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Exposure to toxic metals and per- and polyfluoroalkyl substances (PFAS) and the risk of preeclampsia and preterm birth in the United States: A review

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Abstract

Preeclampsia and preterm birth are among the most common pregnancy complications and are the leading causes of maternal and fetal morbidity and mortality in the United States (U.S.). Adverse pregnancy outcomes are multifactorial in nature and increasing evidence suggests that the pathophysiology behind preterm birth and preeclampsia may be similar – specifically, both of these disorders may involve abnormalities in placental vasculature. A growing body of literature supports that exposure to environmental contaminants in the air, water, soil, consumer and household products serves as a key factor influencing the development of adverse pregnancy outcomes. In pregnant women, toxic metals have been detected in urine, peripheral blood, nail clippings, and amniotic fluid. The placenta serves as a 'gatekeeper' between maternal and fetal exposures, as it can reduce or enhance fetal exposure to various toxicants. Proposed mechanisms underlying toxicant-mediated damage include disrupted placental vasculogenesis, an upregulated proinflammatory state, oxidative stressors contributing to prostaglandin production and consequent cervical ripening, uterine contractions, and ruptured membranes, and epigenetic changes that contribute to disrupted regulation of endocrine and immune system signaling. The objective of this review is to provide an overview of studies examining the relationships between environmental contaminants in the U.S. setting, specifically inorganic (e.g., cadmium, arsenic, lead, and mercury) and organic [e.g., per- and polyfluoroalkyl substances (PFAS)] toxicants, and the development of preeclampsia and preterm birth among U.S. women.

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Introduction

Despite a disproportionally large healthcare expenditure, the United States (U.S.) ranks among the worst of industrialized nations on maternal and perinatal mortality and morbidity metrics.[1,2] Preterm birth (PTB) and preeclampsia are among the most common pregnancy complications and major drivers of maternal and neonatal morbidity and mortality in the U.S.[3,4]

PTB, defined as delivery occurring before 37 weeks of gestation, is a major public health challenge. The rate of PTB in the U.S. in 2018 was 10.02%, and the rate has increased every year since 2015.[5] Approximately two-thirds of PTB are spontaneous, and occur following the spontaneous onset of labor, preterm prelabor rupture of membranes, or cervical insufficiency. The remaining third of PTB are medically-indicated and occur secondary to medical or fetal complications during pregnancy including preeclampsia, pregnancy-associated hypertension, and intrauterine growth restriction. Compared to infants born at term, premature infants experience a higher risk of adverse outcomes including acute and chronic respiratory disease, necrotizing enterocolitis, feeding difficulties, blindness, deafness, intraventricular hemorrhage, and numerous long-term behavioral and social-emotional problems.[6] Premature infants also have a higher risk of neonatal and early childhood mortality; globally, prematurity is the second leading cause of death in children under 5-years old.[7] The Institute of Medicine estimates the annual economic costs of PTB in the U.S. to be $26.2 billion after accounting for the associated medical, educational, and lost productivity costs.[6] Preterm infants incur 10-fold higher medical costs and a 9-fold longer length of hospitalization in their first year of life compared to term infants.[8]

Preeclampsia is the leading cause of medically-indicated PTB and is characterized by new-onset hypertension and is typically accompanied by proteinuria or end-organ damage that begins after 20 weeks' gestation. Preeclampsia is the most common maternal pregnancy morbidity, affecting 8-10% of pregnancies worldwide (8 million cases/year).[9] Unfortunately, the incidence of preeclampsia continues to rise.[9,10] Preeclampsia is associated with both maternal mortality (accounting for 16% of deaths), short-term maternal morbidity (e.g., increased risk of cesarean delivery, placental abruption, prolonged hospital stays, acute renal insufficiency and progression to eclampsia)[4] and long-term maternal morbidity (increased risk of cerebrovascular disease, chronic hypertension, cardiovascular complications, end stage renal disease, and eventual mortality).[11,12] Preeclampsia is also associated with significant neonatal morbidity and mortality. Neonates of mothers with preeclampsia have a 35% increased risk of stillbirth, 2-fold higher risk of neonatal death, and are more likely to be small for gestational age, have low Apgar scores, develop febrile seizures, and be admitted to the Neonatal Intensive Care Unit compared to neonates born to mothers without preeclampsia.[12-15]

The pathogenesis underlying preeclampsia and spontaneous PTB is complex, and is a major focus of obstetric research. There is growing evidence that suggests similarities in the etiologies of some cases of preeclampsia and spontaneous PTB, primarily related to placental ischemia and inflammation.[16] In support of a similar underlying pathophysiology, women with a history of spontaneous PTB carry a 4- to 7- fold higher risk of preterm preeclampsia and 2- to 3- fold higher risk of term preeclampsia in subsequent pregnancies.[17] In the case of spontaneous PTB, there are a number of processes that result in a "final common pathway" of spontaneous PTB including premature activation of the maternal or fetal hypothalamic-pituitary-adrenal axis related to fetal or maternal stressors or an exaggerated inflammatory response related to placental hypoperfusion or to infection, among others.[18] One key fetal stressor that can activate the hypothalamic-pituitary-adrenal axis is uteroplacental ischemia; studies have found a four- to seven-fold increased risk of histologic evidence of placental vascular damage, bleeding, fetal vascular disruption, or lack of normal physiologic conversion of the maternal spiral arteries in preterm versus term deliveries.[19,20] Uteroplacental ischemia then can increase the production of proinflammatory mediators which ultimately enhance prostaglandin production and the degradation of the extracellular matrix of the fetal membranes and of the cervix – contributing to premature rupture of membranes and preterm labor.[21-23]

The pathogenesis of preeclampsia also involves abnormalities in the development of placental vasculature resulting in placental hypoperfusion, hypoxia, or ischemia. Proper placental vascular formation requires the migration of cryotrophoblasts through the decidua and the myometrium to invade the maternal spiral arteries.[24] This invasion induces a transformation of these arteries into high capacitance, low resistance vessels to facilitate good blood flow to the placenta.[25] Extensive angiogenesis is required for proper placental vasculogenesis to ensure the establishment of a suitable vascular network to supply oxygen and nutrients to the fetus. This process relies on a balance of proangiogenic and antiangiogenic factors. Both cryotrophoblast invasion and angiogenesis are thought to be disrupted in the case of preeclampsia.[26] A resultant ischemic placenta may release antiangiogenic factors and proinflammatory cytokines into the maternal circulation, altering maternal systemic endothelial function, leading to hypertensive disorders of pregnancy.[27] The search for triggers of abnormal placentation is an area of ongoing and active research.

There are a number of risk factors that may contribute to the development of the pathology as described above, though in many cases the precise catalyst for the development of spontaneous PTB or preeclampsia remains unknown. Spontaneous PTB and preeclampsia are both complex conditions whose risk factors span, as stated by The Institute of Medicine, "individual-level behavioral and psychosocial factors, neighborhood characteristics, medical conditions, infertility treatments, biological factors, and genetics."[6] Certain risk factors, including black race, low socioeconomic status, extremes of maternal age, and a short interpregnancy interval, are associated with an elevated risk of both preeclampsia and spontaneous PTB.[4,6,28]

Increasingly, exposure to environmental toxicants in air, water, soil, consumer and household products has been recognized as a significant risk factor for adverse pregnancy outcomes, including spontaneous PTB and preeclampsia.[29-32] In pregnant women, toxic

metals have been detected in urine, peripheral blood, nail clippings, and amniotic fluid.[33] The placenta is crucial to the understanding of the mechanistic effects of exposure to environmental contaminants on pregnancy. During pregnancy, the placenta serves as a 'gatekeeper' between maternal and fetal exposures, as it can completely filter or reduce fetal exposure to various toxicants or the opposite as shown by corresponding cord blood levels of certain metals exceeding the levels detected in maternal samples.[34,35] For example, Chen et al. demonstrated that mercury levels in cord red blood cells were 1.5 times higher than levels in maternal red blood cells.[36]

There are a number of proposed mechanisms underlying the influence of environmental toxicants on the development of preeclampsia and preterm birth which will be described in greater detail in the sections to come. In brief, there are several postulated mechanisms by which this occurs. Disrupted trophoblast migration may occur in association with epigenetic changes that alter growth factor signaling, induction of an improper balance of anti-angiogenic factors versus pro-angiogenic factors, or the creation of reactive oxygen species contributing to oxidative stress. In turn, these factors may alter endocrine signaling and/or lead to a proinflammatory state with increased prostaglandin production and subsequent premature cervical ripening, uterine contractions, and rupture of fetal membranes.

The impact of combinations of toxicants, the timing and magnitude of exposure, and the complex interaction between toxicants and the heterogenous set of genetic, behavioral, and biological risk factors are important to consider. Further, a growing body of literature supports the sexually dimorphic effects of some contaminants, where the biologic effects differ by fetal sex; variation that may be explained by epigenetic changes that influence gene and protein expression.[37-39]

This review focuses on a subset of inorganic (cadmium, arsenic, lead, and mercury) and organic (perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) toxicants that are known threats to human health. The purpose of this review is to describe the literature detailing the relationships between exposure to these toxicants and the development of the two most common adverse pregnancy outcomes in the U.S. - PTB and preeclampsia.

Inorganics

Inorganic contaminants represent a group of chemicals that, for the most part, contain no carbon. This group includes substances such as ammonia, hydrogen sulfide, all metals, and most elements. Cadmium, arsenic, lead, and mercury are ranked among the top ten most toxic substances by the Center for Disease Control's Agency for Toxic Substances and Disease Registry (2019), and hence are the focus of the inorganic exposure portion of this review.[40] The most common means of exposure to these substances is via ingestion through drinking water and food sources, inhalation of cigarette smoke or products of industrial processes, or contact with paint or soil.[41] Though the Center for Disease Control has established recommended advisory human blood levels for pregnant women for lead (5.0 μg/dL) and mercury (3.5 μg/L),[42,43] no advisory blood levels for arsenic and cadmium currently exist for pregnant women.[41]

Exposure to inorganic contaminants is common. The Center for Disease Control's National Health and Nutrition Examination Survey reported on the urine, blood, and serum metal concentrations among both pregnant and nonpregnant women in the U.S. from 1999-2016 and found that the detection rate for arsenic, lead, mercury and cadmium among both pregnant and non-pregnant women of childbearing age ranged from 83-99%, with higher mean urine total arsenic, urine mercury, and urine lead levels in pregnant compared to nonpregnant women.[44] A recent study of 210 pregnant women across six counties in North Carolina evaluated exposure to cadmium, mercury, lead, and arsenic, and >55% of pregnant women had detectable levels of each tested metal; some women had blood levels exceeding the 95th percentile for the U.S. population.[41]

Across the U.S., exposure levels vary by location but also by race and socioeconomic status.[45-47] For example, non-Hispanic Black race has been associated with increased cadmium exposure compared to non-Hispanic White race.[41,48] Adverse pregnancy outcomes also vary by race. For example, the rate of PTB is 16% for non-Hispanic Black women compared to 11% for non-Hispanic White women.[46] It is unknown whether metal exposures are a significant contributor to this disparity or whether both the disparities in exposure and outcomes are a result of health inequities. Literature regarding exposure to inorganic toxicants and PTB is summarized in Table 1, and the relationship between these exposures and preeclampsia is summarized in Table 2.

Cadmium

The most common human exposure to cadmium is through food, and low levels are detected in nearly all foods.[49,50] Exposure to cadmium can also occur through inhalation of cigarette smoke and through occupational exposures to industrial processes such as manufacturing and construction. Cadmium levels in smokers are 4-5 times higher than in nonsmokers. A 2016 estimate found that approximately 7.2% of expectant mothers in the U.S. smoked while pregnant.[51] Cadmium levels in pregnant women exposed to secondhand smoke are 2-fold higher than unexposed women.[41]

The exact mechanisms underlying pregnancy related toxicity in relation to cadmium exposure are emerging. Kippler et al. demonstrated an inverse relationship between cadmium concentration in the placenta and zinc in cord blood indicating that cadmium may disrupt zinc transfer to the fetus.[52] Insufficient zinc transfer can interfere with DNA/RNA transcription and has been shown to play a role in adverse pregnancy outcomes including spontaneous PTB and growth restriction.[52] In the case of preeclampsia, Brooks et al.[53] postulate that cadmium may disrupt key proangiogenic factors involved in proper placental vasculogenesis. Specifically, cadmium may induce unfavorable effects on the process of trophoblast migration that is critical to proper placentation, mechanistically by disrupting transforming growth factor beta (TGF-β) signaling through the epigenetic development of microRNAs in placental trophoblast cells that target the TGF-β pathway. Inadequate trophoblastic migration means that the spiral arteries remain high resistance, low capacitance vessels – ultimately contributing to placental hypoperfusion, maternal hypertension, and the development of preeclampsia.[54]

There is evidence for sexually dimorphic effects of cadmium during pregnancy. Kippler et al. found that though levels of cadmium in maternal blood were associated with cord blood DNA methylation in both male and female fetuses, in female fetuses, hypomethylation occurred in genes associated with organ development, bone morphology, and bone mineralization whereas in male fetuses, hypermethylation occurred in genes related to cell death.[55] These differences in methylation in male and female fetuses may explain why some studies have found that cadmium exposure is associated with lower birthweight, smaller head circumference and smaller crown-heel length in female but not male offspring.[52,56,57] Mechanistic research in mouse models would be warranted to test this hypothesis.

While the evidence suggesting an association between cadmium exposure and PTB exists in international settings,[58-60] there are fewer U.S. studies relating cadmium exposure and spontaneous PTB. In contrast, there are several studies examining the association between cadmium exposure and preeclampsia in the U.S. Liu et al. measured trace and toxic metals in a cohort of Boston women after delivery and found that each one standard deviation increment increase in cadmium in maternal red blood cells was associated with a 15% higher risk of preeclampsia.[61] They also found that each one standard deviation increment in manganese was associated with 32% *lower* risk of preeclampsia.[61] Dawson et al. examined cadmium levels in amniotic fluid from pregnancies complicated by preeclampsia and compared them with normotensive controls.[62] Amniotic fluid cadmium levels were 18% higher in women with preeclampsia compared to normotensive controls.[62] Laine et al. evaluated a cohort of pregnant women exposed to cadmium in the southeast U.S. found that higher levels of cadmium in the placenta were associated with an increased odds of preeclampsia.[63] This study also found that the risk of cadmium-associated preeclampsia increased with lower placental selenium and zinc levels.[63] These findings suggest that minerals such as selenium and zinc may provide some protection against cadmium-associated adverse pregnancy outcomes.

Inorganic Arsenic

Arsenic is found in inorganic and organic forms which are highly toxic and non-toxic, respectively. Inorganic arsenic is found in soil and groundwater thus human exposure occurs primarily through drinking water, often through drinking from unregulated private wells. Exposure to organic arsenic occurs through seafood consumption and is thought to be not harmful to humans. Inorganic arsenic is the focus of this section of the review.

Multiple mechanisms underlying the effects of inorganic arsenic on pregnancy-outcomes have been proposed. Many studies have implicated differences in arsenic metabolism as the primary driver of arsenic-related disease in pregnancy.[64-66] Inorganic arsenic is methylated and then renally cleared.[64] Methyl group availability is impacted by estrogen.[65] Based on levels of methylated metabolites, it has been suggested that more efficient methylation occurs in the first trimester and less efficient methylation in the second and third.[67] Inefficient arsenic methylation correlates with lower folate levels in blood plasma and elevated homocysteine levels in urine;[68] these biomarkers are established risk factors for adverse pregnancy outcomes including preeclampsia.[65]

Researchers have demonstrated the role arsenic plays in inflammation. In the general population, chronic arsenic exposure is an independent risk factor for the development of vascular diseases including hypertension, ischemic heart disease, cerebral infarctions, carotid atherosclerosis.[69,70] Wu et al. identified changes in the transcription level of genes for several proinflammatory cytokines and growth factors that are implicated in the atherosclerotic process.[71] It is plausible that arsenic may have a similar vascular impact in the placental vasculature in the pregnant population; prior studies have demonstrated that arsenic may disrupt normal placental function and development through both proinflammatory effects and effects on placental vasculogenesis.[72,73] Fry, et al. identified 11 key gene expression changes from in utero arsenic exposure associated with a fetal systemic inflammatory response evidenced by an upregulation of proinflammatory cytokines and stress response proteins along with additional biologic alterations in signal transduction, cell adhesion, cell proliferation, and apoptosis.[74]

Inorganic arsenic readily crosses the placenta.[75] Multiple effects of exposure to arsenic on the developing fetus have been described, many in a sexually dimorphic manner with differential effects in male vs. female fetuses. For example, arsenic is known to alter genome-wide DNA methylation in cord blood (greater effects in male vs. females)[76] and epigenetic regulation of stress genes in the mouse frontal cortex (with differential effects by fetal sex).[77] Fei et al.[78] found that maternal arsenic exposure (as quantified by urine samples at 24-28 weeks' gestation) increased the expression of the arsenic transporter, *AQP9*, on placental cells, thereby enhancing arsenic's cytotoxic effect at the level of the placenta. In addition, these researchers found an inverse association between increased *AQP9* expression and decreased *ENPP2* expression. *ENPP2* encodes a phospholipase that catalyzes the conversion of lysophosphatidylcholine to lysophosphatidic acid, which activates cell surface receptors to regulate processes such as angiogenesis, early embryonic development, embryo implantation, parturition, and so on – processes integrally related to preeclampsia and spontaneous PTB.[78] *AQP9* expression has been found to be elevated in preeclamptic mothers[79] and decreased *ENPP2* is associated with hypertension in pregnancy.[80]

The literature on arsenic exposure and adverse pregnancy outcomes, particularly low birth weight, is more robust in global contexts in which levels of arsenic exposure are higher (above the maximum contaminant level for drinking water of 10 μg/L set by the World Health Organization and the U.S. Environmental Protection Agency. However, a growing number of studies are examining adverse effects from lower exposure in more highly regulated settings such as in the U.S.

In a pilot study, Johnson et al.[81] measured arsenic levels in the amniotic fluid of pregnant women in their second trimester who had had a spontaneous PTB in North Carolina from 2003 to 2015, compared to matched controls who delivered at term. Arsenic was detected in all fluid samples, with a mean arsenic level of 16.3 μg/L. Notably, for three-fourths of the amniotic fluid samples' arsenic level exceeded the 10 μg/L EPA drinking water. Notably, "normal" and "abnormal" concentrations of arsenic in amniotic fluid has not been determined. The researchers found no statistical difference in arsenic levels between cases and controls (17.29 μg/L versus 15.26 μg/L, $p = 0.24$) and no correlation between arsenic

levels and gestational age at delivery (R = 0.042, p=0.79). Arsenic levels were also similar in the amniotic fluid of male and female fetuses.

In a study of the California's Office of Statewide Health Planning and Development birth cohort from 2009 to 2012 (1.8 million births), arsenic exposure through drinking water was weakly associated with preterm birth; for an increase of 1.38 parts per billion of arsenic, the adjusted odds ratio for PTB was 1.01 (95% CI 1.00, 1.013, p= 0.01).[82] Almberg et al. studied pregnant women in Ohio between 2006-2008 with to relatively low levels of arsenic exposure (mean serum concentrations 0.5 to 12.2 μg/L) and spontaneous PTB among women between 2006-2008. They found an 8-10% increase in the odds of spontaneous PTB per every 1 μg/L increase in arsenic in the drinking water for counties with a <20% and <10% rate of private well water usage in both crude and covariate-adjusted models (aOR for counties with <20% private well water = 1.08, 95% CI 1.02, 1.14; aOR for counties with <10% private well water = 1.10, 95% CI 1.06, 1.15).[83]

Shi et al. studied rates of PTB among pregnant women in a region of New Hampshire that relies largely on unregulated private well water as a drinking source[84] The researchers subdivided arsenic exposure values into three categories: ≥ 1.0-4.9 μg/L, ≥ 5.0-9.9 μg/L, and ≥ 10 μg/L and stratified their study population by age (<20 years old or ≥ 20 years old). They found positive Pearson correlation coefficients across all three exposure levels and across both age groups. The strongest association between arsenic exposure and PTB was in the sample of "younger" mothers exposed to the highest level of arsenic (>10 μg/L).[84] This study included any delivery occurring before 37 weeks and did not differentiate between spontaneous versus medically-indicated preterm births. There is a growing body of U.S.-based population studies examining the associations between arsenic exposure during pregnancy and the development of preeclampsia and/or PTB.

Mercury

Exposure to mercury occurs predominately through consumption of contaminated fish but can also occur from inhalation of vapors from dental amalgams or industrial processes, such as coal burning, mining, or waste incineration.[85] The U.S. Environmental Protection Agency sets 0.3 parts per million as the recommended tissue-based water quality criterion for mercury.

Postulated mechanisms by which mercury exposure can contribute to spontaneous PTB relate to mercury's influence in inducing apoptosis, disrupting the endocrine system thereby impacting reproductive hormones and finally inducing oxidative stress.[86] More specifically, reactive oxygen species activate NF-kappa B inducing proinflammatory cytokine production and *COX-2* expression, enhancing prostaglandin production contributing to cervical ripening, uterine contraction, and membrane rupture.[87]

Bashore et al. collected maternal urine and neonatal cord blood samples and examined the relationship between PTB and mercury levels in an urban immigrant community in Brooklyn, NY and found no association.[88] Similarly, in cord blood samples from pregnant mothers in Rhode Island (mean mercury concentration 0.52 μg/L) there was also no

association between serum mercury levels and PTB.[48] In contrast, another study from a Rhode Island sample found that women who delivered before 35 weeks were more likely to have hair mercury levels at or above the 90th percentile (0.55 μg/L), though the odds ratio for delivery before 37 weeks was not significant.[89] In a small Boston-based sample, Chen et al. found significantly higher levels of mercury in maternal and cord plasma and red blood cells of preterm compared with term deliveries.[36]

In a South Carolina cohort, Burch et al. examined mercury exposure through fish consumption and rates of PTB (and term low birth weight). The researchers found that women residing in regions with elevated total mercury concentrations (>0.62 ppm) in fish have an increased likelihood of delivering a term low birthweight infant compared to women residing in areas with lower fish total mercury levels. Interestingly, the study did not find a similar association in the case of PTB; instead, it found positive associations between mercury exposure and PTB when mercury levels were more mid-range (>0.17-0.62 ppm) and furthermore, found *reduced* odds of PTB with higher exposure (>0.62 ppm). This study highlights the importance of the consideration of the confounding effect of fish consumption during pregnancy, which may provide a source of omega-3 fatty acids and other nutrients important to the developing fetus while increasing the risk, on the other hand, of the potential negative sequelae of mercury exposure).[45]

There is a growing body of U.S.-based literature examining population level associations between mercury exposure during pregnancy and rates of preeclampsia, though hypothesized mechanisms whereby mercury may contribute to the development of preeclampsia most relate to its impact on the development of reactive oxygen species; studies have found lower concentrations of the antioxidant enzymes that counterbalance ROS, including glutathione peroxidase and superoxide dismutase, in mothers with preeclampsia.[54]

Lead

Lead levels in the general population have decreased by approximately 80% since lead was phased out of gasoline in the 1970s,[90] however human exposure still occurs through contaminated dust and soil, drinking water, lead-based paint, cigarette smoke, byproducts of industrial processes, and ceramics glazes, among others.

Similar mechanisms underlie lead's impact on PTB as mercury's. Irwinda et al.'s postulate lead exposure also upregulates reactive oxygen species inducing oxidative stress and a proinflammatory cascade that ultimately contributes to early cervical ripening, uterine contraction, and membrane rupture and PTB.[87]

U.S. based literature looking at the association between lead exposure and PTB is as follows. Perkins et al. examined the relationship between relatively low levels of lead exposure (mean red blood cell lead level 1.2 μg/dL) and PTB in an eastern Massachusetts sample. After adjusting for age, race, BMI, and smoking, the authors found no significant difference in preterm delivery between mothers in the highest versus lowest lead quartiles. However, after stratifying by fetal sex, they found that women carrying male fetuses were

more likely to deliver preterm.[91] This finding suggests that fetal sex may influence the effect of lead on birth outcomes. Sex-specific associations between lead exposure during pregnancy and adverse pregnancy outcomes, such as head circumference, birthweight, ponderal index, among others, is an emerging area of research. Numerous studies posit that these adverse effects of lead exposures are more pronounced in male fetuses[92-94] possibly related to the sex-specific function of the placenta.[95] In other words, male fetuses growing at a faster rate with greater nutrient demands may experience a greater disruption when lead exposures impact placental function.

Zhu et al. evaluated a large cohort in New York exposed to low levels of lead (average exposure level 2.1 μg/dL) and similarly found no association between lead exposure and levels and PTB, though the analysis was not stratified by fetal gender.[96] In a cohort of predominately Hispanic pregnant women in California, blood lead levels at or above the maximum containment level 10 μg/dL were significantly associated with an elevated odds of PTB. For each unit increase in blood lead levels above 10 μg/dL, there was an average decreased of 0.3 days of gestation, but during the second trimester, each unit increase in maternal blood level above 10 μg/dL was associated with a decrease of 1 day of gestation.[97] Satin et al. also evaluated lead exposure in air among pregnant women in California (mean cord blood levels 5 μg/dL). In the sample studied, a cord blood lead level that exceeded 5 μg/dL yielded a relative risk for prematurity of 2.9 (CI 0.9-9.2) and a population attributable risk of 46.8%, showing a statistically significant association between cord blood lead levels and prematurity.[98] In contrast, Berkowitz et al. evaluated birth outcomes in five high lead exposure (via air pollution) towns in Shoshone County, Idaho, where a fire destroyed the pollution control device of local lead smelter plant but found no association with PTB.[99]

There are some hypothesized mechanisms by which lead may influence the development of preeclampsia. Kahn et al. cite lead's positive association with vasoconstrictors such as endothelin, adrenaline, and noradrenaline and its negative association with vasodilators such as nitric oxide and adenosine triphosphatase.[54] With regards to population-level literature, Sowers et al. evaluated maternal blood lead concentrations longitudinally throughout pregnancy, and found that lead levels were significantly higher at every time point after 12 weeks' gestation among women who ultimately developed preeclampsia.[100] Rabinowitz found an association between lead exposure during pregnancy and the pregnancy induced hypertension, but not preeclampsia.[101] Dawson et al. found that lead levels were 68% elevated in early and 57% elevated in late 3rd trimester pregnancies with preeclampsia as compared to non-preeclamptic cases.[62] In a second study, Dawson et al. identified significant elevations in red blood cell lead levels in preeclamptic patients compared with normotensive controls.[102]

Combinations of metals

While the effect of any individual metal toxicant on PTB and preeclampsia has not been fully elucidated, even less is known about combinations of toxic metals and their effect on these outcomes. Much of the literature on the impact of toxicant exposure on health outcomes focuses on single agents or simple two-way interaction models. However real-life exposures more often than not occur in mixtures.[103] Given the complex cellular processes

that play into the pathways leading to PTB and preeclampsia, it is reasonable to believe that heavy metals may interact and interfere with each other in either a positive or negative relationship. Studying mixtures of toxic metal exposures is an emerging area of research and is under active study by several research groups.[103,104]

Models such the Bayesian kernel machine regression offer novel statistical methods to study the influence of mixtures of metals[103] on health outcomes. Niedzwiecki et al. took another tack by piloting an approach to identify the components of metal mixtures that spatially colocalized with biologic response markers[104] within certain tissues. They applied their model to human placental tissue in the case of a low birth weight versus normal birth weight fetus. They hypothesized that placental inflammation contributed to the development of a low birth weight fetus and were able to map patterns of metal accumulation to local sites of inflammation in placental tissue, observing that inflammatory sites coincided with variations in iron, zinc, and manganese exposures.

Serrano et al. found that mixtures of industrial air pollutants were associated with a higher risk of PTB.[105] Sanders et al. examined the impact of mercury and lead exposure in pregnant women on epigenetic changes in cervical tissue.[106] A total of 17 micro RNAs were identified that were significantly associated with maternal mercury and lead exposure, that are gene targets involved in reproductive system morphology and in the development of preeclampsia.[106] Finally, Kim et al. evaluated the association between exposure to 17 different metals and PTB. The study created three groupings of exposures based on the principal components of the metals involved: toxic metals, essential metals, and metals with seafood as the source of common exposure. Analyses revealed a positive association between exposure to the essential metal group (copper, selenium, and zinc) and PTB with copper as the most important driver of the association.[107]

Organic Toxicants

Per- and polyfluoroalkyls (PFAs) also called perflourinated compounds (PFCs) are a category of man-made chemicals that have been used in industry and consumer products globally since the 1950s. The category includes perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA or C8), perfluorononanoic acid (PFNA), perfluorohexane sulfonic acid (PFHxS), perfluordecanoic acid (PFDeA), and 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-propanoic acid (GenX), though PFOS and PFOA have been the two most commonly used in the United States. Due to their long half-lives, molecular stability, hydrophobicity and lipophobicity, these chemicals have been useful for nonstick cookware, water repellant clothing, stain resistant carpets, cosmetic products, paper coatings, and fire-fighting foams. The downside to their stability and long half-lives is their persistence in the environment and in the human body (estimated half-life for PFOA in the human body is 4.37 years).[108] It has been estimated that PFOA can be detected in approximately 95% of individuals residing in the U.S.[109] The main route of exposure for humans to PFAs is through consumption of contaminated food and water. Exposure can also occur through inhalation of air or dust containing PFA particles.

Exposure to PFOA and PFOS has received considerable attention over the past decade due to concerns about the effects of PFAS on human health. The EPA and CDC's environmental agencies including the National Center for Environmental Health (NCEH) and the Agency for Toxic Substances and Disease Registry (ATSDR) have classified PFAs as "emerging contaminants" and have created drinking water standards, specifying that levels of PFOA and PFOS may not exceed more than 70 parts per trillion. Further, these national agencies have championed reduction and phase-out campaigns, new use rules, and stewardship programs in an attempt to decrease levels of PFAs in the environment. The Center for Disease Control's National Health and Nutrition Examination Survey has conducted biomonitoring to measure PFOA and PFOS levels in a representative sample of the U.S. population over time and the trend shows declining serum concentrations of PFOA and PFOS.[44] Despite these efforts, it is estimated that more than 95% of the U.S. population has measurable levels of PFAs in their bodies;[110] unfortunately, thresholds of harm are uncertain.

An unintended side effect of the phase out efforts occurred with the production of GenX, which was thought to be a "sustainable replacement" for PFOA in particular. GenX has received attention during the past few years due to findings of high levels of the compound in drinking water sources. One producer of GenX is the Fayetteville, N.C. Chemours manufacturing facility which had disposed of the product in the Cape Fear River, a main source of local drinking water. Rising community pressure from the Cape Fear River case spurred additional investigations and studies that are underway.

Data on the impact of GenX exposure on animal and human health continues to emerge. While initially considered a safer alternative due to being less toxic and less bioavailable than PFOA,[111] new data from in vitro studies bring that conclusion into question especially with regards to hepatocellular toxicity and effects on lipid metabolism.[112,113] With regards to its impact on reproductive health, a recent 2019 study by Conley et al. demonstrated low birth weight in rats exposed to elevated levels of GenX.[114] Blake et al studied the effects of GenX on mice placentas and found that mice exposed to GenX experienced atrophy, necrosis, and congestion of the placental labyrinth which is suggestive of impaired placental function.[115] In our review, no studies were identified demonstrating an association between GenX exposure and these specific adverse pregnancy outcomes of PTB and preeclampsia in humans in the U.S. Additional studies looking at human reproductive toxicity and GenX's impact on general human health are needed. An EPA toxicity assessment is ongoing.[116]

The effects of exposure of PFOA and PFOS during pregnancy has been a focus of both animal and human research studies during the past decades, yet the science related to adverse pregnancy outcomes is still evolving. Both chemicals have been detected in maternal blood, umbilical cord blood, and breastmilk. A major U.S. investigation (initiated in response to a class action lawsuit), termed the "C8 Health Project" was conducted in the Parkersburg, Virginia area in 2002. It was discovered that six water districts' water supply had been contaminated with PFOA for over 50 years. This project involved interviews and surveys to collect demographic information, medical histories, information about health behaviors, and serum measurements of about 70,000 individuals. This investigation found that individuals in this area had blood concentrations of PFOA that were on average 500%

higher than individuals in the NHANES study. Additionally, the C8 health project found "probable" links between PFOA exposure and multiple medical conditions including hypercholesteremia, ulcerative colitis, thyroid function, testicular cancer, kidney cancer, preeclampsia, and pregnancy-induced hypertension.[117]

There are multiple hypothesized mechanisms underlying the harm caused by PFOA and PFOS. PFOA alters the peroxisome proliferator-activated receptor alpha (PPARα) signaling pathway in murine models.[118] PPARα is known to regulate lipid and glucose homeostasis, inflammation, cell proliferation and differentiation. Alterations to PPARα may influence pregnancy and fetal outcomes; in mice and rats, there is evidence of an association with reduced birth weight, neonatal death, and reduced postnatal growth.[119] Unfortunately, it is unclear how translatable these animal model findings are to humans.[120] PFAs are also suspected to cause toxicity through endocrine disruption particularly with regards to reproductive hormone pathways, estrogen- and androgen-receptor transactivity, and thyroid dysfunction. However, current evidence remains stronger in mice than humans at this time.[121] Finally, it has been shown that PFAs play a role in decreasing trophoblast migration, invasion, and inflammatory signaling *in vitro* which may preliminarily suggest an underlying mechanism behind a relationship between PFAs exposure and preeclampsia.[122]

Discrepancies exist within the literature on the relationship between exposure to PFOA and PFOS and PTB, but several studies point to a positive association (Table 3). Studies on low exposure levels have been conducted outside of the U.S., though this review focuses on US based studies as follows.[123-128]

Sagiv et al.[129] examined the plasma concentrations of PFOS and PFOA in pregnant women in eastern Massachusetts around 9 weeks of gestation. The median plasma concentration was found to be 25 ng/mL and 5.8 ng/mL for PFOS and PFOA, respectively. The researchers found over 2-fold odds of PTB among women with concentrations of PFOS in the highest quartile as compared to those in the lowest quartile. There was no relationship between PFOA and PTB found. Interestingly, they also identified differences in association between PFOS and gestational length by sex; associations with PFOS were stronger among males than among females. No such differences were identified in the case of PTB.

Researchers evaluating C8 Health Project data, examined the relationship between high PFOA and/or PFOS exposures in residents of the mid-Ohio Valley region and PTB.[119,130-133] Nolan et al. compared the frequency of PTB between 2003 and 2005 among mothers who obtained their drinking water from the contaminated source only, partially from the contaminated source, and not at all from the contaminated source. They found no significant differences in the rate of PTB based on the source of drinking water. Stein et al. compared rates of PTB between 2000-2005 to corresponding serum PFOA and PFOS concentrations measured in 2005-2006 (assuming levels measured in 2005/6 corresponded to levels at the time of pregnancy) for the broader C8 Health Project and found that neither PFOS nor PFOA showed any association with PTB. Savitz et al. used a fate-transport model to create an improved estimate of serum PFOA levels at the time of pregnancy for pregnancies between 1990-2006, then compared these estimates to rates of PTBs, controlling for age, parity, education, smoking, and calendar time. In three studies using

slightly different sample sizes, estimation and analytical techniques, Savitz et al. again found no significant relationship between serum PFOA concentration and PTB. Finally, Darrow et al. built on the Savitz et al. work to study pregnancies that occurred in a later time period, between 2005-2010, conducting the first prospective study of this population. Again, no association was found between exposure to PFOA or PFOS and PTB.

Two papers found an association between exposure to PFOS/A and preeclampsia (Table 4). Stein et al. (described above) concluded that preeclampsia was weakly associated with PFOA and PFOS exposures above the median but did not show a dose-response gradient. Additionally, the adjusted odds ratio for preeclampsia for PFOS exposure above the 90th percentile was elevated. Savitz et al. (as described above) found a weak association between PFOA exposure and preeclampsia based on both continuous exposure indices and analysis by quintiles. However, in both cases, the results are considered preliminary and further research is needed.

The suggestive toxicological evidence in animals and impact on general human health of PFAs point to the potential for PFOA and PFOS to have adverse effects on pregnant mothers and on fetal development. Further research needs to be conducted to investigate the precise impact of PFOS and PFOA on the adverse pregnancy outcomes of PTB and preeclampsia.

Conclusions

PTB and preeclampsia are leading contributors to the morbidity and mortality of women and infants in the United States and the precise etiologies underlying these complex and heterogenous conditions remain largely unknown. Thus, information regarding the role of critical, yet potentially modifiable, exposures is urgently needed. Animal studies have demonstrated reproductive toxicity with many of the studied toxicants. Research is emerging that postulates on the mechanistic underpinnings of toxicant-mediated damage in human pregnancies related to disrupted placental vasculogenesis, an upregulated proinflammatory state, oxidative stressors contributing to prostaglandin production and early cervical ripening, uterine contractions, and ruptured membranes, epigenetic changes that contribute to disrupted regulation of endocrine and immune system signaling, and so on.

Current population level data suggest that exposure to organic and inorganic toxicants may be significantly associated with the development of PTB and preeclampsia. However, there remains significant heterogeneity among studies of environmental exposures during pregnancy. These differences range from the populations included, the methods of data acquisition (e.g., birth certificate or population level data vs. smaller prospective studies), outcome definitions (all PTB vs. medically-indicated PTB such as preeclampsia vs. SPTB), timing of biologic sampling in relation to timing of delivery, type of sample obtained, definitions of “high” toxicant levels, and analytic strategies. In addition, many studies found relatively low levels of toxic exposures, reducing the ability to make conclusions regarding dose-dependent effects. Further, the lack of standardization in the definition of “high” or “abnormal” toxicant levels limits the ability to compare results across cohorts.

Future work can expand upon this base of information in several ways. Several papers summarized in this review highlight that sexual dimorphism may mask adverse associations; nonetheless, the majority of studies were and remain fetal gender agnostic. With further elucidation of the relationship between specific environmental contaminants and adverse pregnancy outcomes, new strategies for prevention of adverse pregnancy outcomes can be pursued. For example, robust biomonitoring programs across the United States, such as Minnesota's Family Environment Exposure Tracking project, could improve the monitoring and surveillance of exposure levels among the pregnant (and general) U.S. population.[134] Further, defining acceptable toxicant concentration thresholds for pregnant women and clinical standards of preconception and prenatal care in the setting of varied exposure environments will assist in identifying the populations at risk.

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AJOG at a Glance:

Why was this study conducted?

- Inorganic (e.g., cadmium, arsenic, lead, and mercury) and organic [e.g., per- and polyfluoroalkyl substances (PFAS)] toxicants have known consequences on human health
- This review summarizes the current U.S.-based literature regarding the relationship between these toxicants and adverse pregnancy outcomes.

What are the key findings?

- Inorganic and organic toxicants are widespread and may be associated with preterm birth and preeclampsia in a sexually dimorphic manner
- Challenges to this research include relatively low exposure levels in the U.S. compared to international settings, a lack of consensus regarding abnormal exposure thresholds, and understudied effects of simultaneous exposure to a combination of potentially beneficial vs. detrimental substances

What does this study add to what is already known?

- This review provides a summary of how inorganic and organic toxicants may be associated with preeclampsia and preterm birth
- The review highlights the need to identify modifiable risk factors contributing to perinatal outcomes.

Condensation: Inorganic and organic toxicants are ubiquitous in the environment; growing evidence suggests an association between exposure to these contaminants and adverse pregnancy outcomes (e.g., preeclampsia, preterm birth).

Table 1.

Studies evaluating the association between exposure to inorganic toxicants (arsenic, cadmium, mercury, lead) in biologic specimens and PTB.

First author, publication year	Specimen	Type of study	Sample size and population	Toxicant	Risk of PTB
Johnson, 2019[135]	Amniotic fluid	Retrospective case control	42 North Carolina mothers seen at university hospital for 2nd trimester amniocentesis	Inorganic arsenic	No statistically significant correlation between 2nd trimester amniotic fluid arsenic level and gestational age at delivery ($p = 0.79$; $r^{***} = 0.042$)
Huang, 2018[82]	Drinking water	Retrospective cohort	1.8 million All California singleton live births	Inorganic arsenic	aOR 1.01 (95% CI: 1.00, 1.013), p= 0.01 for PTB vs. term birth for an increase of 1.38 parts per billion (ppb) in arsenic average.
Almberg, 2017[83]	Drinking water	Retrospective cohort	428,804 Ohio, population level data	Inorganic arsenic	aOR 0.99 (95% CI 0.98, 1.01) for entire state aOR=1.10 (95% CI 1.06,1.15) for counties with < 10% private well use aOR=1.08 (95% CI 1.02, 1.14) for counties with <20% private well use
Shi, 2016[84]	Drinking water	Retrospective cohort	187,851 New Hampshire, population level data	Inorganic arsenic	Maternal age <20: $r^{**} = 0.70$ (unadjusted); r=0.55 (adjusted for town-level income) Maternal age ≥20: r^{**}=0.19 (unadjusted); adjusted r not calculated
Bashore, 2014[88]	Cord blood, maternal urine	Prospective cohort	191 Brooklyn, NY prenatal clinic	Mercury	Cord blood Hg (n=66): OR 0.65 (95% CI 0.38, 1.12) Creatinine-corrected urine Hg (n=144): aOR 0.78 (95% CI 0.38, 1.59)
Burch, 2014[45]	Locally caught fish	Retrospective cohort	357,996 South Carolina, population level data	Mercury	1st quartile (≤0.17 ppm Hg): ref 2nd quartile (>0.17-0.29 ppm Hg): OR 1.09 (95% CI 1.06, 1.13) 3rd quartile (>0.29-0.62 ppm Hg): OR 1.09 (95% CI 1.05-1.13) 4th quartile (>0.62 ppm Hg): OR 1.02 (95% CI 0.98, 1.06)
Chen, 2014[36]	Maternal plasma vs cord plasma. Maternal red blood cells vs cord red blood cells.	Retrospective cohort	50 African-American Mother-infant pairs from Boston Birth Cohort	Mercury	Maternal plasma r^{***}=0.507 (p=0.0002) Cord plasma r^{***}=0.420 (p=0.0024) Maternal red blood cells r^{***}=0.315 (p=0.0257) Cord red blood cells r^{***}=0.293 (p=0.0392)
King, 2013[48]	Cord blood	Prospective cohort	538 Rhode Island residents	Mercury	No association (numbers not reported)
Xue, 2007[89]	Maternal hair sample	Prospective cohort	1,226 Michigan prenatal care clinics from 5 communities	Mercury	Delivery <37 weeks: aOR 1.55 (95% CI 0.7, 2.9) Delivery <35 weeks: aOR 3.0 (1.3, 6.7)
Perkins, 2014[91]	Maternal red blood cells	Prospective cohort	949 Mother-infant pairs, Massachusetts	Lead	Highest vs. lowest lead quartiles): OR 1.85 (95% CI 0.79, 4.34) Male child (highest vs. lowest lead quartiles) OR 5.51, (95% CI 1.21, 25.15) Female child (highest vs. lowest lead quartiles) OR, 0.82 (95% CI 0.24, 2.85)
Zhu, 2010[96]	Maternal red blood cells	Retrospective cohort	43,288 New York State, population level	Lead	Maternal red blood cell lead levels at or before delivery

First author, publication year	Specimen	Type of study	Sample size and population	Toxicant	Risk of PTB
					Highest quartile lead level vs. lowest quartile: aOR 1.04 (95% CI 0.89, 1.22)
Jelliffe-Pawlowsk, 2006[97]	Maternal whole blood	Retrospective cohort	262 Mother-infant pairs, California	Lead	aOR=3.2 (95% CI 1.2, 7.4) for maximum whole blood lead levels ≥ 10 μg/L
Berkowitz, 2006[99]	Air	Retrospective cohort	169,878 Idaho, population level	Lead	aOR 1.17 (95% CI 0.95, 1.45)
Satin, 1991[98]	Cord blood	Retrospective cohort	723 Mothers delivering in 5 hospitals across 5 cities in California	Lead	Relative risk=2.9, 95% CI (0.9, 9.2) Population attributable risk=47%

* aOR=adjusted odds ratio

** r=Pearson's correlation coefficient

*** r=Spearman's correlation coefficient

Table 2.

Studies evaluating the association between exposure to inorganic toxicants (arsenic, cadmium, mercury, lead) and preeclampsia.

First author's last name and pub. year	Biologic or Environmental Specimen	Type of study	Sample size	Toxicant	Risk of Preeclampsia
Liu, 2019[136]	Maternal red blood cells	Prospective cohort	1274 Mothers delivering at Boston Medical Center enrolled in the Boston Birth Cohort	cadmium	1 standard deviation increment in cadmium was associated with 15% higher risk of preeclampsia (95%CI 0.98,1.36)
Laine, 2015[63]	Placental tissue	Nested case control	172 Multicenter study of women in southeastern US	cadmium	aOR = 1.5 (95% CI 1.1, 2.2)
Dawson, 1999[62]	Maternal red blood cells	Prospective cohort	29 Mothers delivering at University of Texas Medical Branch	Cadmium and lead	Maternal red blood cell cadmium levels elevated 18% in late 3rd-trimester pregnancies Lead elevated 68% in early and 57% in late third-trimester pregnancies
Sowers, 2002[100]	Maternal whole blood	Retrospective cohort	705 Mothers receiving prenatal care at 3 clinics in Camden, NJ	lead	Whole blood lead level changed by 0.02 μg/dL in preeclamptic women for every 0.01 μg/dL change in women without
Dawson 2000[102]	Maternal red blood cells	Retrospective case control	39 (n=20 normotensive; n=15 mild preeclampsia, n=4 preeclampsia with severe features) Mothers delivering between 29 and 43 weeks at University of Texas Medical Branch	lead	Elevated maternal red blood cell Pb in severe preeclamptic (1.79 +/− 0.22) vs. mild preeclamptic (mean 1.71 +/− 0.35) vs. normotensive (mean 1.35 +/− 0.27) women, p<=0.001
Rabinowitz, 1987[101]	Cord blood	Retrospective cohort	3,851 Consecutive deliveries at Boston Hospital for Women	lead	lead 6.3 ug/dL: RR 1.7 (95% CI 1.3, 2.1) lead 15 ug/dL: RR 2.2 (95% CI 1.5, 2.9) lead 25 ug/dL: RR 2.5 (95% CI 1.5, 3.5)

Table 3.

Studies evaluating the relationship between exposure to organic toxicants (perfluorooctane sulfonic acid and perfluorooctanoic acid) and PTB.

First author's last name and pub. year	Biologic or Environmental Specimen	Type of study	Sample size and population	Toxicant	Risk of PTB
Sagiv, 2018[129]	Maternal plasma	Retrospective cohort	1645 Eastern Massachusetts birth cohort across 8 multispecialty group practices	PFOS, PFOA	aOR 2.4 (95% CI 1.3, 4.4) for highest PFOS quartile vs lowest; no association with PFOA
Darrow, 2013[119]	Maternal serum	Prospective cohort	1,330 (n=158 for PTB) Mothers living in the Mid-Ohio Valley near Parkersburg, WV DuPont plant (C8 Health Project)	PFOA, PFOS	No association
Savitz, 2012[131]	Maternal serum	Retrospective case control	3,613 for PTB Mothers living in the Mid-Ohio Valley near Parkersburg, WV DuPont plant (C8 Health Project)	PFOA	No association
Savitz, 2012[130]	Maternal serum	Retrospective cohort	11,737 Mothers living in the Mid-Ohio Valley near Parkersburg, WV DuPont plant (C8 Health Project)	PFOA	No association
Nolan, 2009[132]	Maternal serum	Cross-sectional	1,555 All live births in Washington County, Ohio	PFOA	No association
Stein, 2009[133]	Maternal serum	Retrospective cohort	1,845 (PFOA), 5,262 (PFOS) Mothers living in the Mid-Ohio Valley near Parkersburg, WV DuPont plant (C8 Health Project)	PFOA, PFOS	No association

Table 4.

Studies evaluating the relationship between exposure to organic toxicants (perfluorooctane sulfonic acid and perfluorooctanoic acid) and preeclampsia.

First author's last name and pub. year	Biologic or Environmental Specimen	Type of study	Sample size and population	Toxicant	Risk of Pre-E
Stein, 2009[133]	Maternal serum	Retrospective cohort	1,845 (PFOA), 5,262 (PFOS) Mothers living in the Mid-Ohio Valley near Parkersburg, WV DuPont plant (C8 Health Project)	PFOS, PFOA	PFOA aOR=1.3, 95% CI (0.9, 1.9) for exposures above median PFOS aOR=1.3, 95% CI (1.1, 1.7) for exposures above median PFOS aOR=1.6, 95% CI (1.2, 2.3) above the 90th percentile
Savitz, 2012[130]	Maternal serum	Retrospective cohort	11,737 Mothers living in the Mid-Ohio Valley near Parkersburg, WV DuPont plant (C8 Health Project)	PFOA	OR=1.13, 95% CI (1.00, 1.26) for an interquartile shift in log-transformed PFOA. OR = 1.1-1.2 for upper three quartiles of exposure.