia occurrence among the participants (within rounding error). The overall contribution of exposure uncertainty to total uncertainty (including participant sampling variance) was low, around 7%.

In contrast, in the MC simulation II, when epistemic uncertainty is added along with the inter-individual variability in the same exposure parameters, both the absolute serum PFOA concentration predictions (Table 3.2) and the rank order of estimated serum PFOA concentrations (the lowest mean rank correlation between the estimated and the original predicted serum concentrations was 0.77 for the years 2003, 2004 and 2005 as seen in Figure 3.2) were moderately impacted. The mean AOR was reduced by 25% (from 1.12 to 1.09). The total contribution on exposure uncertainty to the total uncertainty also increased to nearly 33%. These results support previous literature that suggests that non-differential variability and epistemic uncertainty in independent parameters of individual-level exposure reconstruction models and pharmacokinetic models can lead to bias in the effect estimates of environmental epidemiological studies towards the null and reduce the power as well as the precision of these studies (Thomas et al., 1993; Armstrong, 1998).

Although the probability distributions for each of the exposure parameters in MC simulation I were derived from empirical evidence/self-reported values (percentile estimates of water ingestion rate distributions for standard water ingestion rates based on the self-reported ranges of the number of cups of water consumed in a day, PFOA half-life based on the Olsen et al., 2007 study, and PFOA volume of distribution based on the Butenhoff et al., 2004 study), the choice of probability distributions reflecting epistemic uncertainty in MC simulation II for the PFOA half-life (two times the log standard deviation of the variability distribution) and PFOA volume of distribution (five times the log standard deviation of the variability distribution) were based on subjective judgments, with less clear interpretability. For example, the 95% probability interval (PI) of the half-life epistemic uncertainty distribution is 1.59-7.61 years and that of the volume of distribution is 0.006-6.09 L/Kg. As a sensitivity analysis, we also looked at an uncertainty distribution for the volume of distribution with a log standard deviation which is 10 times that used in the variability analysis. The 95% probability interval for this analysis is between 0.0002-195.6 L/Kg, resulting in a 50% decrease (from 1.12 to 1.06) in the mean AOR, but the analysis produced an implausible serum PFOA concentration predictions with a mean of 23604.6 (95% PI: 4643.9-151368.5) ng/mL, orders of magnitude larger than 2005-2006 measured serum PFOA concentrations among consented C8 Health Project participants (n=48998) for which the 95% PI was 4.3-530.4 ng/mL. An epistemic uncertainty distribution for the volume of distribution with five times the standard deviation of the variability distribution is more plausible considering the resulting mean (95% PI) PFOA serum concentrations among the 300 iterations was 267.6 (63.5, 578.8). It is to be noted that there is a data gap with respect to PFOA volume of distribution in humans, with the Butenhoff et al., (2004) monkey study being the only source of this information. Other existing PK models (Andersen et al., 2006; Tan et al.,

2008;Loccisano et al., 2012;Loccisano et al., 2013)of PFOA in rats, monkeys and humans have all used the volume of distribution results of the Butnhoff et al. (2004) study to examine the kinetics of PFOA. However, choosing the appropriate epistemic uncertainty distributions (for half-life and volume of distribution) for MC simulation II is inherently subjective, as epistemic uncertainty refers to unmeasured attributes.

Our previously published uncertainty analysis study in the PFOA exposure assessment modeling system on the C8 Heath Project/C8 Science panel study population (Avanasi et al., 2016a) focused on correlated exposure uncertainty in the environmental fate and transport model predicted public water district PFOA water concentrations (correlated within each participant over the years and between participants with a shared drinking water source). Despite larger uncertainties in the fate and transport models, the impact of correlated exposure uncertainty on the epidemiological association is negligible compared to the impact of variability/epistemic uncertainty in independent exposure parameters seen here. Our previous study (Avanasi et al., 2016a) showed that shared uncertainty, substantially impacted the absolute PFOA serum concentration predictions, but only mildly impacted the rank order of estimated serum PFOA concentrations (the lowest mean rank correlation between the estimated and the original predicted serum concentrations was 0.89) and did not impact the mean AOR between PFOA and preeclampsia. These results seemed counter-intuitive, considering that large changes to exposure assignments might be expected to cause large change in the epidemiological results. Together, these two studies suggest that in the PFOA exposure assessment modeling system, independent sources of error are more likely to change the rank order of exposure of participants and in turn impact the AOR of association than correlated uncertainty arising out of shared exposure sources. This may be due to relatively large differences (spanning several orders of magnitude)

in PFOA concentrations between water districts for the C8 Science Panel study area (Shin et al., 2011a), so that the rank order of exposure among participants is mostly preserved despite large changes to the PFOA groundwater concentration for each water district.

Because MC simulation evaluates the impact of adding parameter variability/uncertainty to an analysis rather than "correcting" for it, the AORs reported in Tables 3.3 and 3.4 reflect the sensitivity of the epidemiologic results to exposure uncertainty rather than corrected values. Thus, the true AOR for the epidemiological association between PFOA and preeclampsia in this study population may be higher than 1.12, with a wider confidence interval than originally estimated. Nonetheless, the epidemiological association between PFOA and preeclampsia in this study population is not very sensitive to variability/uncertainty in the retrospective exposure assignments. Notably, a prospective analysis of the same study population reported an AOR of 1.27 (95% CI: 1.05, 1.55) for PFOA and pregnancy-induced hypertension using measured serum concentrations and 2005-2010 birth records instead of modeled exposure assignments and self-reported health outcomes (Darrow et al., 2013). Preeclampsia is a type of pregnancy-induced hypertension that also includes proteinuria; the presence or absence of preeclampsia was not recorded on the birth certificates and pregnancy-induced hypertension was not included on the C8 Health Project questionnaire (C8 Science Panel, 2011). Together, the retrospective and prospective studies show consistent associations between PFOA and pregnancy-induced hypertension in this study population, with low sensitivity to exposure uncertainty.

3.5 Conclusions

In the uncertainty analysis presented here, we studied the impact of realistic inter-individual variability/epistemic uncertainty in independent exposure parameters including the standard and self-reported water ingestions rates, PFOA half-life, and PFOA volume of distribution on the predicted serum PFOA concentrations and the association between PFOA and preeclampsia in the participants of the C8 Health Project. Analysis of variability and epistemic uncertainty in these independent parameters changes the rank exposure among the study participants enough to cause a 25% bias towards the null. This result is in line with the previous literature which suggested that independent exposure measurement error can bias the effect estimate of an epidemiology study and suggests that the true AOR of association between PFOA and preeclampsia in the C8 Health Project/C8 Science Panel study population might be higher than originally reported with a wider confidence interval considering the effects of exposure uncertainty. We found it useful to study the impacts of these two types of exposure uncertainty (independent vs. correlated) separately. We think that future epidemiology studies with complex exposure scenarios and multiple sources of variability/uncertainty can separate out the two kinds of uncertainty and study them separately to better understand their potential impacts and to what extent, if any, they threaten the validity of epidemiological studies.

CHAPTER 4: IMPACTS OF GEOCODING UNCERTAINTY ON RECONSTRUCTED PFOA EXPOSURES AND THEIR EPIDEMIOLOGICAL ASSOCIATION WITH PREECLAMPSIA

Raghavendhran Avanasi

Hyeong-Moo Shin

Verónica M. Vieira

Scott M. Bartell

Chapter 4 is reproduced with permission from Environmental Research. R.Avanasi, HM. Shin, V.M. Vieira, S.M. Bartell. (in review) Impacts of geocoding uncertainty on reconstructed PFOA exposures and their epidemiological association with preeclampsia. Copyright 2016 Environmental Research

4.1 Introduction

Geographic Information Systems (GIS) have been used in numerous environmental health studies for assessing the exposure of participants to contaminants of interest via proximity analysis, integration of environmental monitoring data, individual-level exposure estimation, design of exposure metrics, and reconstructing exposure through activity patterns (Ali et al., 2002; Bell et al., 2001; Bellander et al., 2001; Beyea and Hatch, 1999; Elgethun et al., 2003; Floret et al., 2003; Nuckols et al., 2004; Reynolds et al., 2003; Rull and Ritz, 2003; Shin et al., 2011a; Vieira et al., 2010; Vieira et al., 2013). The use of GIS in environmental exposure assessment can improve our understanding of the associations between environmental exposures and adverse health outcomes (Beyea and Hatch, 1999; Nuckols et al., 2004).

Geocoding, the process of matching addresses to geographic locations (latitude and longitude), is an important step in using GIS for exposure assessment (Bonner et al., 2003). One primary application of geocoding is to assign individual-level environmental exposures based on their location in an exposed geographic area (Elgethun et al., 2003; Shin et al., 2011a; Vieira et al., 2013; Ward et al., 2005). Partial matching of addresses, such as a street name without the house number or a ZIP code without a specific street, or errors in geocoding can lead to positional errors in the exposure assessment, potentially leading to exposure mischaracterization. This can impact the validity of the epidemiological studies that use the resulting exposure estimates (Bonner et al., 2003; Elgethun et al., 2003; Vieira et al., 2010; Vieira et al., 2013). Researchers and the National Institutes of Health have called for more investigation into the potential impacts of geocoding uncertainty on the results of epidemiological studies (Henry and Boscoe, 2008; US Department of Health and Human Services, 2014; Zandbergen, 2009). A recent report from a Health and Environmental Sciences Institute (HESI) workshop also

recommended the characterization and evaluation of uncertainty in environmental epidemiology studies to better understand the potential sources of bias and to utilize results from epidemiological analyses for risk assessment (Burns et al., 2014).

The C8 Science Panel studies investigated associations of perfluorooctanoate (PFOA) serum concentrations predicted by a GIS-based exposure assessment (Shin et al., 2011a, b) with a variety of adverse health outcomes such as ulcerative colitis, kidney and testicular cancer, pregnancy outcomes, abnormal thyroid function, and abnormal kidney function (Barry et al., 2013; C8 Science Panel, 2011; Lopez-Espinosa et al., 2012; Savitz et al., 2012a; Savitz et al., 2012b; Steenland et al., 2013; Watkins et al., 2013). Predicted serum PFOA concentrations for 2005-2006 were well correlated ($r_s = 0.68$) with measured serum PFOA concentrations in the same year. Geocoding was used to locate participant residential addresses geographically to assign air and water PFOA concentrations for each year, over 58 years-1951 to 2008. This was done by spatially joining the addresses with the pipe distribution networks of the six participating public water districts (PWDs) to which all the consented participants of the C8 Health Project belonged (Shin et al., 2011b; Vieira et al., 2013). About 12% of the addresses (mostly rural addresses) with ZIP codes within the six PWDs could not be geocoded and thus population weighted ZIP code centroids were used to assign PWDs and the corresponding PFOA water concentrations. The assignment of population weighted ZIP code centroids for addresses that could not be geocoded to the street level can be considered as a single geographic imputation method (analogous to a mean imputation method). Such imputation or geocoding at a coarse spatial resolution can introduce geographic bias/positional errors in the exposure classification (Henry and Boscoe, 2008; Zandbergen, 2009). Also, it has been noted that there is greater

potential for positional errors when geocoding rural addresses compared to geocoding urban addresses (Vieira et al., 2010; Ward et al., 2005).

The aim of this study is to evaluate the potential impacts of geocoding uncertainty on the estimated serum PFOA concentrations of participants in the C8 Health Project. Specifically, we examine the impacts of single geographic imputation, which may have resulted in mischaracterized water PFOA concentrations for those participants geocoded to ZIP code centroids. We also examine the corresponding impact on the association between the estimated serum PFOA concentrations and the occurrence of preeclampsia (Savitz et al., 2012), an epidemiological analysis that has been discounted for the use of modeled rather than directly measured serum PFOA concentrations (Johnson and Sutton, 2014; Koustas et al., 2014). We use Monte Carlo (MC) simulation to assign alternate geographic locations within the reported ZIP code for all residential addresses that were geocoded to a ZIP code centroid and the reported work addresses, and recalculate the prediction of serum PFOA concentrations and the epidemiological association with preeclampsia for each set of alternate geographic locations.

4.2. Materials and methods

4.2.1. PFOA exposure assessment

The PFOA exposure assessment by Shin et al. (2011a, b) had two distinct modeling components. The first part of the PFOA exposure assessment used a suite of environmental fate and transport models to predict yearly PFOA outdoor air and groundwater concentrations for 1951-2008 in the region surrounding the Washington Works facility and the six impacted PWDs. Detailed explanation of the PFOA fate and transport modeling can be found in Shin et al. (2011a). Briefly, the modeling system utilized yearly PFOA release rates from the Washington Works facility, along with PFOA physicochemical properties, local meteorology, and

hydrogeology to predict the yearly air and water concentrations of PFOA for the area serviced by the six PWDs: the City of Belpre, Little Hocking Water Association, Tuppers Plains Chester Water District, the Village of Pomeroy Water District, Lubeck Public Service District, and Mason County Public Service District. The model also estimated PFOA exposure for shallower private drinking water wells located in the study area.

Next, an integrated exposure and pharmacokinetic model system was used to predict the yearly serum PFOA concentrations for all consented participants in the C8 Health Project study. This model system utilized the predicted yearly PFOA air and water concentrations (Shin et al., 2011a), standard inhalation and standard/self-reported tap water ingestion rates (U.S. EPA, 2009), PWD pipe distribution networks, along with self-reported participant information collected through a questionnaire as part of the C8 Health Project (Frisbee et al., 2009). These included detailed participant residential/work histories and participant demographics such as age, gender, and body weight. Based on the self-reported information, the drinking water source at each residential history was categorized as public, private, bottled water, or mixed. GIS was then used to link participant residential addresses with modeled air and water PFOA concentrations and predict yearly combined inhalation and ingestion (total) exposure doses for all the participants. A one-compartment pharmacokinetic model was then applied to estimate the yearly serum PFOA concentrations based on a single elimination half-life. More details on the exposure reconstruction/pharmacokinetic modeling are described by Shin et al. (2011b).

4.2.2. GIS

GIS methods were used to assign historical outdoor air and groundwater concentrations for each participant. With respect to ingestion exposure, GIS was used first to map the pipe distribution systems of the six PWDs included in the exposure modeling system (Shin et al., 2011b). Next, the participant residential addresses were geocoded using TeleAtlas and ArcView/NAVTEQ (Vieira et al., 2010). Among the residential addresses with ZIP codes in any of the six PWDs, approximately 12% of the addresses could not be geocoded to the street level (Shin et al., 2011b; Vieira et al., 2013) and hence, a population-weighted ZIP code centroid was used to assign environmental concentrations instead of the street level geocode. Later, within the GIS, the geocoded addresses were spatially joined with the PWD pipe distribution system to assign PWD-specific annual average PFOA water concentrations to those addresses that were serviced by any specific PWD. As described in the text and Figure 1 of the Shin et al. (2011b) study, based on the participant's geocoded residential address, the PFOA water concentrations were assigned for each reported residence for each participant. Any discrepancies between the self-reported water sources and the geocoded water sources (~ 9% of the addresses) were reviewed manually to determine the most likely source. For the participant work histories, the PFOA water concentrations were assigned based on self-reported public water sources. Street level addresses were not available for work histories but ZIP codes were reported for over half (55%) the work locations. 54.3% of the pregnancies had at least one reported work location during the year of pregnancy; this statistic was 54.8%, 52.5% and 41.1 % for 1 year, 2 years and 5 years previous to the year of the pregnancy. For participants with both residential and work histories, 70% of drinking water was assumed to come from the home and 30% from the work location (Shin et al., 2011b). For inhalation exposure, the participant's geocoded address and ZIP

centroid were used to assign PFOA outdoor air concentrations based on the annual average air concentration predictions (Shin et al., 2011a). For most of the study participants, drinking water ingestion was the major exposure route during the period of epidemiological investigations described below (Shin et al., 2011b; Vieira et al., 2013; Vieira et al., 2010).

4.2.3. Epidemiological study

One of the C8 Science Panel epidemiological studies focused on pregnancy outcomes including preeclampsia among 10,189 pregnancies (730 preeclampsia cases) that occurred between 1990 and 2006 in this population (Savitz et al., 2012a). The analysis used generalized estimating equations to estimate the association between preeclampsia and estimated serum PFOA in the year of pregnancy, adjusting for confounding by parity, maternal age, education level and smoking status. The study reported an adjusted odds ratio (AOR) of 1.13 (95% confidence interval (CI): 1.00, 1.28) per interquartile range (IQR) of log (natural) serum PFOA concentrations (nanograms per milliliter-ng/mL). We obtained approval from the Institutional Review Board (HS#2013-9421) at the University of California, Irvine to use those study data to conduct our MC analyses. We restricted our analysis to 10,149 pregnancies with 725 preeclampsia cases, by removing 25 mothers who had previously worked at the Washington Works facility. The resulting modified AOR per IQR was similar: 1.12 (95% CI: 1.00, 1.26).

We utilized the same PFOA exposure assessment model system, the same epidemiological model, and MC simulation to evaluate the potential impact of positional errors due to the use of population weighted ZIP code centroids (instead of the actual known address geocodes) on the estimated serum PFOA concentrations and the association with preeclampsia. MATLAB (The Mathworks Inc., Natick, MA, 2000), R (http://www.r-project.org/), and ArcGIS (ESRI) were used to perform these analyses.

4.2.4. MC simulations I and II

In order to evaluate the impact of mischaracterized exposure due to geocoding uncertainty on PFOA serum concentration predictions and epidemiological associations with preeclampsia, we conducted two types of Monte Carlo (MC) simulations: (1) simulation I using residential addresses only and (2) simulation II using residential and work addresses.
In the MC simulation I, the geocodes (latitude and longitude coordinates) of those residential addresses that were originally assigned to a ZIP code centroid were varied, and the serum PFOA concentration predictions and the epidemiological association with preeclampsia were re-calculated using the same exposure, pharmacokinetic, and epidemiological models. In each of 200 MC iterations (n= 200 was chosen based on the Monte Carlo error being < 1%), every residential address that had used a ZIP code centroid was reassigned a randomly selected alternate geocode within the same ZIP code (thereby reassigning the PFOA water concentrations according to the new geocoded location). In the secondary analysis (MC simulation II), in addition to handling residential addresses as described in MC simulation I, for each work address we reassigned a randomly selected alternate geocode within the reported ZIP code and the corresponding PFOA water concentrations were assigned. The exposure assessment model and the epidemiological analysis were repeated for each MC iteration to obtain plausible new serum PFOA concentration predictions and the AOR for the association of PFOA and preeclampsia.

Approximately 7.6 % (n= 2,046) of the residential addresses reported by our study participants had originally been geocoded to a ZIP code centroid. First, the ZIP codes (n=37) that were serviced by one of the 6 PWDs and the pipe distribution networks of the 6 PWDs are projected in the North American Datum of 1983 (NAD83) projection as shown in Figure 4.1. Then, a grid of points was created using the ZIP code extent (each ZIP code had at least 15 grid

points and up to 489 grid points). The grid points were on average 905 meters apart in the 37 ZIP codes. Then during each iteration for MC simulation I, for each residential history address that used a ZIP code centroid, a grid point was randomly sampled from within the corresponding ZIP code and the drinking water source and PFOA water concentration were re-assigned with those corresponding values from the sampled grid point. The random grid point represents a possible location (within the ZIP code for the specific residential history) of the participant's residence. In the MC simulation II, in addition to residential geocoding uncertainty discussed above, for each participant's work address a grid point was randomly sampled from within the corresponding ZIP code and the drinking water source and PFOA water concentration were re-assigned using the corresponding values from the sampled grid point. In the MC simulations, we studied the impact of geocoding uncertainty on the PFOA exposure only through drinking water ingestion and not through inhalation of contaminated air. Therefore, the inhalation exposures for the participants were not varied in the MC simulations I and II.

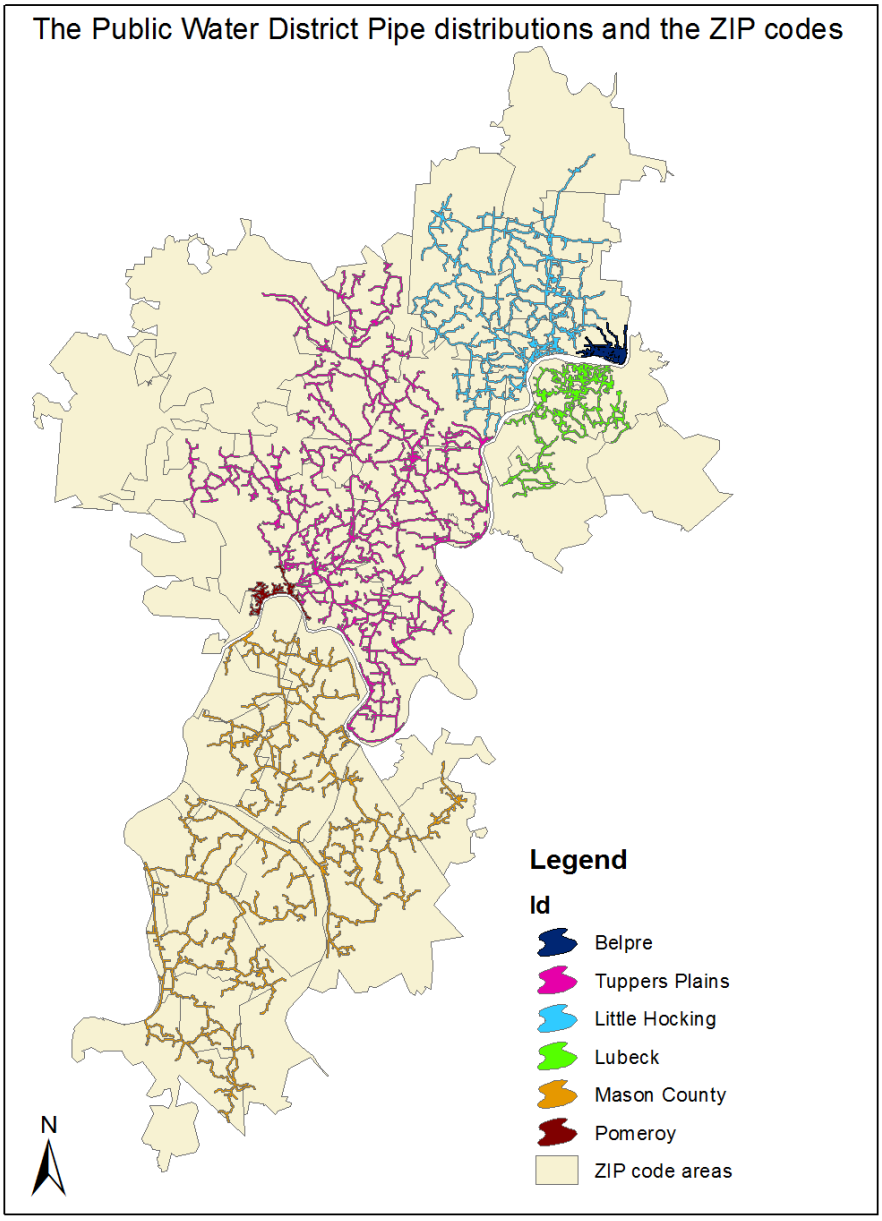

Figure 4.1: The image of the ZIP codes that is supplied by the pipe networks belonging to the 6 participating PWDs in the PFOA exposure assessment

To illustrate the MC methodology, consider a participant who had a residential address in ZIP code of 45769, but a ZIP code centroid was used due to insufficient address information. In our analysis, we created a grid of 335 points evenly spaced across this ZIP code area as seen in Figure 4.2 (panel a). This ZIP code is serviced by two different participating PWDs (Tuppers Plains and Pomeroy) and some parts of the ZIP code are not served by any of the participating PWDs and therefore treated as private wells as shown in Figure 4.2 (panel b). In the MC simulation, suppose a grid point 'A' was randomly sampled in the first iteration and used as the new residential address for that participant. PFOA water concentrations for Pomeroy PWD were then used in assigning the exposure for that iteration. For iteration 2, suppose a grid point 'B' was sampled and used as the new residential address for that participant. PFOA water concentrations for Tuppers Plains PWD would then be used to assign that participant's exposure for iteration 2. Alternately, if a grid point 'C' was sampled, the water source was treated as private and PFOA water concentrations from a shallow drinking water well in that location were assigned. Hence, for any participant with a residential address in ZIP code of 45769, there are three different possible assignments of PFOA water concentrations. The PFOA air concentrations were not varied, but were assigned as discussed in the GIS methodology section.

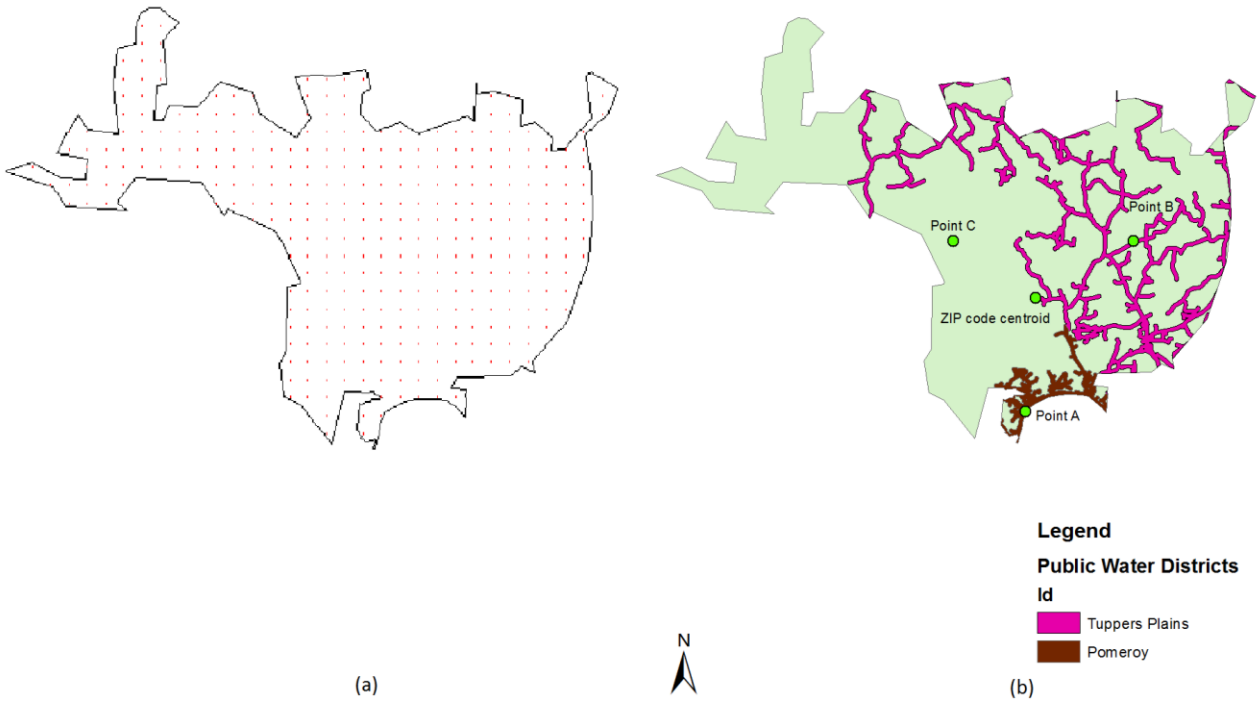

Figure 4.2: Outline of ZIP code 45769 with panel (a) showing the grid created for MC simulation and panel (b) illustrating the MC simulation methodology

Following the reassignment of geocodes and ingestion exposure via new water concentration assignment, participant serum PFOA concentrations for each MC iteration were computed and the epidemiological model was fit to obtain the AOR of preeclampsia occurrence (per IQR), for each of the 200 iterations of the MC simulation. Summary statistics for the serum PFOA concentrations for the 10,149 participants were calculated for each MC simulation. We then compared the serum PFOA concentrations from the MC simulation with the originally assigned serum PFOA concentrations by plotting the rank correlation between them for the 10,149 participants between the years 1990 and 2006. We also calculated summary statistics for the epidemiological results from the MC simulations (200 iterations) and compared them with the original AOR.

We also computed a measure of the relative contribution of geocoding uncertainty (uncertainty due to potential positional errors in the use of ZIP code centroids versus street address geocodes) to the total uncertainty in the epidemiological association of PFOA with preeclampsia (in addition to the participant sampling variability calculated as part of the confidence interval of the epidemiological association) using the law of total variance as described in our previous uncertainty analysis (Avanasi et al., 2016a). In brief, the contribution of the geocoding uncertainty is calculated by the formula var(b) = E(var(b|X)) + var(E(b|X)). In this formula, b corresponds to the log odds parameter estimate, X is a collection of individual exposure estimates, E is the expected value and var is the variance. The relative contribution of geocoding uncertainty to the total uncertainty was calculated by the formula var(E(b|X)) / var(b).

4.3. Results

The impact of the geocoding uncertainty on the serum PFOA concentration predictions (ng/mL) was studied by calculating median, mean, and 25^{th} and 75^{th} percentiles of each MC iteration for both MC simulations. These statistics were calculated for the subset of pregnancies with at least one residential history with a ZIP code centroid (centroid subset, n = 3,266) and for all the 10,149 study participants in MC simulations I and II. The mean and 95% probability intervals (PI) of the above mentioned summary statistics among the 200 MC iterations in comparison with the modified Savitz et al. (2012a) serum PFOA concentrations are shown in Table 4.1. We found minimal to no impact on the serum PFOA concentration predictions due to the presence of the geocoding uncertainty in MC simulation I, while there was a moderate impact in MC simulation II (with the mean serum PFOA concentrations among all the participants increasing from 51.1 ng/mL in the modified original analysis to 55.5 ng/mL).

Table 4.1: The mean and the 95% probability interval (PI) of the median, mean, 25th and 75th percentile serum concentrations at birth (ng/mL), for the study participants, for each of the 2 Monte Carlo simulations (200 iterations per simulation)

Simulation	Median (95% PI)	Mean (95% PI)	25^{th} percentile (95% PI)	75^{th} percentile (95% PI)
Modified original	9.4	51.1	5.1	32.5
Modified original Centroid Subset (n= 3,266)	8.3	50.3	5.0	27.1
MC simulation I Centroid Subset (n= 3,266)	7.4 (7.3, 7.5)	49.9 (48.7, 51.0)	5.1 (5.1, 5.2)	24.1 (23.1, 25.2)
MC simulation I (n= 10,149)	9.1 (9.0, 9.1)	51.9 (51.5, 52.2)	5.1 (5.1, 5.1)	32.3 (31.8, 32.7)
MC simulation II (n= 10,149)	10.9 (10.8, 11.0)	55.5 (55.1,55.9)	5.2 (5.2, 5.2)	40.1 (39.3, 40.8)

For the MC simulation I, we calculated the rank correlation between the simulated and the original serum PFOA concentrations for the centroid subset between the years 1990 and 2006 and the mean (95 % probability interval) over the 200 MC iterations was obtained for each year. The lowest mean rank correlation for the centroid subset (n=3,266) was that of year 1999: 0.92 (0.92, 0.93). On the other hand, the lowest mean rank correlation for all participants (n=10,149) was for the year 2002: 0.97 (0.96, 0.97), suggesting little change in the rank exposure among

centroid subset participants after accounting for geocoding uncertainty. For the MC simulation II, the addition of geocoding uncertainty in work addresses caused a reduction of rank correlation compared with the MC simulation I. The lowest mean rank correlation for all the 10,149 participants was for the year 1999: 0.93 (0.92, 0.93).

The impact of geocoding uncertainty in the residential addresses (MC simulation I) on the AOR of preeclampsia occurrence was minimal with the mean and the 95% probability interval of AOR being 1.12 (1.00, 1.25). This 95% probability interval includes the contribution of both the sampling variability among the participants and the geocoding uncertainty propagated in the MC simulation. Comparing it to the modified original analysis, the AOR per IQR (95% confidence interval) was 1.12 (1.00, 1.26). The contribution of the geocoding uncertainty in residential addresses only to the total uncertainty was found to be 1.1%. For the MC simulation II (geocoding uncertainty in both residential and work addresses), the AOR of preeclampsia occurrence increased with the mean and 95% probability interval of AOR was 1.17 (1.04, 1.32), which is a 41% bias away from the null, when compared with the AOR of 1.12 (1.00, 1.26) in the original modified analysis. The contribution of the geocoding uncertainty to the total uncertainty was found to be 2.6%.

4.4. Discussion

Geocoding uncertainty due to the use of ZIP code centroids for exposure assessment had little impact on the serum PFOA concentration predictions of the participants in the Savitz et al. (2012a) study as seen in Table 4.1. The mean rank correlation between the MC simulation I predicted serum PFOA concentrations and the original modified serum PFOA concentration predictions was high (0.97), suggesting little change in the rank exposure among the participants.

Subsequently, there was negligible impact on the association with preeclampsia. The contribution of geocoding uncertainty to total uncertainty (including participant sampling variability) was minor (1.1%). These results suggest that the use of ZIP centroids versus street level residential addresses does not substantially impact the validity of the reported association between serum PFOA concentrations and the occurrence of preeclampsia in the C8 Health Project population.

Interestingly, in MC simulation II, when we accounted for geocoding uncertainty in workplace addresses, there was a moderate increase in the mean and the 75th percentile serum PFOA concentrations (as seen in Table 4.1), and also a moderate decrease in the rank exposure among participants compared to that in MC simulation I. This indicates a bias away from the null for the association of PFOA and preeclampsia – a mean AOR (95% probability interval) of 1.17 (1.04, 1.32) compared to the original AOR of 1.12 (1.00, 1.26). For participants with reported work histories, addition of uncertainty in the spatial location of a work history within the self-reported ZIP code resulted in a 41% increase in the AOR of preeclampsia occurrence. Because MC simulation explores the impact of adding positional uncertainty to the geocodes rather than correcting for it (Gryparis et al., 2009; Avanasi et al., 2016a; Avanasi et al., 2016b), these results suggest that if we had more accurate locations of participant work addresses the AOR of preeclampsia occurrence might have been lower than previously reported. Previous literature suggests that positional error due to inaccurate geocoding or geocoding rural route addresses can potentially lead to exposure mischaracterization and bias in epidemiological study results (Vieira et al., 2010; Vieira et al., 2013; Elgethun et al., 2003; Bonner et al., 2003; Ward et al., 2005). We further investigated this bias away from null result since previous literature suggests that non-differential exposure mischaracterization causes a bias towards the null (not away from the null)

in epidemiological studies (Armstrong, 1998). In this specific epidemiological analysis, we found a different proportion of work addresses among cases (64.3%) compared to controls (53.5%) in the year of pregnancy. We think that this difference could potentially be responsible for a differential mischaracterization (instead of non-differential), with respect to the uncertainty in the work history of participants, resulting in a bias away from the null. In addition, from Table 4.1, we find that the mean serum PFOA concentrations among all the participants has increased from 51.1 (ng/mL) in the modified original analysis to 55.5 (ng/mL) for the MC simulation II, thereby contributing more to the potential differential exposure mischaracterization.

The relatively mild impact of residential address geocoding uncertainty can be expected as the residential addresses were usually available at the level of street address, and because the geocoded and self-reported water source assignments were manually crosschecked using GIS. In addition, only 7.6% of the participant residential histories used a ZIP code centroid in this study. In contrast, more participants (as discussed in the GIS section earlier) had geocoding uncertainty in work histories due to the lack of street addresses. Alternative work location geocodes appear to be able to change participant water sources enough to modify the rank order of exposure and cause a bias in the AOR of preeclampsia.

We had previously studied other sources of uncertainty in this PFOA exposure assessment model (Shin et al., 2011a, b) including shared uncertainty in the PFOA water concentrations (Avanasi et al., 2016a) and inter-individual variability/epistemic uncertainty in independent exposure parameters such as the standard and self-reported water ingestions rates and pharmacokinetic parameters including PFOA elimination half-life and PFOA volume of distribution (Avanasi et al., 2016b). Our previous studies found that correlated uncertainty (shared uncertainty in the PWD PFOA water concentrations due to uncertainties in source

emissions and our fate and transport model) had negligible impact on the rank order of exposure among participants and the AOR of association with preeclampsia, although it had substantial impact on the serum PFOA concentrations. In contrast, independent sources of error in water ingestion rates and pharmacokinetic parameters moderately influenced the rank exposure and caused a bias towards the null in the association with preeclampsia. Together with these two studies, the geocoding uncertainty analysis yields a detailed understanding of potential impacts of various sources of uncertainty in the PFOA exposure assessment modeling system on the specific epidemiological association with preeclampsia.

4.4.1. Limitations

Epidemiological studies of other health outcomes that were part of the C8 Science Panel studies might or might not have a similar result as they include different sets of participants with different residential and work histories. In addition, it has been suggested that the impact of errors in geocoding on exposure assessment depends on spatial variation of the exposure (Wards et al., 2005). Therefore, the results presented here can inform judgments about the reliability of the Savitz et al. (2012a) preeclampsia findings but may not be generalizable to the impact of geocoding uncertainty on other C8 Science Panel epidemiological studies, or other environmental epidemiological studies that used ZIP code centroid geo-coordinates to represent non-geocoded addresses in their exposure assessment. Also, the current analysis investigates the impact of geocoding uncertainty (residential and work addresses) only on the PFOA exposure through drinking water ingestion. We did not consider inhalation route of exposure because the contribution of inhalation exposure to overall exposure for participants in the Savitz et al., 2012a study (between the years 1990 and 2006) was minimal as discussed in the Avanasi et al. (2016a)

study. However, its inclusion could result in slight increases in the total uncertainty attributed to geocoding.

Our findings are also limited by sampling alternate residential and work locations from throughout the entire identified ZIP codes. Importantly, road maps of the region suggest that not all areas are developed or inhabited. Future analyses using MC simulation could restrict the grid to areas that are highly likely to be developed or inhabited, such as areas within a fixed distance of roadways, thereby assigning more realistic alternate residential and work locations for participants.

Our results for MC simulation II are likely to be sensitive to the proportion of drinking water obtained from residential versus work addresses. Although the assumption that 30% of drinking water came from work addresses provided valid predictions of PFOA serum concentrations (Shin et al., 2011b), the actual proportion likely differs widely among participants. Future studies in this population or in other populations with contaminated drinking water might benefit from more attention to water sources at participants' workplaces, and to the extent to which each participant consumes tap water while at work.

4.4.2. Conclusions

In the MC simulation study presented here, we studied the potential impact of geocoding uncertainty due to the missing street level residential addresses and self-reported ZIP codes of work addresses (for the PFOA exposure assessment participants in the Savitz et al. (2012a) study) by assigning alternate geographic locations within the reported ZIP code and recalculating the serum PFOA concentrations. We repeated the epidemiological study associating these estimated serum PFOA concentrations with the occurrence of preeclampsia (Savitz et al., 2012a)

to examine if the use of alternate residential/work locations has any impact on the study results. We found that geocoding based uncertainty in residential addresses did not have any significant impact on the serum PFOA concentration predictions and the epidemiological association with preeclampsia seems to be robust, with little bias. The addition of geocoding based uncertainty in work history moderately impacts the rank exposure among the participants and causes a 41% bias away from the null in the AOR of preeclampsia occurrence. The analysis presented here is one approach to estimating the potential impacts of positional errors in a geocoding-based exposure assessment on exposure estimates and epidemiological study results. Future exposure studies and epidemiological studies that rely on participant locations could benefit from explicit analysis of the impacts of geocoding-based uncertainties.

CHAPTER 5: SUMMARY AND CONCLUSIONS

5.1 Summary of findings

For my dissertation research, I evaluated the different sources of input parameter uncertainty/variability as causes of exposure measurement error in the C8 exposure assessment and studied their impacts on the serum PFOA concentration predictions and the epidemiological association with preeclampsia among the C8 Health Project population. I used MC simulation methodology for the different uncertainty analysis, presented and discussed my results in each chapter.

In Chapter 2, I used a three-component MC simulation methodology to characterize random and systematic uncertainty in the PFOA PWD water concentrations allowing for specification of correlations in exposure measurement errors across years and across individuals with shared exposure sources. The incorporation of autocorrelated and shared uncertainty in our water concentration estimates produced a highly variable set of plausible serum PFOA concentrations; however, it had less impact on the rank order of estimated serum PFOA concentrations among the study participants and also the AOR of preeclampsia occurrence. Exposure uncertainty contributed anywhere between 5 and 31 % to the total uncertainty (including regression parameter variance) in this analysis.

In Chapter 3, I utilized Monte Carlo simulation to propagate inter-individual variability/epistemic uncertainty in other key factors in the exposure assessment and reanalyzed the epidemiological association. Inter-individual variability in independent exposure parameters including water ingestion rates, the serum PFOA half-life, and the volume of distribution for PFOA mildly impacted the serum PFOA concentration predictions and there was a negligible impact on the epidemiological association with preeclampsia and the contribution of variability 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 (a 25% bias towards the null), and the contribution of exposure uncertainty to the total uncertainty was increased up to 33%.

In Chapter 4, I examined the impacts of single geographic imputation of addresses geocoded to ZIP code only, rather than to street address, which may have resulted in mischaracterized water PFOA concentrations experienced by those participants. I used Monte Carlo (MC) simulation to assign alternate geographic locations within the reported ZIP code for all work addresses and residential addresses geocoded to ZIP code only, rather assigning the ZIP code centroid. I found that geocoding based uncertainty in residential addresses did not have any significant impact on the serum PFOA concentration predictions and the epidemiological association with preeclampsia. Interestingly, the addition of geocoding based uncertainty in work history moderately impacted the rank exposure among the participants and caused a 41% bias away from the null in the AOR of preeclampsia occurrence. If the exposure model assumption is correct that 30% of drinking water exposure comes from work for employed participants, these results suggest that future studies of this type should obtain more detailed information on work histories, allowing for street-level geocoding.

5.2 Conclusions

The use of uncertain PWD PFOA water concentrations as a surrogate for uncertainty in a number of potential uncertain/variable parameters used in the suite of environmental models (Shin et al., 2011a) was due to the complexity of the suite of fate and transport models used, which takes many days to run. A Monte Carlo uncertainty analysis for each uncertain parameter would require an impractical amount of computer time and was avoided based on our results of the first uncertainty analysis (Chapter 2). Our screening-level assessment suggests that correlated exposure measurement error produced by parameters affecting water concentrations may produce substantial changes in PFOA serum estimates but contribute only modestly to overall uncertainty regarding the epidemiologic association between PFOA and preeclampsia; thus we chose not to follow up with more detailed uncertainty analysis for those parameters.

Realistic inter-individual variability and epistemic uncertainty in the selected independent parameters (water ingestion rates, the serum PFOA half-life, and the volume of distribution) change the rank exposure among the study participants enough to cause a 25% bias in the AOR towards the null. This result supports the previous literature which suggested that independent exposure measurement error can bias the effect estimate of an epidemiology study. Thus the true AOR of association between PFOA and preeclampsia in the C8 Health Project population might be higher than originally reported (with a wider confidence interval), considering the effects of exposure uncertainty.

The potential impact of geocoding uncertainty in street level residential addresses and self-reported ZIP codes of work addresses together suggests that if we had more accurate locations of participant work addresses, the AOR of preeclampsia occurrence might have been less strong than previously reported. The work history information that was collected as a part of

the C8 Health Project could have been more detailed and comprehensive, but with sufficient resources participants could still be re-contacted with a request to provide more detailed work histories.

I found it useful to study the impacts of the different types of exposure uncertainty (independent, correlated, geocoding-based) separately. I think that future environmental epidemiology studies with complex exposure scenarios and multiple sources of variability/uncertainty can separate out the different kinds of uncertainty and study them separately to better understand their individual impacts and to what extent, if any, they threaten the validity of epidemiological studies. Also, we had initially expected a stronger impact of uncertainty in the fate and transport model parameters on the rank exposure and the AOR of preeclampsia occurrence, given the strong impact on the serum PFOA concentration predictions. However, we did not find this and the results were counter-intuitive, suggesting that the although the absolute exposure to PFOA among the participants changed, the relative change between participants was not big enough to impact the epidemiological study results.

5.3 Recommendation for future studies

We study the impacts of the different types of exposure uncertainty (independent, correlated, geocoding-based) separately; a combined analysis of all three types of exposure uncertainty in this environmental modeling-epidemiology model system could shed light on the combined effect of the different sources of uncertainty in the C8 exposure assessment and the epidemiological association with preeclampsia. Also, considering the uncertainty in the confounders used in the Savitz et al., 2012a study could be a possible addition to the present uncertainty analysis. Measurement error in the confounders could also have an impact on the AOR, by causing bias in either direction as suggested by previous studies (Marshall and Hastrup,

1996; Savitz and Baron, 1989). Parity, maternal age, and education level are likely to have been reported accurately by most participants; however, smoking is often subject to under-reporting, particularly among pregnant women (Shipton et al., 2009; Ford et al., 1997). Considering additional confounders in the Savitz et al., 2012a study could also be a future direction.

Drinking water ingestion is a major exposure route (versus inhalation) for our study population in all years, except for the participants who consumed water from Little Hocking before 1974 and those who consumed water from Belpre before 1990 (Shin et al. 2011b). Given this, and the fact that the epidemiological analysis included pregnancies occurring only between 1990 and 2006, we chose to model uncertainty only for the drinking water concentrations in this analysis, not perturbing the original inhalation exposure estimates. The addition of uncertainty and variability in the original inhalation exposure estimates could contribute to the overall uncertainty in this environmental epidemiology study. This could be a potential future analysis, but we expect it to not cause much change to the present results as drinking water ingestion is the major exposure route in this population.

Other epidemiological studies conducted by the C8 Science Panel might or might not have similar results for exposure uncertainty analyses. This is because they include a different set of participants whose shared exposure sources, individual-level independent exposure parameters and residential/work addresses might differ (including more/less ZIP code centroids) from the Savitz et al., 2012a study; thereby holding more/less uncertainty in exposures, or different rank exposures among the epidemiology study participants. One future direction for research is to study the impact of these exposure uncertainties (exposure measurement error) within the C8 Health Project population on other important C8 Science Panel epidemiological studies linking

PFOA exposure with cholesterol, colitis, uric acid, kidney and testicular cancer, and thyroid disease.

REFERENCES

Ali, M., Emch, M., Donnay, J.P., 2002. Spatial filtering using a raster geographic information system: Methods for scaling health and environmental data. Heal. Place 8, 85–92. doi:10.1016/S1353-8292(01)00029-6

Andersen, M.E., Clewell, H.J., Tan, Y.M., Butenhoff, J.L., Olsen, G.W., 2006. Pharmacokinetic modeling of saturable, renal resorption of perfluoroalkylacids in monkeys-Probing the determinants of long plasma half-lives. Toxicology 227, 156–164. doi:10.1016/j.tox.2006.08.004

Anzai, N., Kanai, Y., Endou, H., 2006. Review Organic Anion Transporter Family : Current Knowledge. J Pharmacol Sci 426, 411–426

Armstrong, B.G., 1998. Effect of measurement error on epidemiological studies of environmental and occupational exposures. Occup. Environ. Med. 55, 651–6

Avanasi, R., Shin, H.-M., Vieira, V.M., Savitz, D. a., Bartell, S.M., 2016a. Impact of Exposure Uncertainty on the Association between Perfluorooctanoate and Preeclampsia in the C8 Health Project Population. Environ. Health Perspect. doi:10.1289/ehp.1409044

Avanasi, R., Shin, H.-M., Vieira, V.M., Bartell, S.M., 2016b. 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. Environ. Res. 146, 299–307. doi:10.1016/j.envres.2016.01.011

Bainbridge, S.A., Roberts, J.M., 2008. Uric acid as a pathogenic factor in preeclampsia. Placenta 29 Suppl A, S67–72. doi:10.1016/j.placenta.2007.11.001

Bainbridge, S.A., Roberts, J.M., Versen-ho, F. Von, Koch, J., Edmunds, L., Hubel, C.A., 2009. Uric acid attenuates trophoblast invasion and integration into endothelial cell monolayers 440–450. doi:10.1152/ajpcell.00593.2008

Baker D, Niewenhuijsen MJ. 2008. Environmental epidemiology: study methods and application. New York, NY: Oxford University Press Inc.

Barry, V., Winquist, A., Steenland, K., 2013. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ. Health Perspect. 121, 1313–1318. doi:10.1289/ehp.1306615

Bartell, S.M., Calafat, A.M., Lyu, C., Kato, K., Ryan, P.B., Steenland, K., 2010. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ. Health Perspect. 118, 222–8. doi:10.1289/ehp.0901252

Bartell, S.M., Griffith, W.C., Faustman, E.M., 2004. Temporal error in biomarker-based mean exposure estimates for individuals. J. Expo. Anal. Environ. Epidemiol. 14, 173–9. doi:10.1038/sj.jea.7500311

Bell, E.M., Hertz-picciotto, I., Beaumont, J.J., Epidemiology, S., Mar, N., 2015. A Case-Control Study of Pesticides and Fetal Death Due to Congenital Anomalies Linked references are available on JSTOR for this article : 12, 148–156

Bellander, T., Berglind, N., Gustavsson, P., Jonson, T., Nyberg, F., Pershagen, G., Järup, L., 2001. Using geographic information systems to assess individual historical exposure to air pollution from traffic and house heating in stockholm. Environ. Health Perspect. 109, 633–639. doi:10.1289/ehp.01109633

Berkson L. 1950. Are there two regressions? J Am Stat Assoc 45:164–180

Beyea, J., Hatch, M., 1999. Geographic exposure modeling: A valuable extension of geographic information systems for use in environmental epidemiology. Environ. Health Perspect. 107, 181–190. doi:10.2307/3434482

Bonner, M.R., Han, D., Nie, J., Rogerson, P., Vena, J.E., Freudenheim, J.L., 2003. Positional accuracy of geocoded addresses in epidemiologic research. Epidemiology 14, 408–12. doi:10.1097/01.EDE.0000073121.63254.c5

Bradman A, Kogut K, Eisen EA, Jewell NP, Quirós-Alcalá L, Castorina R, et al. 2013. Variability of organophosphorous pesticide metabolite levels in spot and 24-hr urine samples collected from young children during 1 week. Environ. Health Perspect. 121(1):118–124

Burmaster, D.E., Anderson, P.D., 1994. Principles of good practice for the use of Monte Carlo techniques in human health and ecological risk assessments. Risk Anal. 14, 477–81

Butenhoff, J.L., Kennedy, G.L., Hinderliter, P.M., Lieder, P.H., Jung, R., Hansen, K.J., Gorma, G.S., Nokers, P.E., Thomford, P.J., 2004. Pharmacokinetics of perfluorooctanoate in cynomolgus monkeys. Toxicol. Sci. 82, 394–406. doi:10.1093/toxsci/kfh302

C8 Science Panel, 2011. Probable link evaluation of pregnancy induced hypertension and preeclampsia 1–6

Calafat, A., Kuklenyik, Z., Reidy, J.A., Caudill, S.P., Tully, J.S., Needham, L.L., 2007. Serum Concentrations of 11 Polyfluoroalkyl Compounds in the U . S . Population : Data from the National Health and Nutrition Examination Survey (NHANES) 1999 - 2000. Environ. Sci. Technol. 2237–2242

Carroll RJ, Ruppert D, Stefanski LA, Crainicieanu CM. 2006.Measurement error in nonlinear models: a modern perspective. Boca Raton, FL: Chapman and Hall/CRC Press LLC.

Darrow, L.A., Stein, C.R., Steenland, K., 2013. Serum Perfluorooctanoic Acid and Perfluorooctane Sulfonate Concentrations in Relation to Birth Outcomes in the Mid-Ohio Valley, 2005-2010. Environ. Health Perspect. 2005–2010

Elgethun, K., Fenske, R. a., Yost, M.G., Palcisko, G.J., 2003. Time-location analysis for exposure assessment studies of children using a novel global positioning system instrument. Environ. Health Perspect. 111, 115–122. doi:10.1289/ehp.5350

Finley, B., Paustenbach, D., 1994. The benefits of probabilistic exposure assessment: three case studies involving contaminated air, water, and soil. Risk Anal. 14, 53–73

Floret, N., Mauny, F., Challier, B., Arveux, P., Cahn, J.-Y., Viel, J.-F., 2003. Dioxin emissions from a solid waste incinerator and risk of non-Hodgkin lymphoma. Epidemiology 14, 392–8. doi:10.1097/01.ede.0000072107.90304.01

Ford, R.P., Tappin, D.M., Schluter, P.J., Wild, C.J., 1997. Smoking during pregnancy: how reliable are maternal self reports in New Zealand? J. Epidemiol. Community Health 51, 1–2

Frisbee, S.J., Brooks, a. P., Maher, A., Flensborg, P., Arnold, S., Fletcher, T., Steenland, K., Shankar, A., Knox, S.S., Pollard, C., Halverson, J. a., Vieira, V.M., Jin, C., Leyden, K.M., Ducatman, A.M., 2009. The C8 Health Project: Design, Methods, and Participants. Environ. Health Perspect. 117, 1873–1882. doi:10.1289/ehp.0800379

Gallo, V., Leonardi, G., Genser, B., Lopez-Espinosa, M.J., Frisbee, S.J., Karlsson, L., Ducatman, A.M., Fletcher, T., 2012. Serum perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) concentrations and liver function biomarkers in a population with elevated PFOA exposure. Environ. Health Perspect. 120, 655–660. doi:10.1289/ehp.1104436

Granger, J.P., Alexander, B.T., Bennett, W. a, Khalil, R. a, 2001. Pathophysiology of pregnancy-induced hypertension. Am. J. Hypertens. 14, 178S–185S

Gryparis, A., Paciorek, C.J., Zeka, A., Schwartz, J., Coull, B. a., 2009. Measurement error caused by spatial misalignment in environmental epidemiology. Biostatistics 10, 258–274. doi:10.1093/biostatistics/kxn033

Gustafson P. 2003. Measurement error and misclassification in statistics and epidemiology: impacts and Bayesian adjustments. Boca Raton, FL: Chapman and Hall/CRC Press LLC.

Han, X., Nabb, D.L., Russell, M.H., Kennedy, G.L., Rickard, R.W., 2012. Renal elimination of perfluorocarboxylates (PFCAs). Chem. Res. Toxicol. 25, 35–46. doi:10.1021/tx200363w

Heid IM, Küchenhoff H, Miles J, Kreienbrock L, Wichmann HE. 2004. Two dimensions of measurement error: Classical and Berkson error in residential radon exposure assessment. J Expo Sci Environ Epidemiol 14, 365–377

Heinig, M., Johnson, R.J., 2006. Role of uric acid in hypertension, renal disease, and metabolic syndrome. Cleve. Clin. J. Med. 73, 1059–1064

Henry, K. a, Boscoe, F.P., 2008. Estimating the accuracy of geographical imputation. Int. J. Health Geogr. 7, 3. doi:10.1186/1476-072X-7-3

Hundley, S.G., Sarrif, a M., Kennedy, G.L., 2006. Absorption, distribution, and excretion of ammonium perfluorooctanoate (APFO) after oral administration to various species. Drug Chem. Toxicol. 29, 137–45. doi:10.1080/01480540600561361

Johnson, P., Sutton, P., 2014. The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Fetal Growth. Env. Heal. … 122, 1040–1051. doi:10.1289/ehp.1307893

Kang, D., Finch, J., Nakagawa, T., Karumanchi, S.A., Kanellis, J., Granger, J., Johnson, R.J., 2004. Uric acid , endothelial dysfunction and pre-eclampsia : searching for a pathogenetic link. J. Hypertens. 22, 229–235. doi:10.1097/01.hjh.0000098227.37783.8e

Kennedy, G.L., Butenhoff, J.L., Olsen, G.W., O'Connor, J.C., Seacat, A.M., Perkins, R.G., Biegel, L.B., Murphy, S.R., Farrar, D.G., 2004. The Toxicology of Perfluorooctanoate, Critical Reviews in Toxicology. doi:10.1080/10408440490464705

Koustas, E., Lam, J., Sutton, P., Johnson, P.I., Atchley, D.S., Sen, S., Robinson, K. a, Axelrad, D. a, Woodruff, T.J., 2014. The Navigation Guide - evidence-based medicine meets environmental health: systematic review of nonhuman evidence for PFOA effects on fetal growth. Environ. Health Perspect. 122, 1015–27. doi:10.1289/ehp.1307177

Lau, C., Anitole, K., Hodes, C., Lai, D., Pfahles-Hutchens, A., Seed, J., 2007. Perfluoroalkyl acids: a review of monitoring and toxicological findings. Toxicol. Sci. 99, 366–94. doi:10.1093/toxsci/kfm128

Laughon, S.K., Catov, J., Powers, R.W., Roberts, J.M., Gandley, R.E., 2011. First trimester uric acid and adverse pregnancy outcomes. Am. J. Hypertens. 24, 489–95. doi:10.1038/ajh.2010.262

Leeman, L., Fontaine, P., 2008. Hypertensive disorders of pregnancy. Am. Fam. Physician 78, 93–100.

Limpert, E., Stahel, W. a., Abbt, M., 2001. Log-normal Distributions across the Sciences: Keys and Clues. Bioscience 51, 341. doi:10.1641/0006-3568(2001)051[0341:LNDATS]2.0.CO;2

Loccisano, A.E., Campbell, J.L., Butenhoff, J.L., Andersen, M.E., Clewell, H.J., 2012. Evaluation of placental and lactational pharmacokinetics of PFOA and PFOS in the pregnant, lactating, fetal and neonatal rat using a physiologically based pharmacokinetic model. Reprod. Toxicol. 33, 468–90. doi:10.1016/j.reprotox.2011.07.003

Loccisano, A.E., Longnecker, M.P., Campbell, J.L., Andersen, M.E., Clewell, H.J., 2013. Development of PBPK models for PFOA and PFOS for human pregnancy and lactation life stages. J. Toxicol. Environ. Health. A 76, 25–57. doi:10.1080/15287394.2012.722523

Lopez-Espinosa M, Mondal D, Armstrong B, Bloom MS, Fletcher T. 2012. Thyroid Function and Perfluoroalkyl Acids in Children Living Near a Chemical Plant. Environ. Health Perspect. 120:1036–1041; doi:10.1289/ehp.1104370

Mazzali, M., Hughes, J., Kim, Y.-G., Jefferson, J. a., Kang, D.-H., Gordon, K.L., Lan, H.Y., Kivlighn, S., Johnson, R.J., 2001. Elevated Uric Acid Increases Blood Pressure in the Rat by a Novel Crystal-Independent Mechanism. Hypertension 38, 1101–1106. doi:10.1161/hy1101.092839

Mazzali, M., Kanellis, J., Han, L., Feng, L., Xia, Y.-Y., Chen, Q., Kang, D.-H., Gordon, K.L., Watanabe, S., Nakagawa, T., Lan, H.Y., Johnson, R.J., 2002. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am. J. Physiol. Renal Physiol. 282, F991–7. doi:10.1152/ajprenal.00283.2001

Morgan G, Henrion M, Small M. 1990.Uncertainty: a guide to dealing with uncertainty in quantitative risk and policy analysis. New York, NY: Cambridge University Press

The National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy*. *American Journal of Obstetrics and Gynecology* **183,** s1–s22 (2000)

Nolan, L. a, Nolan, J.M., Shofer, F.S., Rodway, N. V, Emmett, E. a, 2010. Congenital anomalies, labor/delivery complications, maternal risk factors and their relationship with perfluorooctanoic acid (PFOA)-contaminated public drinking water. Reprod. Toxicol. 29, 147–55. doi:10.1016/j.reprotox.2009.10.012

Nuckols, J.R., Ward, M.H., Jarup, L., 2004. Using geographic information systems for exposure assessment in environmental epidemiology studies. Environ. Health Perspect. 112, 1007–1015. doi:10.1289/ehp.6738

Olsen, G.W., Burris, J.M., Ehresman, D.J., Froehlich, J.W., Seacat, A.M., Butenhoff, J.L., Zobel, L.R., 2007. Half-life of serum elimination of perfluorooctanesulfonate,perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ. Health Perspect. 115, 1298–305. doi:10.1289/ehp.10009

Özkaynak H, Frey HC, Hubbell B. 2008. Characterizing variability and uncertainty in exposure assessments improves links to environmental decision-making. EM (Pittsburgh Pa) 58(7):18–22

Panaretakis, T., Shabalina, I.G., Grandér, D., Shoshan, M.C., DePierre, J.W., 2001. Reactive oxygen species and mitochondria mediate the induction of apoptosis in human hepatoma HepG2 cells by the rodent peroxisome proliferator and hepatocarcinogen, perfluorooctanoic acid. Toxicol. Appl. Pharmacol. 173, 56–64. doi:10.1006/taap.2001.9159

Paul, a Z., 2009. Geocoding Quality and Implications for Spatial Analysis. Geogr. Compass 3, 647–680

Paustenbach, D.J., Panko, J.M., Scott, P.K., Unice, K.M., 2007. A methodology for estimating human exposure to perfluorooctanoic acid (PFOA): a retrospective exposure assessment of a community (1951-2003). J. Toxicol. Environ. Health. A 70, 28–57. doi:10.1080/15287390600748815

Post, G.B., Cohn, P.D., Cooper, K.R., 2012. Perfluorooctanoic acid (PFOA), an emerging drinking water contaminant: a critical review of recent literature. Environ. Res. 116, 93–117. doi:10.1016/j.envres.2012.03.007

Prentice, R.L., Tinker, L.F., Huang, Y., Neuhouser, M.L., 2013. Calibration of self-reported dietary measures using biomarkers: an approach to enhancing nutritional epidemiology reliability. Curr Atheroscler Rep 15, 353. doi:10.1007/s11883-013-0353-5

Qian, Y., Ducatman, A., Ward, R., Leonard, S., Bukowski, V., Lan Guo, N., Shi, X., Vallyathan, V., Castranova, V., 2010. Perfluorooctane sulfonate (PFOS) induces reactive oxygen species (ROS) production in human microvascular endothelial cells: role in endothelial permeability. J. Toxicol. Environ. Health. A 73, 819–36. doi:10.1080/15287391003689317

Reynolds, P., Von Behren, J., Gunier, R.B., Goldberg, D.E., Hertz, A., Smith, D.F., 2003. Childhood cancer incidence rates and hazardous air pollutants in California: An exploratory analysis. Environ. Health Perspect. 111, 663–668. doi:10.1289/ehp.5986

Rosner B. 2010. Fundamentals of biostatistics. Boston, MA: CENGAGE Learning

Rothman KJ, Greenland S, Lash TL. 2008. Modern epidemiology. Philadelphia, PA: Lippincott Williams and Wilkins

Rull, R.P., Ritz, B., 2003. Historical pesticide exposure in California using pesticide use reports and land-use surveys: An assessment of misclassification error and bias. Environ. Health Perspect. 111, 1582–1589. doi:10.1289/ehp.6118

Sarnat, S.E., Klein, M., Sarnat, J. a, Flanders, W.D., Waller, L. a, Mulholland, J. a, Russell, A.G., Tolbert, P.E., 2010. An examination of exposure measurement error from air pollutant spatial variability in time-series studies. J. Expo. Sci. Environ. Epidemiol. 20, 135–46. doi:10.1038/jes.2009.10

Savitz, D. a, Stein, C.R., Bartell, S.M., Elston, B., Gong, J., Shin, H.-M., Wellenius, G. a, 2012. Perfluorooctanoic acid exposure and pregnancy outcome in a highly exposed community. Epidemiology 23, 386–92. doi:10.1097/EDE.0b013e31824cb93b

Savitz, D.A., Stein, C.R., Elston, B., Wellenius, G.A., Bartell, S.M., Shin, H., Vieira, V.M., Fletcher, T., 2012. Children's Health Relationship of Perfluorooctanoic Acid Exposure to

Pregnancy Outcome Based on Birth Records in the Mid-Ohio Valley. Environ. Health Perspect. 120, 1201–1207

Shankar, A., Xiao, J., Ducatman, A., 2011a. Perfluoroalkyl chemicals and elevated serum uric acid in US adults. Clin. Epidemiol. 3, 251–8. doi:10.2147/CLEP.S21677

Shankar, A., Xiao, J., Ducatman, A., 2011b. Perfluoroalkyl chemicals and chronic kidney disease in US adults. Am. J. Epidemiol. 174, 893–900. doi:10.1093/aje/kwr171

Shimokura, G.H., Savitz, D. a, Symanski, E., Symansk, E., 1998. Assessment of Water Use for Estimating Exposure to Tap Water Articles ' Contaminants Environmental. Environ. Heal. 106, 55–59

Shin, H.-M., Vieira, V.M., Ryan, P.B., Detwiler, R., Sanders, B., Steenland, K., Bartell, S.M., 2011a. Environmental fate and transport modeling for perfluorooctanoic acid emitted from the Washington Works Facility in West Virginia. Environ. Sci. Technol. 45, 1435–42. doi:10.1021/es102769t

Shin, H.-M., Vieira, V.M., Ryan, P.B., Steenland, K., Bartell, S.M., 2011b. Retrospective exposure estimation and predicted versus observed serum perfluorooctanoic acid concentrations for participants in the C8 Health Project. Environ. Health Perspect. 119, 1760–5. doi:10.1289/ehp.1103729

Shin H-M, Steenland K, Ryan PB, Vieira VM, Bartell SM. 2014. Biomarker-based calibration of retrospective exposure predictions of perfluorooctanoic acid. Environ Sci Technol 48(10):5636–5642

Shipton, D., Tappin, D.M., Vadiveloo, T., Crossley, J. a, Aitken, D. a, Chalmers, J., 2009. Reliability of self reported smoking status by pregnant women for estimating smoking prevalence: a retrospective, cross sectional study. BMJ 339, b4347. doi:10.1136/bmj.b4347

Sibai, B.M., Ewell, M., Levine, R.J., Klebanoff, M. a., Esterlitz, J., Catalano, P.M., Goldenberg, R.L., Joffe, G., 1997. Risk factors associated with preeclampsia in healthy nulliparous women. Am. J. Obstet. Gynecol. 177, 1003–1010. doi:10.1016/S0002-9378(97)70004-8

Steenland, K., Tinker, S., Shankar, A., Ducatman, A., 2010. Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with uric acid among adults with elevated community exposure to PFOA. Environ. Health Perspect. 118, 229–33. doi:10.1289/ehp.0900940

Steenland, K., Zhao, L., Winquist, A., Parks, C., 2013. Ulcerative colitis and perfluorooctanoic acid (PFOA) in a highly exposed population of community residents and workers in the Mid-Ohio Valley. Environ. Health Perspect. 121, 900–905. doi:10.1289/ehp.1206449

Stein, C.R., Savitz, D. a, Dougan, M., 2009. Serum levels of perfluorooctanoic acid and perfluorooctane sulfonate and pregnancy outcome. Am. J. Epidemiol. 170, 837–46. doi:10.1093/aje/kwp212

Tan, Y.M., Clewell, H.J., Andersen, M.E., 2008. Time dependencies in perfluorooctylacids disposition in rat and monkeys: A kinetic analysis. Toxicol. Lett. 177, 38–47. doi:10.1016/j.toxlet.2007.12.007

Thomas, D., Stram, D., Dwyer, J., 1993. EXPOSURE MEASUREMENT ERROR : Influence on Expo sure-Disease Relationships and Methods of Correction. Annu. Rev. Public Heal. 14, 69–93

Tsuchiya, A., Duff, R., Stern, A.H., White, J.W., Krogstad, F., Burbacher, T.M., Faustman, E.M., Mariën, K., 2012. Single blood-Hg samples can result in exposure misclassification: temporal monitoring within the Japanese community (United States). Environ. Health 11, 37. doi:10.1186/1476-069X-11-37

US Department of Health and Human Services, 2014. Available: http://grants.nih.gov/grants/guide/pa-files/PA-15-010.html [accessed 1January 2016]

U.S. EPA (Environmental Protection Agency). 2011. Exposure Factors Handbook: 2011 Edition. Available: http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252 [accessed 1 February 2015]

Vieira, V., Hoffman, K., Fletcher, T., 2013. Assessing the Spatial Distribution of Perfluorooctanoic Acid Exposure via Public Drinking Water Pipes Using Geographic Information Systems. Environ. Health Toxicol. 28, e2013009. doi:10.5620/eht.2013.28.e2013009

Vieira, V.M., Howard, G.J., Gallagher, L.G., Fletcher, T., 2010. Geocoding rural addresses in a community contaminated by PFOA: a comparison of methods. Environ. Health 9, 18. doi:10.1186/1476-069X-9-18

Wagner, L.K., 2004. Diagnosis and management of preeclampsia. Am. Fam. Physician 70, 2317–24

Ward, M.H., Nuckols, J.R., Giglierano, J., Bonner, M.R., Wolter, C., Airola, M., Mix, W., Colt, J.S., Hartge, P., 2005. Positional accuracy of two methods of geocoding. Epidemiology 16, 542–547. doi:10.1097/01.ede.0000165364.54925.f3

Watkins, D.J., Josson, J., Elston, B., Bartell, S.M., Shin, H., Vieira, V.M., Savitz, D.A., Fletcher, T., Wellenius, G.A., 2013a. Environmental health perspectives. Environ. Health Perspect.

Watkins, D.J., Josson, J., Elston, B., Bartell, S.M., Shin, H., Vieira, V.M., Savitz, D.A., Fletcher, T., Wellenius, G.A., 2013b. Exposure to perfluoroalkyl acids and markers of kidney

function among children and adolescents living near a chemical plant. Environ. Health Perspect. 121, 625–30

Wu, J., Jiang, C., Jaimes, G., Bartell, S., Dang, A., Baker, D., Delfino, R.J., 2013. Travel patterns during pregnancy: comparison between Global Positioning System (GPS) tracking and questionnaire data. Environ. Health 12, 86. doi:10.1186/1476-069X-12-86

Yao, X., Zhong, L., 2005. Genotoxic risk and oxidative DNA damage in HepG2 cells exposed to perfluorooctanoic acid. Mutat. Res. 587, 38–44. doi:10.1016/j.mrgentox.2005.07.010

Zamorski, M., Green, L., 2001. NHBPEP Report on High Blood Pressure in Pregnancy : A Summary. Am. Fam. Physician 263–270

Zeger, S.L., Thomas, D., Dominici, F., Samet, J.M., Schwartz, J., Dockery, D., Cohen, a, 2000. Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ. Health Perspect. 108, 419–26

Zoccali, C., Maio, R., Mallamaci, F., Sesti, G., Perticone, F., 2006. Uric acid and endothelial dysfunction in essential hypertension. J. Am. Soc. Nephrol. 17, 1466–71. doi:10.1681/ASN.2005090949

1.1 Background

1.1.1 The C8 exposure assessment

Perfluorooctanoic acid (PFOA)

Ammonium Perfluoroocatanoate (APFO) is a surfactant that was used in the manufacture of perfluorinated compounds with multiple applications including non-stick cook ware, stain-free carpets and clothing, food contact paper etc. Once in the environment, APFO dissociates into the Perfluorooctanoate anion (PFOA) and ammonia. PFOA is also known as ‘C8’, owing to the fact that the structure has a per-fluorinated eight carbon backbone with a carboxylate group. This unique chemical structure gives the molecule high stability and surfactant properties which makes it very useful in consumer and industrial applications (Paustenbach et al., 2007; Post et al., 2012). Unfortunately, the stability also makes the chemical highly persistent in the environment (Lau et al., 2007). The major sources of PFOA to the environment include direct

and indirect emissions from manufacturing facilities around the world. As a result, PFOA is ubiquitous in various environmental media including surface water, soil, sediment, ground water, as well as in biological media including blood samples from wildlife and human beings (Lau et al., 2007; Paustenbach et al., 2007; Post et al., 2012). Exposure sources to humans include occupational exposure, contaminated drinking water, air, and food, non-stick cookware, and household dust (Lau et al., 2007; Paustenbach et al., 2007). The median blood level of PFOA in the non-institutionalized U.S. population (in the NHANES study) was reported to be 5 ppb (Calafat et al., 2007).

PFOA is amphiphilic in nature and is absorbed through oral, inhalational and dermal routes of exposure. The distribution of PFOA is highest in the liver, followed by serum proteins (primarily albumin), kidneys, lungs and other tissues (Hundley et al., 2006). Once inside the human body, PFOA is not metabolized and the excretion half-life has been estimated at 2.3-3.8 years (Bartell et al., 2010; Olsen et al., 2007). Renal and fecal elimination are primary routes of excretion of PFOA from the human body (Han et al., 2012). In animal models, PFOA has been shown to cause benign tumors of the liver, pancreas and the testes through the PPAR-α agonist mechanism. PFOA has been shown to cause weight loss, hepatic hypertrophy and necrosis, immune suppression, neurobehavioral effects, reproductive effects, and developmental effects (Kennedy et al., 2004; Lau et al., 2007; Post et al., 2012). Epidemiological studies have been based on occupational and community exposures, and mostly cross-sectional study designs; some with modest associations between PFOA exposure and cholesterol, hyperuricemia, and elevated liver enzymes, colitis, thyroid disease, kidney and testicular cancer, pregnancy induced hypertension/preeclampsia (Steenland et al., 2010; Lau et al., 2007; Post et al., 2012; C8 Science

Panel, 2011; Steenland et al., 2013; Barry et al., 2013; Savitz et al., 2012a, Savitz et al., 2012b, Lopez-Espinosa et al., 2012; Gallo et al., 2012; Watkins et al., 2013; C8 Science Panel, 2011).

The C8 Health Project

The C8 Health Project is a cross-sectional epidemiologic study of 69,030 people who lived near a primary U.S. PFOA production facility, located in the Mid-Ohio Valley near Parkersburg, West Virginia. Formed in 2005, the study is a result of a settlement between DuPont and local residents who may have suffered adverse health consequences due to their PFOA exposures. C8 Health Project participants constitute the most highly exposed sentinel population in the world, with serum PFOA concentrations up to thousands of times larger than typically found in the US general population (Frisbee et al., 2009). APFO was used in the manufacture of fluoropolymers at the Mid-Ohio Valley production facility since the 1950s. For decades, large amounts of PFOA were released into the atmosphere through emissions from air stacks as well as effluent discharge into the Ohio River. The surrounding air, surface soil, surface water and subsurface water had been contaminated with PFOA through wet/dry deposition onto the surface, leaching through the vadose zone, and transport in the ground water aquifers. As a part of the C8 Health Project, a retrospective PFOA exposure assessment was conducted at UCI (Shin et al., 2011a, Shin et al., 2011b).

The C8 exposure assessment included PFOA release assessment, integrated fate and transport modeling, and dose reconstruction to predict the exposure dose to each individual in the C8 Health Project from 1951 to 2008. First, historic PFOA emission rate estimates for the DuPont facility were obtained from a previous study conducted by Paustenbach et al. in 2007. Using these estimates with the physiochemical properties of PFOA and the historic local meteorological and geologic characteristics, a suite of environmental fate and transport models

including AERMOD, PRZM-3, BreZo, MODFLOW, and MT3DMS were applied to generate predicted concentrations of PFOA in the air, surface water and ground water around the facility (Shin et al., 2011a). The predicted air and water concentrations were utilized along with individual residential/work histories, demographics (age, gender, body weight), standard exposure factors (air inhalation rate, drinking water ingestion rate), historical pipe installation information of public water supply and a single compartment pharmacokinetic model to reconstruct the PFOA exposures of the study population and predict their yearly serum PFOA concentrations (Shin et al., 2011b). Among all participants (N = 43,449), the Spearman's rank correlation coefficient between the estimated and the 2005-2006 observed serum PFOA concentration (measured as a part of the C8 Health Project) was 0.67 (Shin et al, 2011b). Median