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## Environmental contaminant exposures and preterm birth: A comprehensive review

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### Abstract

Preterm birth is a significant public health concern, as it is associated with high risk of infant mortality, various morbidities in both the neonatal period and later in life, and a significant societal economic burden. As many cases are of unknown etiology, identification of the contribution of environmental contaminant exposures is a priority in the study of preterm birth. This is a comprehensive review of all known studies published from 1992 through August 2012 linking maternal exposure to environmental chemicals during pregnancy with preterm birth. Using PubMed searches studies were identified that examined associations between preterm birth and exposure to 5 categories of environmental toxicants, including persistent organic pollutants, drinking water contaminants, atmospheric pollutants, metals and metalloids, and other environmental contaminants. Individual studies were summarized and specific suggestions made for future work in regard to exposure and outcome assessment methods as well as study design, with the recommendation of focusing on potential mediating toxicological mechanisms. In conclusion, no consistent evidence was found for positive associations between individual chemical exposures and preterm birth. By identifying limitations and addressing the gaps that may have impeded the ability to identify true associations thus far, this review can guide future epidemiologic studies of environmental exposures and preterm birth.

Preterm birth is a significant public health concern, as it is associated with high risk of infant mortality, various morbidities in both the neonatal period and later in life, and a significant societal economic burden (Behrman and Butler 2007; Cole et al. 2011; Guellec et al. 2011; Kochanek et al. 2012). Furthermore, despite a recent plateau, rates of preterm birth increased over 30% between 1981 and 2006 (Martin et al. 2011). Several causes of spontaneous preterm birth have been identified, including maternal stress, infection and inflammation, uterine distension (in pregnancies with multiple-births or abnormal amounts of amniotic fluid), cervical insufficiency, and placental dysfunction; however a large proportion with unknown etiology remain. In addition, although a variety of known risk factors predict preterm birth, including African American race, history of preterm delivery, low socio-economic status, and alcohol and cigarette use (Behrman and Butler 2007), these associations are largely unexplained. For these reasons the Institute of Medicine and the Surgeon General have called on the scientific community to investigate additional contributors to preterm birth risk, particularly those that may be related to environmental factors (Ashton et al. 2009; Behrman and Butler 2007).

Many environmental chemicals deserve investigation in this context because of (1) prevalent exposures, (2) demonstrated reproductive toxicities in animal studies, (3) ability to cross the placenta, and (4) association with other adverse birth outcomes that may result from related mechanisms. Despite this likelihood, the number of epidemiologic studies assessing relationships between environmental exposures and preterm birth are few, and the inconsistencies and limitations numerous. These factors make a comprehensive review of the literature both possible and also valuable for future research. This study will: (1) identify

and summarize studies to date examining environmental toxicants in relation to preterm birth; (2) provide tables and figures summarizing key study components and results; (3) illustrate the limitations in current studies, both in respect to specific classes of exposures and also overall; and (4) draw conclusions from the literature and suggest specific steps for improvement in future investigations. This base of knowledge will strengthen the probability of identifying toxicant exposures that may be involved in preterm birth, and possibly inform future public health and clinical measures for its prevention.

## METHODS

In order to provide a comprehensive summary of the studies of preterm birth and environmental chemicals to date, a list of exposures of interest was first compiled from the Center for Disease Control and Prevention's Fourth National Exposure Report (CDC 2009). Air pollution was excluded in the present paper, as studies in relation to birth outcomes have been extensively reviewed recently (Bonzini et al. 2010; Shah and Balkhair 2011). However, it is important to note the results from these studies in the context of environmental contaminant exposure and preterm birth, so the findings from these reviews were summarized. Polycyclic aromatic hydrocarbon (PAH) and volatile organic compound (VOC) exposures, which also occur primarily through inhalation of contaminated air, were examined in more detail because they were not included in recent reviews. Environmental tobacco smoke (ETS) was also excluded in this review as relevant studies on ETS specifically have recently been reviewed and meta-analyzed (Salmasi et al. 2010).

After identifying exposures of interest PubMed was used to perform searches of each individual exposure, as well as groups of exposures for completeness, with the terms "preterm" or "premature." Any paper using these terms was considered for review, although definitions of preterm birth may have differed slightly between papers. Most classified preterm birth as delivery before 37 weeks completed gestation, the most widely used definition, and those that did not are indicated in the results. Studies were included if they examined environmental exposure in the mother or gestational compartment (e.g., amniotic fluid, umbilical cord blood, or placental tissue) either during pregnancy or at birth and if they examined differences in these levels among subjects delivering/delivered preterm compared to term. This excluded studies where exposure was estimated before or after the timeframe of pregnancy, and in some ecologic studies where timing of exposure was difficult to determine. Although these studies may be pertinent, especially for persistent organic pollutants that have the ability to accumulate in human tissue, we excluded these papers for the sake of conciseness and because such measurements may be less robust in the prediction of preterm birth. Our criteria also excluded exposures that were occupational in nature and exposures measured in fathers, as well as any study that looked at gestational age only and not the dichotomous outcome of preterm birth. Finally, only studies that were published in English were included. For contaminants with a dearth of studies on this outcome, particularly relevant papers that might have otherwise been excluded were discussed in the text for completeness, but were not included in the tables or figures. Our online searches were supplemented with studies identified in the most recent reviews of environmental exposures and birth outcomes published in 2008 (Stillerman et al. 2008; Wigle et al. 2008; Windham and Fenster 2008) as well as those described in chapter 8 of the textbook *Preterm Birth: Causes, Consequences, and Prevention* published in 2007 by the Institute of Medicine of the National Academies (Behrman and Butler 2007). We included all papers meeting our criteria that were published between 1992 and August 2012.

After compiling the relevant studies and dividing them into appropriate groups, information from each paper was summarized as follows. First, in text important characteristics of each individual study were described, highlighting any limitations and strengths that should be

either avoided or emulated in future investigations. An alpha level of 0.05 was used to indicate statistically significant findings; however, as relationships with  $p > 0.05$  should not necessarily be considered null, confidence intervals are reported with effect estimates for a better estimate of precision. Where it was relevant to make a comparison between exposure levels in a given study and current averages, chemical levels measured in women from the CDC's Fourth National Exposure Report (2003–2004) were presented. Second, tables were created listing key characteristics of studies within each grouping. Finally, in forest plots odds ratios (OR) observed for each study were displayed by environmental exposure to provide a visual depiction of the existing data (Neyeloff et al. 2012). Results from studies that examined differences in levels of exposure in preterm vs. term births but did not calculate OR were excluded from figures.

## RESULTS

Studies were divided into broader categories, including: persistent organic pollutants (POP), drinking water contaminants, atmospheric pollutants, metals and metalloids, and other environmental contaminants. Although some chemicals qualified for more than one group, these were described only once in the category that was perceived to be most fitting. In addition to these chemicals there were many others for which searches were performed but that were not found to be examined in relation to preterm birth in any studies listed on PubMed. These included: POP (trichlorophenol, pentachlorophenol, mirex, and the Agent Orange components 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid); non-persistent pesticides (phenylphenol, acetochlor, alachlor, metolachlor, *N,N*-Diethyl-*meta*-toluamide [DEET], the carbamate insecticides carbofuran and propoxur, and pyrethroid insecticides); drinking water contaminants (perchlorate); and other environmental contaminants (phenols, triclosan, parabens, many volatile organic compounds such as xylene and dibromomethane, and acrylamide).

## PERSISTENT ORGANIC POLLUTANTS

Persistent organic pollutants (POP) including organochlorine pesticides such as dichlorodiphenyltrichloroethane (DDT) and hexachlorobenzene (HCB), polychlorinated biphenyls (PCB), dioxin, perfluorinated compounds such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), and, of more recent interest, polybrominated diphenyl ethers (PBDE), have been explored in a large number of studies for potential relationships with preterm birth (Table 1, Figure 1).

### Organochlorine Pesticides

Dichlorodiphenyltrichloroethane (DDT) is an organochlorine pesticide that was used commonly in agricultural settings in the US until 1972 when it was banned because of adverse effects on wildlife (ATSDR 2002c). However exposure still occurs in the US to a lesser degree through consumption of contaminated food and water. Additionally DDT is still used as a pesticide and for preventing the spread of malaria in many other places in the world (ATSDR 2002c). The primary component of DDT pesticides is the isomer *p,p*-DDT but there are also smaller amounts of *o,p*-DDT. Furthermore, DDT is metabolized into dichlorodiphenyldichloroethylene (DDE) and dichlorodipenyldichloroethane (DDD) in humans. These metabolites as well as the parent compounds are measured in serum as markers of exposure.

Several small case-control studies published before 2000 found significantly higher levels of these organochlorines in cases of preterm delivery compared to controls. Notably, exposure levels in most of these studies were almost an order of magnitude higher than those measured recently in the US (median DDE for females from 2003–2004=1.25 ppb of serum;

see Table 1 for comparisons of study levels) (CDC 2009). The first study to examine this relationship by Saxena and colleagues (1981) ( $n=40$ ) observed that placental tissue and maternal blood taken at delivery from mothers who delivered preterm had higher levels of  $p,p'$ -DDT,  $p,p'$ -DDE, and  $p,p'$ -DDD compared to controls. These results were confirmed by another group ( $n=54$ ) when exposure was measured in umbilical cord blood, but not when it was measured in maternal blood also taken at birth (Procianoy and Schwartsman 1981). However in another study by Wasserman et al. (1982) ( $n=27$ ), where levels were examined in maternal serum during the third trimester, most isoforms of DDT, DDE and DDD were higher in cases compared to controls. Finally Berkowitz et al. (1996) performed a case-control study in New York City ( $n=40$ ) where mothers had much lower exposure levels, and observed no significant differences in  $p,p'$ -DDE levels in maternal serum measured during the first trimester of pregnancy in cases of spontaneous preterm birth compared to controls.

The strongest evidence for a relationship between DDT exposure and preterm birth comes from a cohort study ( $n=2,380$ ) conducted as part of the Collaborative Perinatal Project (CPP) in 11 US cities (Longnecker et al. 2001). Longnecker and colleagues (2001) found that increased maternal exposure to DDT, measured by DDE levels in third trimester serum, was significantly associated with increased OR of preterm delivery, and that there was a dose-dependent effect. Notably, women from the cohort were recruited from 1959–1965, a time when DDT use was at its peak in the US. The most pronounced statistical relationship between DDE and preterm birth was for women with greater than 60  $\mu\text{g/L}$  in serum, about 40 fold higher than levels measured in US females in 2003–2004, compared to women with less than 15  $\mu\text{g/L}$  in serum ( $\text{OR}=3.1$ , 95%CI=1.8 to 5.4) (Longnecker et al. 2001; CDC 2009). Another cohort study conducted during approximately the same time (1959–1967) failed to observe any significant associations in a population of women in San Francisco exposed to similar levels of DDT and DDE, but the sample size and number of preterm cases was much smaller ( $n=420$ , cases=33) (Farhang et al. 2005).

More recent studies that investigated relationships between DDT exposure and preterm birth at levels more consistent with those found currently in the US showed comparatively null results. Ribas-Fitó (2002) and colleagues observed higher levels of  $p,p'$ -DDE in cord serum of preterm newborns compared to those born full term in a small case-control study in Spain ( $n=70$ ), but results were not adjusted for covariates and were observed in a population highly exposed to hexachlorobenzene (HCB). Another study from Mexico City ( $n=233$ ) measured  $p,p'$ -DDE levels in maternal serum at delivery and failed to find any significant differences in  $p,p'$ -DDE concentrations among preterm vs. term births in adjusted regression models (Torres-Arreola et al. 2003). Wood et al. (2007) examined differences in DDE levels in serum from primiparous women taken one day postpartum in a case-control study ( $n=78$ ), and observed no significant association between exposure and odds of spontaneous preterm delivery, defined as <35 weeks gestation, in adjusted analyses. A case-control analysis by Pathak and colleagues (2009) in India measured  $p,p$ -DDT and  $p,p$ -DDE in both maternal and cord blood taken at delivery ( $n=46$ ) and observed no significant differences in unadjusted comparisons of exposure levels from either matrix in cases vs. controls. Wojtynizk et al. (2010) examined three groups of women in Greenland ( $n=572$ ), Ukraine ( $n=611$ ), and Poland ( $n=258$ ) to determine relationships between maternal serum levels of  $p,p$ -DDE at approximately 24 weeks gestation and odds of preterm birth. In adjusted models they failed to find any statistically significant associations, although in Poland, where the geometric mean of  $p,p$ -DDE exposure was 357 ng/g lipid (geometric mean for all US females measured from 2003–2004=241 ng/g lipid) a highly suggestive increase in the odds of preterm birth was reported ( $\text{OR}=2.44$ , 95%CI=0.99 to 6.06) (Wojtyniak et al. 2010).

The latest study, however, with median exposure levels below those currently observed in the US, found significantly elevated DDE in preterm vs. term biological samples. Bergonzi

and colleagues (2011) examined *p,p*-DDE and *p,p*-DDD levels in maternal and cord serum, placenta, and subcutaneous adipose tissue all taken at delivery in a small cohort study in Italy ( $n=70$ ). In adjusted models they observed higher levels of *p,p*-DDE in serum and higher *p,p*-DDT in adipose tissue of mothers who delivered preterm.

Several of the above studies also examined the association between preterm birth and hexachlorobenzene (HCB), an organochlorine pesticide used widely in the US until 1965 primarily for protection of wheat crops (ATSDR 2002a). Similar to DDT, exposure to HCB persists through consumption of contaminated foods, particularly fish, despite its discontinued use. Of the groups that examined HCB in association with preterm birth, only Ribas-Fitó and colleagues (2002) observed a significant difference in exposure levels between cases and controls. However, as mentioned previously, this study was performed in a group of individuals in Spain who were subject to high levels of HCB through air pollution due to residence near an electrochemical factory. An additional study in an agricultural population, where exposures were again elevated compared to what is generally observed in the US, also found an inverse association between HCB exposure and gestational age (Fenster et al. 2006). Other studies, however, have not reported similar results (Bergonzi et al. 2011; Torres-Arreola et al. 2003).

Another organochlorine pesticide, hexachlorocyclohexane (HCH), is also consistently found in the environment though its use in agriculture has been discontinued in the US for over 20 years (ATSDR 2005). It takes on several isomeric forms, and when the  $\gamma$ -HCH isomer is present in >99% of the pesticide used it is more familiarly called lindane. HCH exposure was found at higher levels in cases of preterm birth compared to term births in the early study by Saxena and colleagues (1981), as well as in the Pathak et al. (2009) study where measurements were made in both maternal and cord serum. There was a similar suggestively increased odds of preterm birth in association with HCH exposure in the study in Mexico City, although the effect estimate did not reach statistical significance ( $p=0.08$ ) (Torres-Arreola et al. 2003). Other organochlorine pesticides, including heptachlor/heptachlor epoxide and aldrin/dieldrin, discontinued in the late 1980s but persistent in soil and fatty food products (ATSDR 2002b, 2007a), were linked to preterm birth in the small case-control studies performed by Saxena et al. (1981) and Wasserman et al. (1982) but have not been explored in more recent studies of preterm birth. In the aforementioned study by Fenster and colleagues (2006), the only significant association observed in relation to gestational age was for HCB, and no relationships were observed for HCH or other organochlorine pesticides.

### Polychlorinated Biphenyls (PCB)

In addition to pesticides, other chlorinated industrial chemicals no longer in use continue to be human health threats and may be factors in preterm birth. Polychlorinated biphenyls (PCB) are a group of 209 chemicals that were used in the US until 1977 as lubricants or coolants, electrical insulators, and in various building materials (ATSDR 2000). They do not degrade in the environment and accumulate in fish and marine animals. Exposure to humans occurs primarily through consumption of contaminated foods, and is commonly measured in blood serum samples. The PCB congener 153 is the most highly detected in humans and is used frequently as a marker of overall PCB exposure.

Several of the small case-control studies introduced above have also observed significant differences in summed serum PCB levels in cases compared to controls. It is important to note that while many studies report findings in relation to change in summed PCB levels, this is indicative of a sum of the congeners *measured* which vary widely between studies. Wassermann and colleagues (1982) observed higher levels in maternal 3<sup>rd</sup> trimester serum in preterm cases compared to controls in unadjusted assessments. The study by Ribas-Fitó et

al. (2002) in Spain also noted significantly higher levels in preterm cases compared to controls in measurements made in cord serum. However, Berkowitz and colleagues (1996) did not find marked differences in PCB levels measured in 1<sup>st</sup> trimester maternal serum by case/control status in a matched analysis.

In another analysis from the Collaborative Perinatal Project, a large US-based cohort study ( $n=1,034$ ), Longnecker and colleagues (2005) also did not observe significant associations between summed PCB exposure and preterm birth, although a positive trend in OR was noted with increasing exposure categories in crude models (OR for 2–<3  $\mu\text{g/L}$  vs. <2  $\mu\text{g/L}$  = 1.07, 95%CI=0.65 to 1.77; OR for 3–<4  $\mu\text{g/L}$  vs. <2  $\mu\text{g/L}$  = 1.09, 95%CI=0.63 to 1.88; OR for 4+  $\mu\text{g/L}$  vs. <2  $\mu\text{g/L}$  = 1.51, 95%CI = 0.91 to 2.52). Effect estimates were diminished and confidence intervals widened in adjusted models, particularly with the addition of *p,p*-DDE levels (Longnecker et al. 2005).

More recent studies have been null as well. Wojtynick et al. (2010) did not find significantly altered odds of preterm birth in association with maternal serum levels of PCB-153 in Greenland, Ukraine, or Poland. The study by Bergonzi et al. (2011) in Italy did not observe significantly different levels of summed PCB in maternal or cord serum, placenta, or adipose tissue in samples from preterm vs. term pregnancies. However, as mentioned previously, this was a small cohort study with only 4 preterm deliveries.

Finally, in a large meta-analysis of studies from ENRIECO and OBELIX cohorts examining the relationships between POP exposure and several birth outcomes, no association was observed between PCB-153 and gestational age in any individual study or overall (Govarts et al. 2012).

## Dioxin

Dioxins are compounds unintentionally released into the environment through various industrial processes, such as paper bleaching, drinking water disinfection, and incineration of waste (ATSDR 1998). Of the 75 dioxin congeners, the most toxic and commonly studied is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD). This compound has been associated with many adverse reproductive outcomes in rodent studies, including fetal loss and birth defects (ATSDR 1998). Exposure to humans occurs primarily through consumption of contaminated foods, particularly meat, dairy, and fish (ATSDR 1998).

Despite the well-demonstrated toxicity in animals, no studies meeting our selection criteria have examined the relationship of dioxin exposure and preterm birth. Two studies did investigate this relationship, although they did not examine exposure specifically during pregnancy. However, because (1) half-life of TCDD in humans is long, (2) it is reasonable to argue that measures taken outside the time period of gestation may still be reflective of exposure during pregnancy, and (3) as dioxin has been associated with a range of adverse birth outcomes in animal studies, it is important to mention the exposure in this context. First, Eskenazi and colleagues (2003) examined the relationship between dioxin exposure and preterm birth in women from Seveso, Italy, where an extremely large amount of 2,3,7,8-TCDD was accidentally released in 1976. Most women were approximately 20 years old when the accidental exposure occurred and when serum TCDD levels were measured, and approximately 40 years old when the study was conducted to assess birth outcomes from the interim ( $n=510$  women, 888 pregnancies). Despite high levels of exposure (median=46.6, range=2.5 to 9.14 ppt of lipid), the elevated odds of preterm birth observed in association with TCDD serum measures was not considered significant (adjusted OR for preterm birth in association with 10-fold increase in TCDD=1.5, 95%CI=0.7 to 3.2 for all pregnancies from 1976–1984) (Eskenazi et al. 2003).

A later study by Lin et al. (2006) examined effects of exposure to polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/F) released from a waste incinerator in Taipei, Taiwan. Annual exposure estimates for districts within Taipei were created from models of the incinerator plume, and rates of preterm birth from the exposed districts were compared to rates in a nearby but unexposed region. In 1991, before the incinerator was built, there were no differences in rates of preterm birth between the exposed and unexposed districts; however in 1997, five years after the construction, OR were slightly elevated (OR for districts with 0.03–0.05 pg Toxic Equivalent [TEQ]/m<sup>3</sup> vs. <0.03 pg TEQ/m<sup>3</sup>=1.12, 95%CI=0.94–1.32; OR for districts with >0.05 pg TEQ/m<sup>3</sup> vs. <0.03 pg TEQ/m<sup>3</sup>=1.22, 95%CI=0.97–1.52) (Lin et al. 2006).

Two additional studies of accidental exposure to dioxin, with limited exposure and outcome measurements, have further suggested an association between this class of contaminants and preterm birth (Le and Johansson 2001; Revich et al. 2001). However, analyses with more precise exposure and outcome definitions are necessary to substantiate these results.

### Perfluorinated Compounds (PFC)

Perfluorinated chemicals repel oil, grease, and water and are used to treat carpets and clothing to prevent stains, and are also components of some food containers and wrappers (ATSDR 2009). Through product use and manufacturing they can be released into the environment, and they do not break down in soil or water. Exposure occurs through consumption of contaminated drinking water and food, inadvertent ingestion of indoor dust, and potentially through inhalation (ATSDR 2009). The two compounds produced in largest quantities include perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). Despite efforts to phase out use of these chemicals and/or decrease release into the environment, exposure is still widespread.

A number of recent studies examined the relationship between PFOA and PFOS exposure and preterm birth. Four studies examined associations in populations where exposure levels were relatively low and on the same order of magnitude as those observed in the general US population. Apelberg et al. (2007) measured PFOA and PFOS levels in cord serum from newborns in the Baltimore THREE study, where a relatively high proportion of births were preterm ( $n=293$ , preterm=28). No significant differences in median concentrations were detected, however, in term compared to preterm samples. Fei and colleagues (2007) examined levels of PFOS and PFOA in plasma taken during the first trimester from mothers participating in the Danish National Birth Cohort. Exposure levels were divided into quartiles for analysis. The authors found that mothers with PFOS levels in the third quartile had significantly elevated OR of preterm birth compared to mothers from the first quartile of exposure ( $n=1,400$ , preterm=53). For mothers with levels of PFOA in the second quartile compared to the first OR were significantly higher as well (Fei et al. 2007). Other quartiles, however, were not significantly associated with change in OR, nor was there a significant trend in increasing quartiles for PFOS or PFOA.

Conversely, in the Norwegian Mother and Child Cohort Study, Whitworth and colleagues (2012) found a decreased odds of preterm birth for participants in the highest quartiles of PFOA and PFOS compared to the lowest, with exposure measured in maternal plasma at approximately 17 weeks gestation ( $n=901$ , preterm=35). A smaller study in Alberta, Canada with exposure levels measured in second trimester maternal serum showed no significant associations between PFOA or PFOS and preterm birth ( $n=252$ ; preterm=21) (Hamm et al. 2010). Exposure levels were comparable in the studies by Hamm et al. (2010) (geometric mean for PFOA=1.3 ng/mL; geometric mean for PFOS=7.4 ng/mL) and Whitworth et al. (2012) (median for PFOA=2.2 ng/mL; median for PFOS=13 ng/mL), but

were slightly higher in the study by Fei and colleagues (2007) (mean for PFOA=5.6 ng/mL; mean for PFOS=35.3 ng/mL).

Several studies of populations with high exposure to PFOA as a result of industry-related drinking water contamination in the Mid-Ohio valley, running between Ohio and West Virginia, also reported no significant relationships with preterm birth. In a study by Nolan and colleagues (2009) exposure levels were assigned by whether pregnant mothers resided in areas where drinking water was sourced from a contaminated facility only ( $n=150$ ), partially sourced from that facility ( $n=190$ ), or not at all sourced from that facility ( $n=1,017$ ). No significant differences in frequency of preterm deliveries in mothers who consumed water from the contaminated source or partially from the contaminated source were noted compared to those who consumed no water from that source (Nolan et al. 2009). The C8 Health Project (C8 is a synonym for PFOA) examined this association in several studies in the same region. The original study to examine the odds of preterm birth in association with exposure in this population did not fit our search criteria, as exposure during pregnancy was estimated by serum PFOA and PFOS levels measured at study enrollment some years later (Stein et al. 2009). It is also unlikely that current serum measures accurately reflect historical levels because of high variability in drinking water levels (Bartell et al. 2010; Olsen et al. 2007).

Follow-up papers by the same group, however, improved exposure assessment by using a fate-transport model to incorporate data on serum and historical drinking water PFOA levels into an estimate of maternal exposure during pregnancy. The first study examined these estimates in association with self-reported preterm birth in the C8 Health Project ( $n=11,737$ , preterm=1,843) with no significant results (Savitz et al. 2012a). The second utilized birth records from the same regions of Ohio and West Virginia in order to increase the study size and improve accuracy of outcome measures (cases=3,613, controls=3,695) (Savitz et al. 2012b). In this analysis maternal PFOA levels during early pregnancy were estimated using the same modeling techniques, with maternal residence based on addresses geo-coded from birth records. This, however, may have been associated with some exposure misclassification. Again, Savitz et al. (2012b) reported no significant change in odds of preterm birth associated with PFOA exposure. Finally, in the third analysis, cases of preterm birth from birth certificates were matched to C8 questionnaire data to maximize the quality of both exposure and outcome data ( $n=4,547$ , preterm=405) (Savitz et al. 2012b). In this analysis as well no significant change in odds of preterm birth in association with PFOA exposure was reported.

Another paper examining the association between exposure to perfluorinated compounds and preterm birth measured PFOS, PFOA, perfluorononanoic acid (PFNA), and perfluoroundecanoic acid (PFUA) in cord blood from mothers in a Taiwan cohort ( $n=429$ , preterm~40) (Chen et al. 2012). While no significant associations were observed for PFOA, PFNA, or PFUA, increased PFOS levels were associated with an increased odds of preterm delivery (OR for ln-unit increase in PFOS=2.45, 95%CI=1.47 to 4.08). Further, when PFOS exposure was divided into quartiles and modeled in relation to preterm birth, a significant trend was observed ( $p=0.001$ ) (Chen et al. 2012). In a study from Ottawa, Canada, measuring levels of PFC in cord serum from women with scheduled C-sections, there were no differences observed in levels of PFC in cord serum from preterm compared to term births, however gestational age was inversely associated with PFOS levels ( $n=100$ , preterm=3) (Arbuckle et al. 2012).

Finally, a study in China examined the relationship between exposure to PFOA measured in maternal serum level and preterm birth (Wu et al. 2012). The population included one group residing in Guiyu, China ( $n=108$ ) where there are many facilities and in-home workshops

for recycling electronic waste, a process that results in a large amount of PFOA and other toxin release into the environment, and a control group in Chaonan, China ( $n=59$ ). Wu and colleagues (2012) observed significantly higher levels of PFOA in maternal serum from preterm compared to term deliveries.

### **Polybrominated diphenyl ethers (PBDE)**

Mixtures of PBDE congeners are used as flame-retardants in many consumer goods, namely electronics and furniture. While use of the various commercial mixtures has been or is in the process of being phased out in the US and a number of other countries, many products containing these compounds remain. The continued use and disposal of products containing PBDEs results in their release into the environment and human exposure. One study examined the relationship between exposure to PBDE measured by umbilical cord serum levels and adverse birth outcomes, including but not exclusively preterm birth, in the same cohort mentioned previously in Guiyu and Chaonan, China (Wu et al. 2010). PBDE contamination, like PFC, is prevalent in the Guiyu area as a result of e-waste recycling. In this analysis Wu and colleagues (2010) observed significantly higher levels of various individual and summed PBDE congeners in cord blood from adverse birth outcome pregnancies (stillbirths or babies born preterm or low birth-weight) compared to normal pregnancies. Although the group did not examine preterm birth alone, this study provides suggestive evidence for future investigation of the association between PBDE exposure and preterm birth.

### **Limitations and Recommendations**

In summary, the literature suggests: (1) An association between high levels of DDT exposure and preterm birth; (2) The absence of an association when DDT exposure is at or below levels observed currently in the US; and (3) There is insufficient data to make conclusions about other POP at this time. DDT and its isomers, most commonly studied, were positively associated with OR of preterm birth in all but one of studies where exposure was an order of magnitude above levels currently observed in the US. Studies of lower exposure levels primarily showed null results; although two exceptions provide grounds for further exploration of whether there is a threshold for effect. Studies of other organochlorine pesticides are too few for conclusions to be drawn, but results are similarly suggestive of an effect at higher exposure levels. With PCB, there is no strong evidence for an association with preterm birth, as the studies that did demonstrate effects were small and did not adjust for critical covariates. Literature on PFC and preterm birth was inconclusive when maternal exposures were estimated from levels measured in drinking water sources alone or in combination with data on exposure pathways. However, in studies using biomarkers, data is suggestive of an association between PFOS in particular and preterm birth. Finally, for PBDE exposure, although the single study is suggestive of an association with preterm birth among other adverse pregnancy outcomes, additional studies, particularly with a more specific definition for cases, are necessary.

Several study design aspects will be important to address in the future in order to better assess the relationship between POP exposure and preterm birth. First, exposures need to be measured at more time points during pregnancy, as most have focused on levels in the third trimester or at birth and some longitudinal studies demonstrated varying levels of persistent compounds during pregnancy (Bloom et al. 2007; Glynn et al. 2011). Second, more attention needs to be paid to body mass index (BMI) and other maternal anthropometric measures in these analyses. POP accumulate readily in the environment but also in human fatty tissues. Changes in maternal metabolism and adipose deposits during pregnancy could significantly alter blood and tissue lipid concentrations and consequently measures of POP (Hamel et al. 2003). The potential impact of these processes on the assessment of relationships between

POP measures and birth outcomes need to be more carefully addressed. Finally, in the same vein, many of the more recent studies use exposure concentrations expressed on a lipid-basis in statistical analysis. However, using this method may produce bias and cloud real associations, and alternatively adjusting for serum lipids as a separate covariate in regression models may be preferable (Schisterman et al. 2005). These issues need particular attention in future study of POP exposure and preterm birth.

## DRINKING WATER CONTAMINANTS

Many chemicals used for various purposes can be found in drinking water supplies. In addition, treatment of drinking water with chlorine results in the release of byproducts, such as trihalomethanes (THM), which can also be hazardous. A number of studies investigated the relationship between these contaminants and preterm birth (Table 2, Figure 2).

### Chlorination Disinfection Byproducts

Drinking water is commonly treated with chlorine to kill bacteria. However the reaction of chlorine with various compounds found in the water may result in the formation of potentially hazardous byproducts (disinfection byproducts; DBP), including trihalomethanes (THM: chloroform, bromoform, bromodichloromethane, and dichlorobromomethane) and haloacetic acids (HAA: chloroacetic acid, dichloroacetic acid, trichloroacetic acid, bromoacetic acid, and dibromoacetic acid). Studies of relationships between exposure to THM and preterm birth were systematically summarized and meta-analyzed by Grellier and colleagues (2010). Of 9 studies chosen for inclusion in that study, none found significant associations with preterm birth (Dodds et al. 1999; Gallagher et al. 1998; Hoffman et al. 2008; Kramer et al. 1992; Lewis et al. 2007; Savitz et al. 1995; Wright et al. 2003, 2004; Yang et al. 2007). Likewise, the results of the meta-analysis were insignificant, although a decrease in odds of preterm delivery with increasing THM exposure was suggested (Grellier et al. 2010). Two of these studies also examined the relationship between preterm birth and HAA exposure but did not detect significant results (Hoffman et al. 2008; Wright et al. 2004).

Six other studies that examined odds of preterm birth in association with DBP exposure were excluded because exposures were either inadequately characterized or grouped into too few categories (Grellier et al. 2010). (These studies were similarly omitted from Table 3 and Figure 3 because of the limited value they add to the data on this topic.) Two studies that assigned maternal exposure levels by municipality use of chlorine for drinking water disinfection found a positive association between residence in these areas and odds of preterm birth (Yang et al. 2000; Yang 2004). One study that also used municipality of residence for exposure classification purposes found higher rates of premature delivery in mothers who resided in municipalities where water was treated with chlorine dioxide compared to those who resided where water was treated with chlorine (Tuthill and Schwalm 1992). On the other hand, another analysis that used similar exposure assessment methods found that mothers living in areas where water was chlorinated had significantly decreased odds of preterm birth (OR=0.91, 95%CI=0.84 to 0.99) (Jaakkola et al. 2001). The last two of these 6 studies, again with exposure assigned by maternal water-source treatment with chlorine, did not find any statistically significant associations between chlorine exposure and preterm birth (Kanitz et al. 1996; Kallen and Robert 2000). One additional study that examined preterm birth in association with DBP exposure was excluded from the meta-analysis because of insufficient exposure categorization (Aggazzotti et al. 2004). This study examined levels of THM and other chlorination by-products in tap water samples from mothers' homes, and also incorporated information from a questionnaire. They found no association with chlorination by-products and preterm birth. Finally, two other studies mentioned in association with other birth outcomes in the review also examined preterm

delivery and found no association with THM (Hinckley et al. 2005; Bove et al. 1995). One of these studies also examined levels of HAA in drinking water, but reported no significant relationships with odds of preterm birth (Hinckley et al. 2005). Overall, Grellier and colleagues (2010) concluded that based on the existing literature there was insufficient evidence to indicate an association between THM exposure and any birth outcome, including preterm birth. Similarly, no apparent relationships for HAA emerged, although examining effects of this exposure was not a primary aim in the study.

Since the publication of the meta-analysis by Grellier et al. (2010), 4 new papers have been published examining the relationship between DBP and preterm birth, all with more refined exposure assessment methods. Patelarou and colleagues (2011) examined births from the RHEA cohort in Crete, Greece ( $n=1,359$ ). They measured THM in drinking water sources and administered in-depth questionnaires from which they calculated each subject's personal exposure levels by ingestion, dermal absorption, and inhalation. No significant differences were observed in odds of preterm birth when comparing mothers exposed to levels in the highest tertile compared to the lowest, whether exposure was measured in the 1<sup>st</sup>, 2<sup>nd</sup>, or 3<sup>rd</sup> trimester, or averaged across the duration of pregnancy. In a mother-child cohort in Spain, exposure estimated in a similar fashion was also not associated with odds of preterm birth ( $n=2,074$ ) (Villanueva et al. 2011).

A study of two southeastern US sites of either brominated or chlorinated DBP contamination, however, observed a positive association between DBP exposure and preterm birth. Horton and colleagues (2011) measured THM, HAA, and total organic halide (TOX) concentrations in drinking water weekly or biweekly in drinking water in both communities, and identified a significantly increased odds of preterm delivery for mothers in the 50<sup>th</sup>–75<sup>th</sup> percentile of TOX exposure compared to those <50<sup>th</sup> percentile. The group also observed a significantly increased odds of preterm birth in association with continuous TOX exposure (OR for 10  $\mu\text{g/L}$  increase=1.09, 95%CI=1.03 to 1.16). This finding was within the population residing near a site of brominated-DBP contamination (preterm=401, term=3,109). No significant associations were observed for any other contaminant or any other exposure category (75<sup>th</sup>–90<sup>th</sup> vs. <50<sup>th</sup> percentile or >90<sup>th</sup> vs. <50<sup>th</sup> percentile) within that community or in the community with chlorinated-DBP contamination (Horton et al. 2011).

The most recently published study of DBP and preterm birth was the first to use a maternal biomarker of exposure. Costet and colleagues (2012) examined odds of preterm birth in a nested case-control study within the PELAGIE birth cohort in France (cases=114; controls=399). In addition to the previously used method of identifying THM levels in drinking water supplies and assigning individual exposure levels based on questionnaires designed to characterize ingestion, inhalation, and dermal absorption, they also measured maternal urinary levels of the HAA trichloroacetic acid (TCAA) during early pregnancy. While biomarkers of THM may only reflect very recent exposures, TCAA levels may be valid markers of long-term ingestion of chlorinated water (Kim et al. 1999). In this study urinary TCAA detection was low (6.7%), and concentrations correlated with THM ingestion estimates only in subjects with detectable levels (Costet et al. 2012). No significant results were reported in relation to preterm birth for either exposure assessment method. However, the use of a biomarker for DBP exposure may mark a promising new direction for this line of research.

### Chlorinated Solvents

In addition to DBP, many compounds not used for water-treatment purposes end up in groundwater and drinking water supplies. Trichloroethylene (TCE) and tetrachloroethylene (PCE) are solvents used commonly as metal degreasing agents, and the latter is also used for

spot treatments in dry cleaning facilities (CDC 2009). TCE dissolves slightly in water and evaporates when it reaches the surface, but otherwise can remain in groundwater for long periods of time (ATSDR 1997b). PCE may be degraded more readily by microorganisms in water but can still be found in drinking water sources (ATSDR 1997a). Exposure to these compounds occurs through ingestion of contaminated water or inhalation of vapors.

Bove and colleagues (1995) first examined the relationship between TCE and PCE exposure and birth outcomes in four regions of northern New Jersey from 1985–1988 ( $n=80,938$ ). They assigned exposure levels to pregnant mothers based on water samples analyzed twice annually for contaminant levels, and found no significant associations with preterm birth. Sonnenfeld and colleagues (2001) examined the same relationship in mothers residing on a US Marine Corps base at Camp Lejeune, North Carolina, where there was known contamination of drinking water with PCE ( $n=11,798$ ). They observed slightly elevated odds of preterm delivery in mothers exposed to drinking water from the PCE-containing well for both 4–10 weeks ( $OR=1.3$ ,  $90\%CI=1.0$  to  $1.7$ ) and 11–20 weeks of pregnancy ( $OR=1.3$ ,  $90\%CI=1.1$  to  $1.6$ ) compared to no exposure during pregnancy. Aschengrau et al. (2008) utilized a leaching and transport model to estimate maternal PCE exposure near the time of conception in Cape Cod, Massachusetts, where drinking water pipe linings were found to be contaminated ( $n=2,125$ ,  $preterm=96$ ). No significant elevations in OR were detected. Finally, Forand and colleagues (2011) examined birth outcomes in mothers from Endicott, New York, where exposure to PCE and TCE was thought to occur largely through inhalation as a result of contaminant soil vapor intrusion ( $n=1,440$ ). No elevated risks of preterm birth in women living in the PCE, TCE, or combined contaminated areas were noted compared to women living in non-contaminated areas.

### Limitations and Recommendations

In summary, evidence on a relationship between exposure to any individual drinking water contaminant and preterm birth is currently inconclusive. In some early publications DBP were associated with a significant increase in odds of preterm delivery, but results from more recent studies with more precise exposure assessment methods have been generally null. Drinking water contaminated with chlorinated solvents has been examined in fewer studies, but there is some evidence that exposure to PCE via this route may be related to preterm birth.

These results suggest that studies of drinking water contaminants and preterm birth need more attention to exposure assessment methods. Many studies have been ecologic in nature, linking pregnancy outcomes to exposure indicated by maternal residence in proximity to contamination sources. This may result in a high degree of exposure misclassification, as water consumption varies significantly by individual. Also, ecologic studies are highly subject to confounding as a result of differences in socioeconomic status, additional environmental exposures, and other potentially important factors that differ by region. Data on drinking water contamination levels would best be combined with other known factors, such as water use habits, to provide more accurate exposure assessments. In addition, when possible, studies should consider the use of biomarkers of exposure. Another issue is that contamination of drinking water by one toxicant may be linked to contamination with another. Examination of exposure to mixtures of drinking water pollutants need to be addressed in the future.

### ATMOSPHERIC POLLUTANTS

Studies of air pollutant associations with preterm birth have been reviewed in several recent publications. Criteria air pollutants, including ozone, particulate matter (of sizes  $\leq 2.5$  and  $\leq 10$  microns in aerodynamic diameter,  $PM_{2.5}$  and  $PM_{10}$ , respectively), carbon monoxide

(CO), oxides of nitrogen (NO<sub>x</sub>), and sulfur dioxide (SO<sub>2</sub>) received the most attention (Glinianaia et al. 2004; Shah and Balkhair 2011; Sram et al. 2005). While conclusions from individual reviews have been conflicting, the most recent assessment of the evidence asserted that a relationship exists between SO<sub>2</sub> and PM<sub>2.5</sub> exposures and preterm birth (Shah and Balkhair 2011). Associations with other criteria air pollutants are less definitive (Stillerman et al. 2008).

Environmental tobacco smoke (ETS) exposure in relation to preterm birth has been examined extensively and reviewed recently as well. A meta-analysis that improved upon previous reviews by clearly excluding mothers who were active smokers observed an elevated odds of preterm delivery in relation to ETS exposure in models of crude data (OR=1.2, 95% CI=0.99 to 1.46) which was attenuated in an adjusted analysis (RR=1.07, 95%CI=0.93 to 1.22) (Salmasi et al. 2010). However, other assessments, including one by the US Department of Health and Human Services (2006), have concluded that ETS exposure decreases gestational duration (Stillerman et al. 2008; Wigle et al. 2008).

Other air contaminants, particularly polycyclic aromatic hydrocarbons (PAH) and volatile organic compounds (VOC), received less attention in previous reviews, and hence the literature on the relationships between these exposures and preterm birth was examined here (Table 3, Figure 3).

PAH are released in the combustion of coal, oil and gas, and other organic matter, and humans are exposed through inhalation of contaminated air (ATSDR 1995). Major contributors are inhalation of ETS and PAH bound to particulate matter, which complicates estimation of PAH-specific effects. Additionally, exposure can occur via dietary sources of PAH, for example via consumption of charbroiled foods. Exposure assessment is most commonly performed via air monitoring, but more recently has moved toward biomonitoring with urine measures of hydroxylated PAH metabolites or blood measures of parent compounds or DNA-adducts.

Three studies have used air measurements to assess the relationship between PAH and preterm birth. Vassilev and colleagues (2001) used ambient air monitoring data in New Jersey between 1990 and 1991 to create estimates of average exposure to polycyclic organic matter (including PAHs, arenes, and polyhalo compounds) within each census tract ( $n=214,493$ ). Significantly elevated odds of preterm birth in mothers residing in medium and high PAH-exposure areas compared to mothers residing in low exposure areas (OR for medium compared to low=1.09, 95%CI=1.04 to 1.14; OR for high compared to low=1.25, 95%CI=1.19 to 1.31) were noted in adjusted models. Since maternal tobacco use appeared equally distributed across air pollution categories, no adjustments were made for this factor in the analysis.

In a more recent study in Los Angeles County, where exposures to PAH and other air pollutants are particularly high, Wilhelm et al. (2011) similarly found increased odds of preterm birth in association with an interquartile range increase in ambient total PAH levels averaged across the duration of pregnancy after adjustments for maternal age, race/ethnicity, education, and parity (OR=1.3, 95%CI=1.15 to 1.47;  $n=112,915$ ). Significantly elevated OR were observed for individual PAH (benzo[a]pyrene, benzo[g,h,i]perylene, and naphthalene) as well. Due to the use of birth certificates in the study, they were unable to adjust for maternal smoking or exposure to ETS during pregnancy. A third study that employed the use of personal air monitoring data, collected among non-smoking women during the third trimester of pregnancy, found that African American mothers, but not Dominican mothers, had nearly a 5-fold rise in odds of preterm birth in association with an ln-unit increase in PAH exposure in New York City (OR=4.68, 95%CI=1.84 to 11.9;  $n=224$ ) (Choi et al.

2008). These ORs were reported from models adjusted for maternal pre-pregnancy body mass index, infant sex and parity, season of delivery, and months of gestational ETS exposure.

Studies using various biomonitoring methods have similarly observed a positive association between PAH exposure and preterm birth. Singh and colleagues (2008) performed a small case-control study of non-smoking women in Lucknow, India, between 2005 and 2006, measuring PAH concentrations in placental tissue. Significantly higher levels of two individual PAH (fluoranthene and benzo(b)fluoranthene) in preterm cases ( $n=29$ ) compared to controls ( $n=31$ ) were found, although no adjustments were made for potential confounders. Also, in the aforementioned study of Guiyu, China, where e-waste recycling lead to high levels of environmental pollution, Guo and colleagues (2012) measured 7 carcinogenic PAH in umbilical cord blood in deliveries from Guiyu and from Chaonan, an uncontaminated area, for comparison ( $n=183$ , adverse birth outcomes=18). They observed generally higher values of the PAH measured in cord blood from adverse compared to normal births (adverse birth outcomes included infants born preterm, low birth weight, and with congenital malformations, as well as stillbirths). Furthermore, 2 individual PAH (chrysene and benzo[a]anthracene) were inversely associated with gestational age (Guo et al. 2012). Again, however, no adjustments were made for covariates, namely maternal smoking or ETS exposure.

Volatile organic compounds (VOC) are a large class of compounds that move readily from the liquid phase to air. These include some of the previously described drinking water contaminants, such as TCE and PCE, as well as many others such as acetone, benzene, and formaldehyde. Benzene is one VOC that has received significant attention because of its carcinogenic potential. It is released in many industrial processes into the air, and also from automobile emissions and tobacco smoke. Two studies examined the relationship between maternal benzene exposure and preterm birth. In the previously described study by Wilhelm et al. (2011), significantly increased odds of preterm birth were found in association with an interquartile range increase in benzene (adjusted OR=1.09, 95%CI=1.06 to 1.13). Further, a study in Valencia, Spain, examined benzene exposure measured via ambient air monitors and found elevated odds of preterm birth in individuals exposed to greater than  $2.7 \mu\text{g}/\text{m}^3$  across the duration of pregnancy (OR for  $1 \mu\text{g}/\text{m}^3$  increase in benzene exposure level = 6.46, 95%CI=1.58 to 26.4;  $n=785$ ) (Llop et al. 2010). Formaldehyde exposure was examined in relation to preterm birth in one publication with no significant results (Marozienė and Grazulevičienė 2002), but otherwise no studies examined associations between other VOC exposures and preterm birth.

### Limitations and recommendations

In summary, previous reviews strongly suggest associations between preterm birth and environmental exposures to (1)  $\text{SO}_2$ , (2)  $\text{PM}_{2.5}$ , and (3) ETS. Studies of PAH exposure and preterm birth indicate a relationship, although additional studies that address the importance of PAH compared to other components of the complex mixture, such as PM and ETS, would be useful. Studies on air pollutant exposures and preterm birth suffer from several limitations recently identified by Slama et al. (2008) at the International Workshop on Air Pollution and Human Reproduction. Moving forward, the workshop report called for (1) More prospective studies, (2) Attention to important confounders such as seasonality of exposure/delivery as well as maternal nutrition status (3) Advancement in exposure assessment methods, such as using biomarkers of exposure, and identifying key exposure windows (e.g., first trimester of pregnancy), and (4) Exploration of potential toxicologic mechanisms to explain exposure-outcome relationships (Slama et al. 2008). Addressing

these issues may help to better explore some of the associations observed to date between ambient air pollution exposures and preterm birth.

## METALS AND METALLOIDS

Metal and metalloid exposures have long been studied in association with adverse reproductive outcomes, and some results indicate associations with preterm birth. Although many early studies focused on women with occupational exposures, some also examined the association in populations exposed through ambient levels in the environment (Table 4, Figure 4).

### Lead

The largest number of studies examining the relationship between metal exposure and preterm birth has been for lead (Pb). Exposure to this metal has been well studied in association with adverse birth outcomes since its inclusion in gasoline resulted in high environmental exposures until it was phased out by the Environmental Protection Agency in 1975. Despite these efforts, exposure to Pb still occurs in the general population: It is released into air through various manufacturing processes and in combustion of fossil fuels, which results in inhalation exposures (ATSDR 2007b); use of Pb in pipes can lead to drinking water contamination; ceramics containing Pb glazes can be a source of exposure; and older Pb-based paints can flake leading to exposure via ingestion or inhalation of contaminated dusts. Pb has been associated with a range of adverse health outcomes, and, notably, there seems to be no threshold of exposure for most effects.

Lead exposure in relation to birth outcomes has been well-reviewed. Andrews and colleagues (1994) summarized early findings, including several occupational studies, reporting that Pb exposure was likely associated with increased risk of preterm birth, and that the effects were dose-dependent. The more recent publications are reviewed here.

In a case-cohort study in Mexico City from 1995, Torres-Sánchez et al. (1999) measured levels of Pb in umbilical blood of 161 preterm and 459 full term infants. They found, like previous studies, that increasing Pb levels were significantly associated with preterm birth, but, interestingly, only in infants born to primiparous women. Similar to previous studies, exposure levels in this population were relatively high (mean levels in firstborn preterm infant cord blood=9.77 µg/dL, in firstborn term infants=8.24 µg/dL) (Torres-Sánchez et al. 1999). Another study examining deliveries between 1996–2002 in a population of primarily Hispanic Californian women found that elevated ( $\geq 10$  µg/dL) blood Pb levels during pregnancy were associated with significantly elevated odds of preterm delivery (OR=4.2, 95%CI=1.3 to 13.9;  $n=262$ ) (Jelliffe-Pawlowski et al. 2006).

Since the elimination of Pb from gasoline, mean levels in human blood in the US have dropped almost 80% (Pirkle et al. 1994). Hence, there is particular interest in health effects associated with low exposures, or at blood levels less than 10 µg/dL. Studies of Pb exposure in lower ranges and preterm birth are less consistent. In 2002 Sowers and colleagues (2002) examined blood Pb levels at four time points throughout gestation in 705 pregnant women from Camden, New Jersey, where average blood Pb levels were approximately 1.2 µg/dL. No significant associations were noted with preterm birth, defined as <36 weeks gestation, in either cross-sectional or longitudinal analyses (Sowers et al. 2002). Similarly, in a large cohort study of births in upstate New York, Zhu et al. (2010) found that there was no significant increase in odds of preterm birth with maternal blood Pb measurements in the highest quartile of exposure compared to the lowest (3.1–9.9 µg/dL compared to  $\leq 1$  µg/dL;  $n=43,288$ ). In this study Pb was measured in maternal blood at or before delivery date, and

the average exposure level was 2.1 µg/dL (Zhu et al. 2010). Notably, exposure measurements were taken anywhere between last menstrual period and the date of delivery.

In 2010 Cantonwine et al. (2010a) pointed out that blood Pb levels during certain time points during pregnancy, particularly the first and second trimesters, may be especially predictive of preterm birth. In this study of mother-infant pairs in Mexico City conducted between 1997 and 1999, data showed that a one standard deviation increase in blood Pb levels measured during the second trimester was associated with significantly increased odds of preterm birth (OR=1.75, 95%CI=1.02 to 3.02; *n*=235) (Cantonwine et al. 2010a). However, associations with first or third trimesters, or with measures from umbilical cord blood, were not statistically significant (Cantonwine et al. 2010a). Exposures in this population were somewhat elevated but still below the CDC threshold (mean in whole blood 6.3–7.2 µg/dL in first through third trimesters) (Cantonwine et al. 2010a).

Two other studies found significant associations with preterm birth and low Pb levels in first trimester maternal blood or in placenta. Vigeh and colleagues (2011) observed that elevated maternal first trimester blood Pb levels were significantly associated with increased odds of preterm birth in Tehran, Iran (OR=1.41 with an ln-unit increase in blood Pb level, 95%CI=1.08 to 1.84; *n*=348). Falcon et al. (2003) found significantly higher Pb levels in placenta of adverse pregnancies, including those with premature rupture of the membranes and preterm delivery, compared to normal pregnancies in Spain (*n*=89). Addressing critical windows of exposure is a particularly important aspect of understanding chemical exposure associations with preterm birth; however the evidence for a specific window of susceptibility in relation to Pb exposure is still inconclusive.

### **Cadmium, Arsenic, and Mercury**

Cadmium (Cd) is found naturally in the earth, and is extracted for use in some products like batteries and metal coatings because of its anti-corrosive properties (ATSDR 2008). Low levels are also detected in nearly all foods, making ingestion the most common route of exposure in the general population. Results from studies examining the relationship between Cd exposure and preterm birth have been conflicting. An ecologic study conducted in southern Sweden between 1985 and 1990 found that there was no significant elevation in odds of shortened gestation in women who lived in areas with elevated exposure to Cd (*n*=38,718) (Landgren 1996). However, in a small case-control study from the early 1990s Fagher and colleagues (1993) found higher blood Cd levels in mothers who delivered preterm compared to term. The most recent study, conducted among a small cohort of women in China, found no significant associations between Cd measured in maternal whole blood, cord blood, or placenta and risk of preterm birth, defined as delivery  $\leq 37$  weeks gestation (*n*=44) (Zhang et al. 2004). Finally, one study examining Cd exposure in postnatal urine that did not fit within our inclusion criteria deserves mention since urinary Cd levels may be representative of long-term exposure. Nishijo and colleagues (2002) measured Cd levels 5–8 days following delivery in maternal urine in Toyama, Japan, an area of high Cd contamination (*n*=57, preterm=9). Mothers with high ( $\geq 2$  µg/g creatinine) vs. low ( $<2$  µg/g creatinine) urinary Cd concentrations had higher rates of preterm delivery.

Four studies investigated the relationship between preterm delivery and exposure to arsenic (As), a metalloid that is also found naturally in the environment. Exposure in small amounts may occur through ingestion of contaminated food and water, and higher exposures are possible in areas where As is found naturally at elevated levels in soil and groundwater, such as in certain regions of Bangladesh. All studies of As in relation to preterm birth have assigned exposure based on region of maternal residence, and thus had the aforementioned limitations of ecologic studies, although As species can be measured reliably in spot urine samples (Rivera-Nunez et al. 2010). The above study by Landgren (1996) found a slightly

decreased odds of preterm birth in women who resided in a municipality with less than mean study exposure levels during pregnancy. In a study in Bangladesh, Ahmad and colleagues (2001) found that women residing in areas with high exposure to As ( $>0.05$  mg/L in well water) had significantly higher preterm birth rates compared to women residing in low exposure areas ( $<0.02$  mg/L in well water) ( $n=192$ ). A study in Taiwan found an elevated, although non-significant, odds of preterm birth in association with residence in an area with a history of high well-water levels of As (OR=1.10, 95%CI=0.91 to 1.33;  $n=18,259$ ) (Yang et al. 2003). In a small subset from a cross-sectional study in another region of Bangladesh, Mukherjee and colleagues (2005) examined birth outcomes and observed no differences in rates of preterm birth in mothers exposed to drinking water with 284–400  $\mu\text{g/L}$  ( $n=21$ , preterm=8) or 401–1474  $\mu\text{g/L}$  ( $n=44$ , preterm=12) compared to those exposed to less than 3  $\mu\text{g/L}$  As ( $n=18$ , preterm=2). A study in Inner Mongolia, China, where exposure was assigned to mothers by averaging well-water levels in her respective village, did not find a significant change in odds of preterm birth (OR=1.02, 95%CI=0.72 to 1.44) with residence in a village with high exposure ( $>50$   $\mu\text{g/dL}$ ) ( $n=9,890$ ) (Myers et al. 2010).

Finally, mercury (Hg) exposure, which occurs primarily through ingestion of contaminated fish, has been linked to preterm birth in two epidemiologic studies. The aforementioned study by Landgren (1996) mothers residing in municipalities with greater than mean ground concentrations of Hg had slightly reduced OR for preterm birth. The Pregnancy Outcomes and Community Health (POUCH) Study, which recruited women in 5 communities throughout Michigan between their 15<sup>th</sup> and 27<sup>th</sup> weeks of pregnancy, assessed Hg exposure by measuring levels in hair samples ( $n=1,024$ ) (Xue et al. 2007). After adjustment for covariates including fish consumption, a significantly elevated odds of very preterm birth (defined as  $<35$  weeks gestation) was observed in association with Hg hair levels  $\geq 90^{\text{th}}$  percentile (OR=3.0, 95%CI=1.3 to 6.7), although the odds ratio for delivery  $<37$  weeks gestation was not significant (OR= 1.55, 95%CI=0.7 to 2.9) (Xue et al. 2007).

### Limitations and recommendations

Studies of metal and metalloid exposure and preterm birth provide evidence for an effect of Pb at higher levels, but studies at levels more consistent with current environmental exposure levels, or for Cd, As, or Hg, are inconclusive. Several limitations should be addressed in future studies examining these relationships. For one, investigation of other markers of exposure may be valuable. For example, blood Pb levels may more representative of transient exposures, and not of exposures that are long-term or cumulative. Bone scans are superior for cumulative Pb exposure measurement; however, it may be dangerous to perform them during pregnancy. Exploration of ways to better characterize women's more complete Pb exposure profile before and during pregnancy are recommended. For As, utilizing urinary biomarkers of exposure in studies on preterm birth could strengthen the existing evidence. Future studies should also be designed to identify whether there are increased risks of preterm birth associated with exposure to metals at "background" levels common among the general population, as most studies to date have focused on areas with elevated exposures.

## OTHER ENVIRONMENTAL CONTAMINANTS

In addition to the toxicants described above, numerous others may be capable of causing adverse reproductive outcomes including preterm birth. Identifying any of these potential links is particularly important for those compounds with widespread exposure. Few studies have examined associations between these compounds and preterm birth in particular, but in some instances there is preliminary data suggestive of an effect (Table 5, Figure 5).

## Phthalates

Phthalate diesters are commonly used both as plasticizers in products such as polyvinyl chloride, and also as ingredients in personal care products such as lotions and perfumes. Exposure may occur through ingestion of contaminated food and water as well as product use and is ubiquitous in the general US population, with most metabolites detectable in over 99% of urine samples (Silva et al. 2004). Research has identified phthalates as endocrine disruptors and reproductive toxicants, and two studies have examined the association between exposure and preterm birth. Adibi and colleagues (2009) examined the relationship between di(2-ethylhexyl) phthalate (DEHP) metabolites measured in 3<sup>rd</sup> trimester urine samples and odds of preterm birth in a cohort of women recruited between 2000 and 2004 in the Study for Future Families (SFF) ( $n=283$ ). Significantly decreased odds of preterm birth in association with log-unit increases in the metabolites mono-(2-ethylhexyl) phthalate (MEHP; OR=0.5, 95%CI=0.3 to 0.9), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP; OR=0.5, 95%CI=0.3 to 0.9), and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP; OR=0.4, 95%CI=0.2 to 0.9) were reported. Notably, the proportion of preterm deliveries in this cohort was very low (preterm=14). On the other hand, in a small case-control study of women who gave birth in Mexico City, Meeker et al. (2009) observed significantly increased odds of preterm birth in association with greater than median levels of the metabolites mono-butyl phthalate (MBP; OR=4.5, 95%CI=1.2 to 16.6), mono(2-ethyl-5-carboxypentyl) (MECPP; OR=3.4, 95%CI=1.0 to 12.0), and mono(3-carboxypropyl) phthalate (MCP; OR=3.2, 95%CI=1.0 to 9.8) in adjusted models of levels from 3<sup>rd</sup> trimester urine samples ( $n=60$ ). Results from studies examining exposures in relation to gestational age have been similarly conflicting (Suzuki et al. 2010; Whyatt et al. 2009; Wolff et al. 2008).

## Bisphenol-A (BPA)

BPA is a component of polycarbonate plastics and epoxy resins which are used primarily in the production of hard plastic containers and to line food cans, respectively. Exposure occurs primarily through the ingestion of contaminated food, and levels in urine were detected in over 92% of the US population (Calafat et al. 2008). BPA is weakly estrogenic, and may be associated with adverse reproductive health outcomes. However, only one study investigated the relationship between BPA and preterm birth. In the same case-control group of Mexican women in which urinary phthalate metabolites were measured, Cantonwine and colleagues (2010b) found that 3<sup>rd</sup> trimester total urinary BPA levels were suggestively associated with an increase in birth at  $\leq 37$  weeks gestation ( $n=30$  cases). When case definition was defined as  $< 37$  weeks ( $n=12$  cases) the relationship became statistically significant (Cantonwine et al. 2010b). Furthermore, elevated OR remained in models additionally adjusted for urinary phthalate levels. Although more studies are needed, this evidence is suggestive of a link between BPA exposure and preterm birth.

## Non-persistent pesticides

Persistent organochlorine pesticides have been replaced with a wide variety of nonpersistent pesticides with potential effects on humans that are only beginning to be studied. The general population may be exposed to these compounds through ingestion of food and/or hand-to-mouth contact with contaminated surfaces. Inhalation and dermal exposures may also occur. Exposures to agricultural workers and individuals who reside in agricultural areas are also of concern. Further, for some compounds, contamination of drinking water supplies may pose a threat to the general population.

Organophosphate pesticides are one class of these compounds, including chlorpyrifos, diazinon, malathion, parathion, and others, that are currently in common use in agricultural settings. Eskenazi and colleagues (2004) investigated associations between exposure to these

compounds and preterm birth within the Center for Health Assessment of Mothers and Children of Salinas (CHAMACOS), in a region of high agricultural production and pesticide use. In the cohort of 488 women, parent compounds and metabolites of dialkyl phosphate, chlorpyrifos, malathion, and other organophosphate metabolites were measured in two urine samples collected during gestation. Levels of cholinesterase, which are thought to be depressed by organophosphate exposure, were measured in maternal and cord blood at birth (Eskenazi et al. 2004). Although neither individual nor summed organophosphates or metabolites were associated with a change in odds of preterm birth, decreased cholinesterase (ChE) levels in umbilical and maternal blood were found to be associated with increased risk of preterm birth (adjusted OR=2.3, 95%CI=1.1 to 4.8, and OR=1.6, 95%CI=1.0 to 2.5 for  $\mu\text{mol/min/mL}$  increase in ChE, respectively) (Eskenazi et al. 2004). Although outside our inclusion criteria, the Agricultural Health Study examined exposure to organophosphates as well as other pesticides in relation to birth outcomes in a cohort of 2,246 births (Sathyanarayana et al. 2010). Exposure was based on mother's self-reported pesticide use, and no significant associations were identified.

Atrazine is one of the most used herbicides in agriculture. Although it is not bioaccumulative and breaks down readily in soil and air, it has a long half-life in water and hence poses a potential exposure threat to the general population (ATSDR 2003). Atrazine exposure can be assessed via biomarkers, but all three studies investigating its relationship with preterm birth thus far have estimated exposure by measuring levels in sources of drinking water and assigning subjects' exposure levels based on their proximity to those sources, potentially incurring ecologic bias. The first study examined rates of preterm birth in an agricultural district of France in association with atrazine levels in drinking water distribution units assessed regularly by the district health and social affairs bureau ( $n=3,510$ ) (Villanueva et al. 2005). Slight increases in the odds of preterm birth in association with the mothers' assigned exposure level were noted, although the results did not reach statistical significance. Notably, a high proportion of atrazine measurements in water were below the detection limit in this study.

The second study, by Ochoa-Acuña and colleagues (2009), involved residents in Indiana whose atrazine exposure levels were designated by use of specific Community Water Systems (CWS) where measurements were previously made ( $n=24,154$ ). In this analysis no significant change in prevalence of preterm delivery was identified in association with atrazine exposure category (Ochoa-Acuña et al. 2009). The third and most recent study, however, did report a significant rise in the odds of preterm birth in relation to increased atrazine levels in drinking water. This cross-sectional analysis of all births in Kentucky from 2004–2006 ( $n=71,768$ ) assigned exposure to mothers with average levels measured in their county of residence from 2000–2008 (Rinsky et al. 2012). Despite a high % of measures below assay limits of detection, Rinsky et al. (2012) observed a significantly elevated OR for the group exposed to the highest levels of atrazine compared to the lowest ( $\geq 0.081 \mu\text{g/L}$  vs.  $0 \mu\text{g/L}$ ; OR=1.22, 95%CI=1.16 to 1.29).

### Limitations and Recommendations

For non-persistent pesticides and potential endocrine disrupting compounds, very few studies exist examining their relationship with preterm birth. Evidence is conflicting for an effect of phthalates or atrazine; and although single studies identified relationships with preterm birth for BPA and organophosphate pesticides, additional studies to confirm or refute are necessary. Other issues that need to be addressed within this group of exposures include the following. First, more rigorous exposure assessment methods are necessary, particularly with respect to atrazine. Assigning subject-specific contamination levels by taking measurements in home water samples, adjusting for individual subject water-use

habits (e.g., use of tap water vs. bottle water), or utilizing biomarkers of exposure would all improve on the current studies. For phthalates and BPA, exposure biomarkers have been utilized but studies have been small. In addition, exposure assessment using biomarkers is limited by the fact that these compounds are rapidly metabolized in the human body. Using a single urine sample as an exposure metric may hence lead to measurement error and bias in results. Utilization of multiple exposure measurements throughout pregnancy would improve these estimates, and also help to identify potentially sensitive time points in gestation. Second, as some of these compounds have the potential to act through similar mechanisms, and, as exposure to a single compound might frequently coincide with exposure to another, assessment of effects of mixed exposures needs to be addressed.

## DISCUSSION AND CONCLUSIONS

Overall, the current literature examining associations between environmental contaminant exposures and preterm birth indicates strongly suggestive evidence for effects of some exposures, while results for others are inconclusive: (1) For POP, evidence is **strong** for a relationship between DDE exposure at high levels and preterm birth. Data is **suggestive** for DDE at lower levels and also for PFC, particularly in studies where biomarkers of exposure were used. Associations with other organochlorine pesticides, PCB, and PBDE are **inconclusive**; (2) For Drinking Water Contaminants examined in this review, including THM, HCA, PCE, and TCE, results from studies of preterm birth are **inconclusive**; (3) With regards to air pollution exposures, including criteria air pollutants and ETS (reviewed elsewhere), as well as PAH and VOC (reviewed here), support is **strong** for a relationship between SO<sub>2</sub>, PM, ETS, and PAH exposure and preterm birth, whereas results for other contaminants, including ozone, CO, NO<sub>x</sub>, and VOC are **inconclusive**; (4) Metal and metalloid studies suggest **strong** associations between high Pb exposure and preterm birth, but analyses with lower levels of Pb exposure, and those examining Cd, As, and HG, remain **inconclusive**; and finally (5) other environmental contaminants, including phthalates, BPA, organophosphate pesticides, and atrazine, have been insufficiently studied in this context and results are **inconclusive**.

### Additional studies with robust study designs emphasizing larger numbers of preterm deliveries are necessary

A clear limitation for assessment of potential effects related to several exposures is the small number of studies, despite the call for research on potential environmental causes of preterm birth from the Surgeon General and the Institute of Medicine (Ashton et al. 2009; Behrman and Butler 2007). Additionally, many of the existing studies suffer from small sample sizes and/or small numbers of preterm deliveries. Interestingly, in many instances, the proportions of preterm births in cohort populations are lower than would be expected in their respective countries or communities. This could be a result of truly lower percentage in populations studied, lower participation from individuals with greater likelihood of delivering preterm, or a decrease in preterm deliveries due to selection criteria. Lower participation by individuals who eventually deliver preterm is a challenging issue to address, and may not be a significant problem if that probability is unrelated to exposure status. Selection criteria, on the other hand, need to be more carefully considered in study design. Some advantages to excluding subjects based on criteria that are unrelated to exposure exist. However in some instances there may be, despite being unidentified, relationships between risk factors for preterm birth and environmental exposures. For example, hypertension during pregnancy, a common exclusion factor, may be related to environmental exposures as well, and in fact could be part of the mechanistic pathway underlying a relationship between that exposure and preterm birth. Investigating such variables during statistical analysis as opposed to initial exclusion could not only improve ability to detect associations but also provide

insight into why those relationships exist. Information to be gained needs to be balanced with budget considerations, however, because in order to make a clear comparison between such subgroups a larger sample size is necessary.

### **Nested case-control populations may be particularly useful, but potential consequences of using this study design deserve more careful consideration**

Case-control studies have similar issues with small sample size and potentially problematic exclusion criteria. The latter is compounded by the fact that most case-control studies measuring exposures during pregnancy, particularly those utilizing biomarkers, are nested within larger prospective cohorts. So, while case-control studies may be useful in offering more power in assessing associations between environmental exposures and preterm birth, a frequent consequence is the constraints of the design of the parent cohort study. The exclusion criteria and other study characteristics of the original study need to be carefully considered before undertaking a nested analysis. In general, however, when these limiting factors are minimized, nested case-control studies offer much power for assessing these associations. Further, power in these analyses can be amplified with the creation of collaborations between multiple studies, as has been done recently with European birth cohorts (Vrijheid et al. 2012).

### **Exposure assessment methods need to address effects of contaminants at a range of exposure levels and at additional time points during gestation**

Exposure assessment approaches are limited across the literature on this topic as they are with others. These have been described in regard to individual exposures above. However, several overarching issues exist which should be addressed in future research. First, more precise exposure assessment metrics are necessary. In some instances this may require pairing measurements of contaminant levels in drinking water with questionnaire data to provide more complete information about maternal intake. It may also mean the use of biomarkers of exposure. These measures, however, should be interpreted with caution. For example, maternal physiologic changes that occur during pregnancy can affect where a contaminant is compartmentalized and how diluted it is in various matrices which may greatly impact concentrations measured in biologic specimens. As some of these factors in turn may be related to preterm birth, there is potential for confounding or the possibility for reverse causation in observed associations. For non-persistent compounds, the nature of exposure sources and pathways as well as toxicokinetics for a particular agent, which can greatly impact within-person variability and likelihood for exposure measurement error, need to be carefully considered.

Second, timing of exposure needs to be considered more carefully (Makri et al. 2004). Whether it occurs during the first or third trimester, or uniformly across pregnancy, may be a particularly important component of these relationships. For instance, as suggested by Cantonwine et al. (2010a), Pb susceptibility may be particularly high during the second trimester of pregnancy, but few studies examined the exposure-preterm birth relationship with measures from that time-period. Therefore, real effects may be obscured by lack of studies using exposure measurements from the most sensitive time in gestation. Furthermore, better understanding sensitive time periods of exposure may also be crucial for identifying the mechanisms of effect; for example, exposures during the first trimester may be impairing placentation whereas those in the third trimester may be activating inflammation pathways directly feeding into preterm parturition pathways. While studies among highly exposed populations (i.e., those subjected to specific occupational or environmental sources of exposure) are vital for detecting associations and providing valuable dose-response information at the high end of the exposure distribution, close attention needs to also be paid to effects at lower levels of exposure. It will be especially

important, as efforts are made to reduce particularly high exposures (as with Pb), to determine whether thresholds of effect exist for chemical associations with preterm birth, and to see what shape dose-response relationships follow.

### **Dichotomizing preterm birth by the 37 week cutoff may be insufficient**

Studies have fairly consistently used the clinically recognized time point of 37 completed weeks gestation as a cutoff for indicating preterm birth. This is useful because it offers comparability in the literature both within the context of each exposure and also in relation to mortality and morbidities associated with being born preterm. However, several different aspects of preterm birth may be important to measure in these studies as well. First, preterm births can be separated into multiple categories which few studies in this context have done previously. Preterm births can be both spontaneous, due to largely unknown factors, or they can be induced, which is generally the result of maternal or fetal complications. Combining these categories may be diluting effects. For example, if environmental exposures are playing a larger role in spontaneous preterm births, but not in those that are induced, pooling all cases may be causing, in effect, outcome misclassification and a null bias in results. Spontaneous preterm births can be further categorized as well. McElrath and colleagues (2008), using data from extremely preterm births (<28 weeks) suggested that these data should be divided into two groups based on etiology for epidemiologic studies. These groups include: (1) cases arising from intrauterine inflammation; and (2) those resulting from abnormal placentation. Other divisions, by biological mechanism or clinical presentation, have also been identified previously (Klebanoff and Shiono 1995; Savitz 2008; Savitz et al. 1991). Despite increases in cost and sample size, investigating these more specific outcomes might be helpful in identifying environmental chemical exposures that contribute to risk of preterm birth and also in explaining mechanisms of chemical toxicity.

A second question that arises in assessing preterm birth as an outcome is the 37 week cutoff. In addition to this division, many papers have also examined the relationship between environmental exposures and gestational age at delivery as a continuous outcome. The limitation to this approach is that a change in number of days gestation may be difficult to interpret in terms of clinical relevance, whereas preterm and very preterm have clear adverse associations. However, newer studies suggest that there may be no threshold for an effect of gestational age on neonatal mortality or adverse health outcomes later in life (Boyle et al. 2012; Clark et al. 2009; Zhang and Kramer 2009). A better understanding of the value in measuring associations with preterm birth compared to this continuous measure deserves attention.

### **A better understanding of pathways by which contaminants cause preterm birth is crucial**

Another aspect that has been insufficiently recognized in this area is the understanding of mechanisms that may connect environmental exposures with preterm birth. Identifying the underlying pathways could help to significantly improve future study in many ways: (1) As mentioned previously, understanding mechanism could improve study design and analysis, and the ability to detect true associations; (2) Identifying potential mechanisms in epidemiologic studies could fuel toxicological lab research on the same topic, and combining efforts in these fields could produce powerful results; and (3) Knowledge of a pathway connecting an environmental exposure to preterm birth could inform interventions for remediating effects, where reducing or eliminating exposures is not possible.

### **No studies using contaminant-specific exposure measurements have examined the relationship between preterm birth and mixed exposures**

Assessing exposure to mixtures of chemicals is an important next step (de Rosa et al. 2004). Since pregnant women are exposed to many different toxicants throughout the duration of

pregnancy, this is a more realistic approach to assessing the relationship between a mother's environment and preterm birth. In addition, if many chemicals are acting through similar or complementary mechanisms, there may be additive effects of these combinations that deserve to be explored.

In conclusion, this review comprehensively and systematically summarizes studies that have been conducted to date on environmental chemical exposures and preterm birth, an important public health concern. Furthermore, it identifies specific and general limitations to these studies and provides a framework for future research in this area. Many suggestive relationships have been demonstrated between environmental contaminants and preterm birth, but a larger number of robust studies are necessary to draw clear conclusions in order to positively impact public health and clinical practice.

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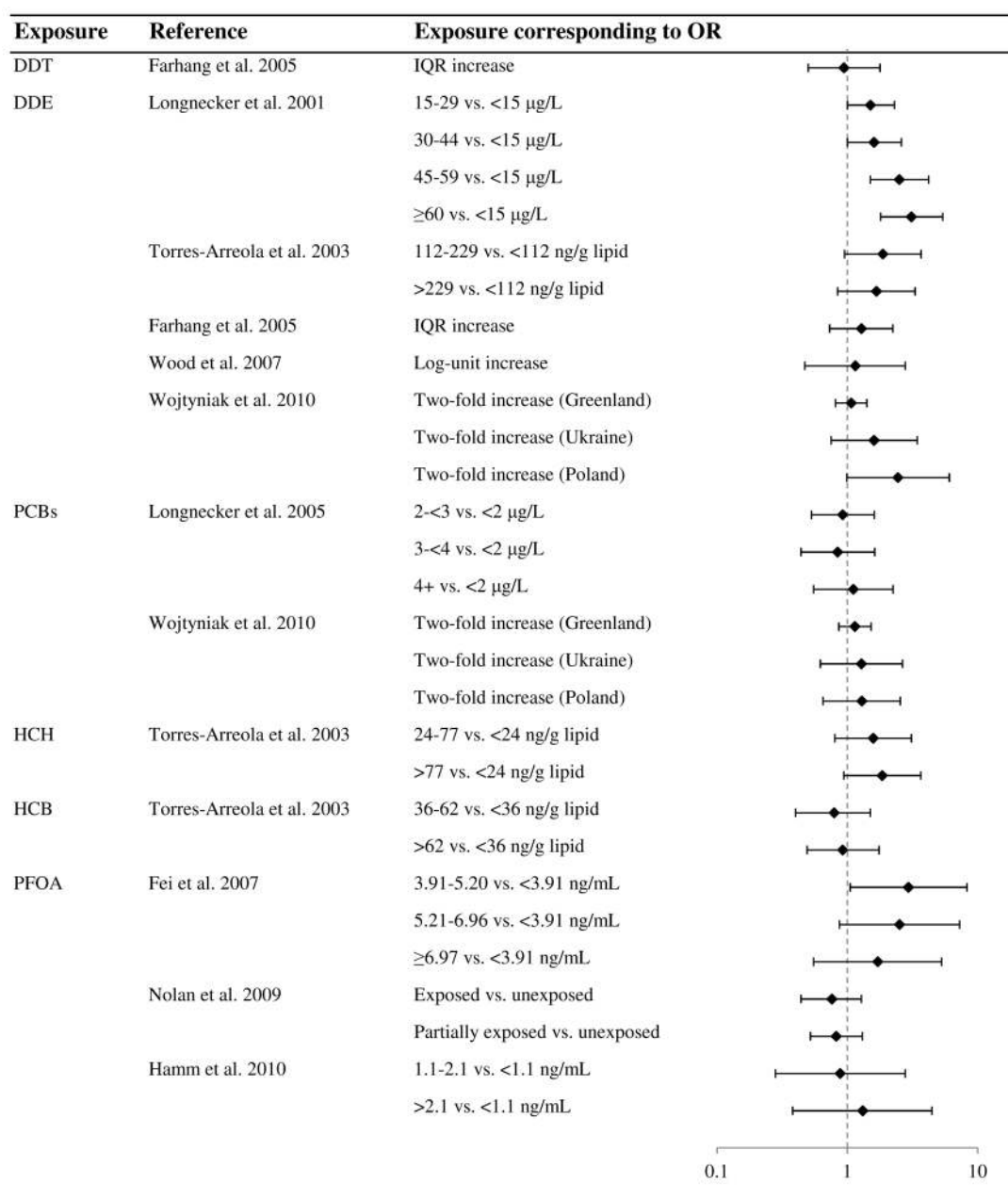
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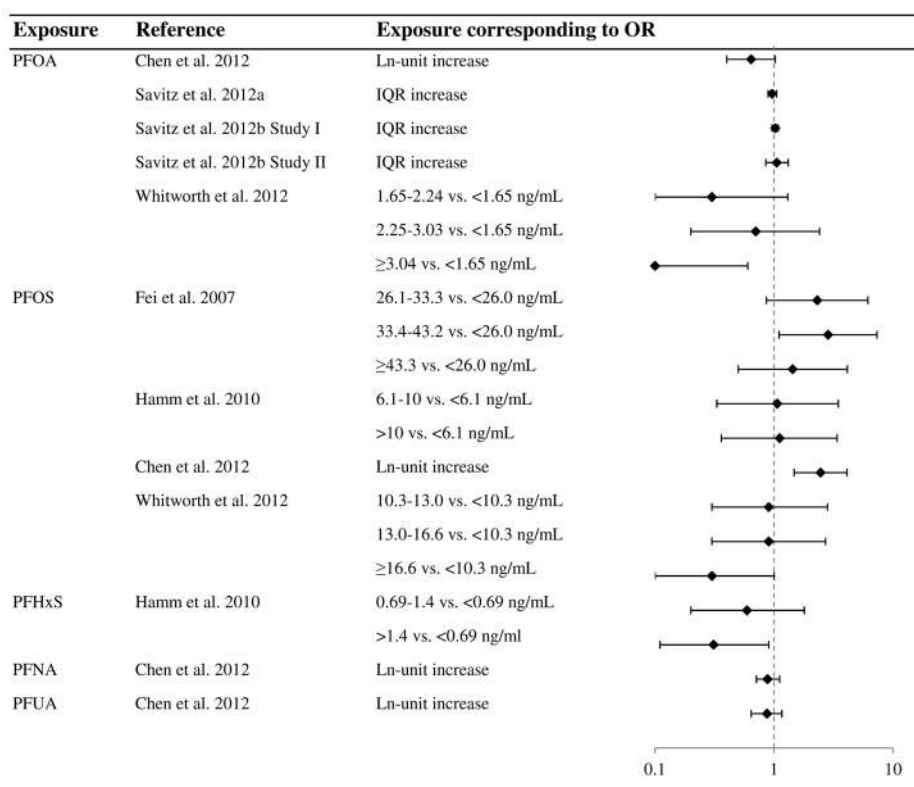
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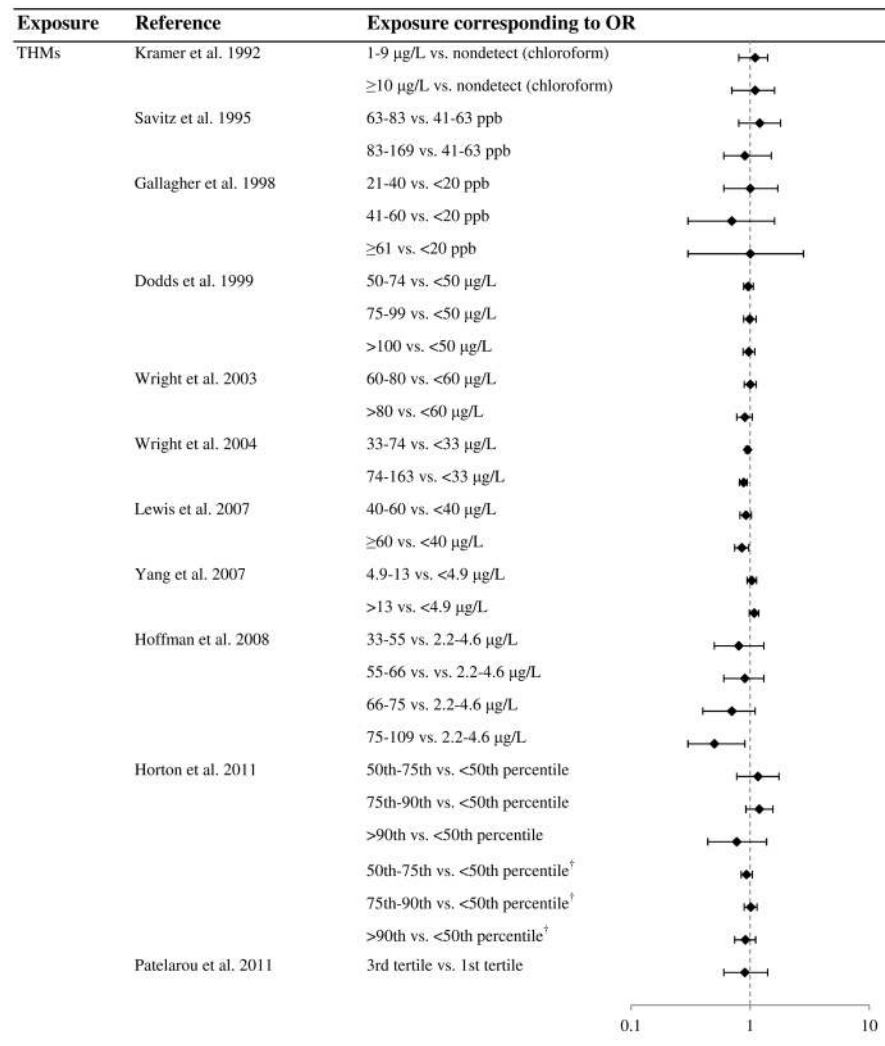
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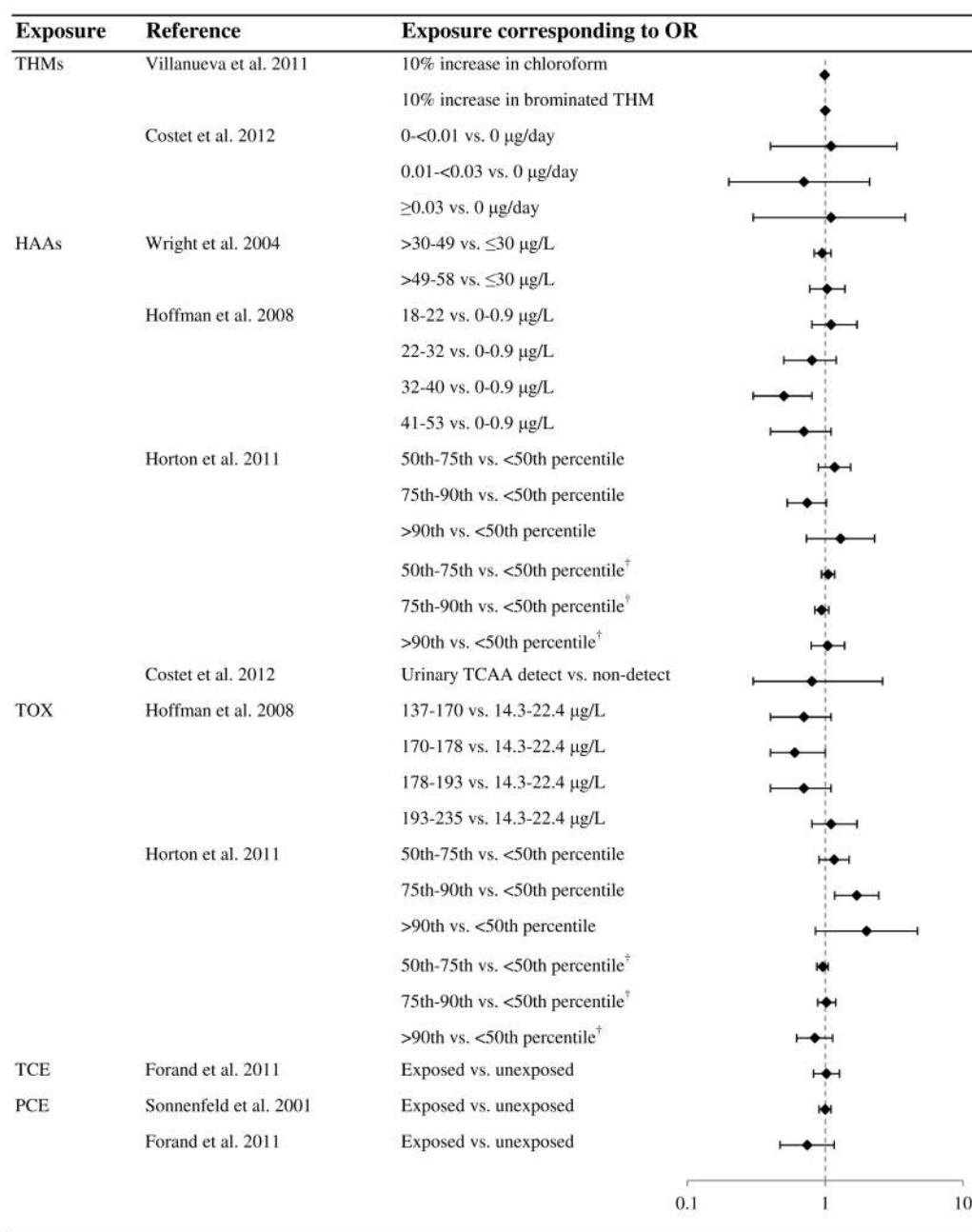


**Figure 1.**

Odds ratios and 95% confidence intervals for studies of persistent organic pollutants in relation to preterm birth

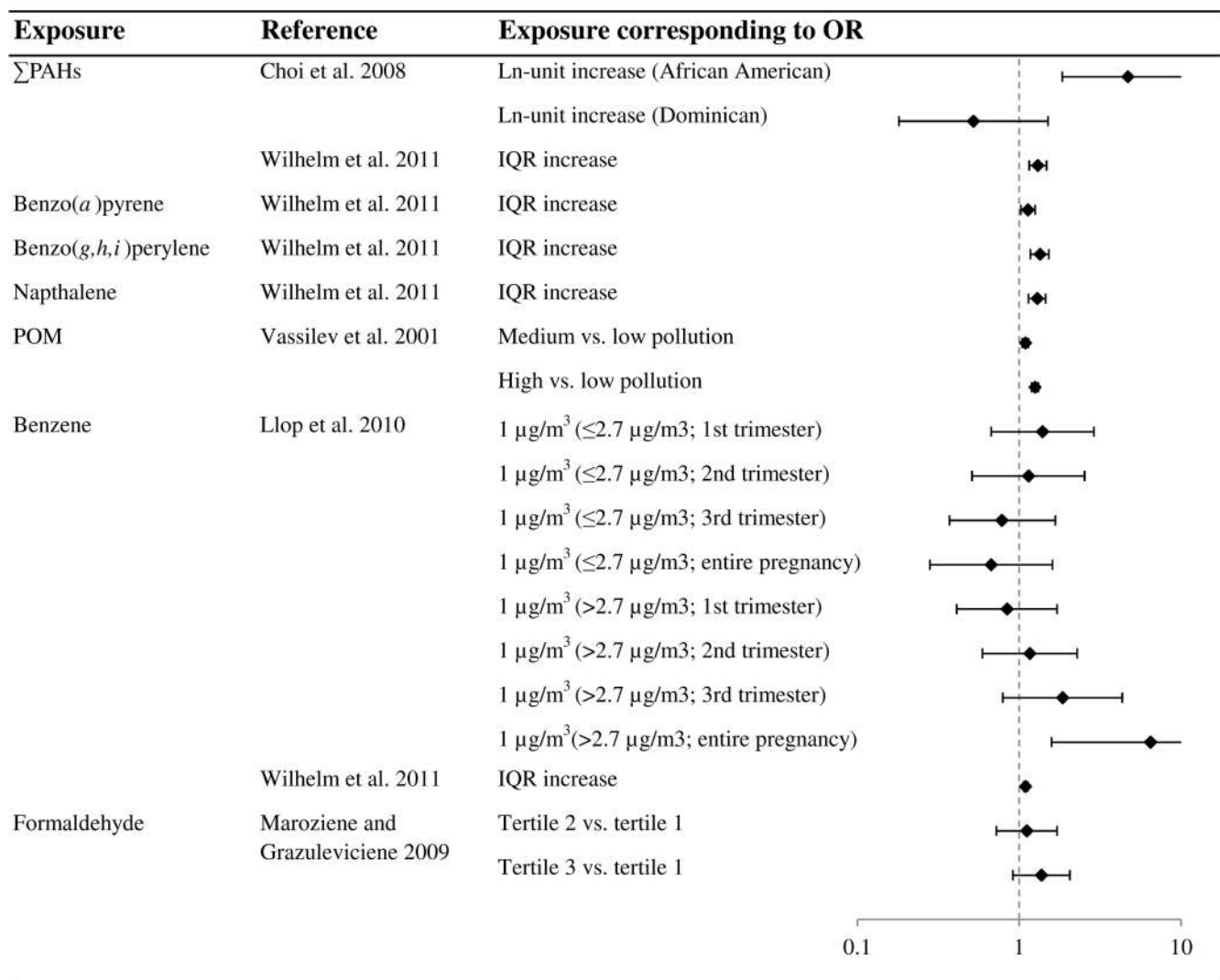
*Note.* Adjusted odds ratios are presented where available. Results for Hamm et al. 2010 are risk ratios. For Longnecker et al. 2005 OR are for summed PCB. For Wojtyniak et al. 2010 OR are for PCB-153. Abbreviations: Dichlorodiphenyltrichloroethane (DDT); dichlorodiphenyldichloroethylene (DDE); polychlorinated biphenyls (PCBs); hexachlorobenzene (HCB); hexachlorohexane (HCH); perfluorooctanoic acid (PFOA); perfluorooctane sulfonic acid (PFOS); perfluorohexane sulfonate (PFHxS); perfluorononanoic acid (PFNA); perfluoroundecanoic acid (PFUA); interquartile range (IQR).



**Figure 2.**

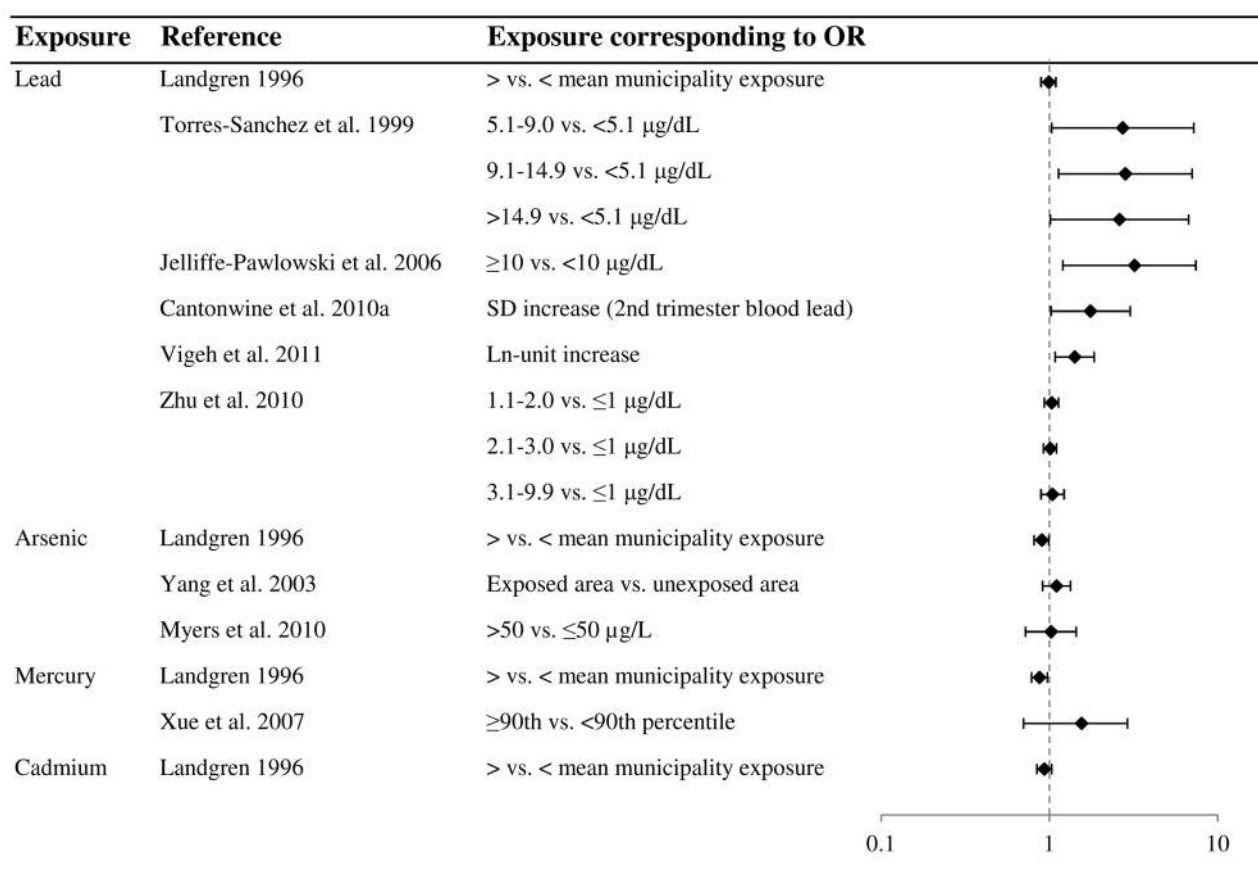
Odds ratios and 95% confidence intervals for studies of drinking water contaminants in relation to preterm birth

*Note.* Adjusted odds ratios are presented where available. Results for Dodds et al. (1999), Hoffman et al. (2008), and Forand et al. (2011) are risk ratios. Results for Lewis et al. (2007) are hazard ratios. Results for Horton et al. 2011 are presented for both brominated and chlorinated (<sup>†</sup>) contamination sites. When OR were given for more than one window of exposure, average exposure across duration of pregnancy was preferentially presented. Abbreviations: Trihalomethanes (THMs); haloacetic acids (HAAs); trichloroacetic acid (TCAA); total organic halides (TOX); trichloroethylene (TCE); tetrachloroethylene (PCE).

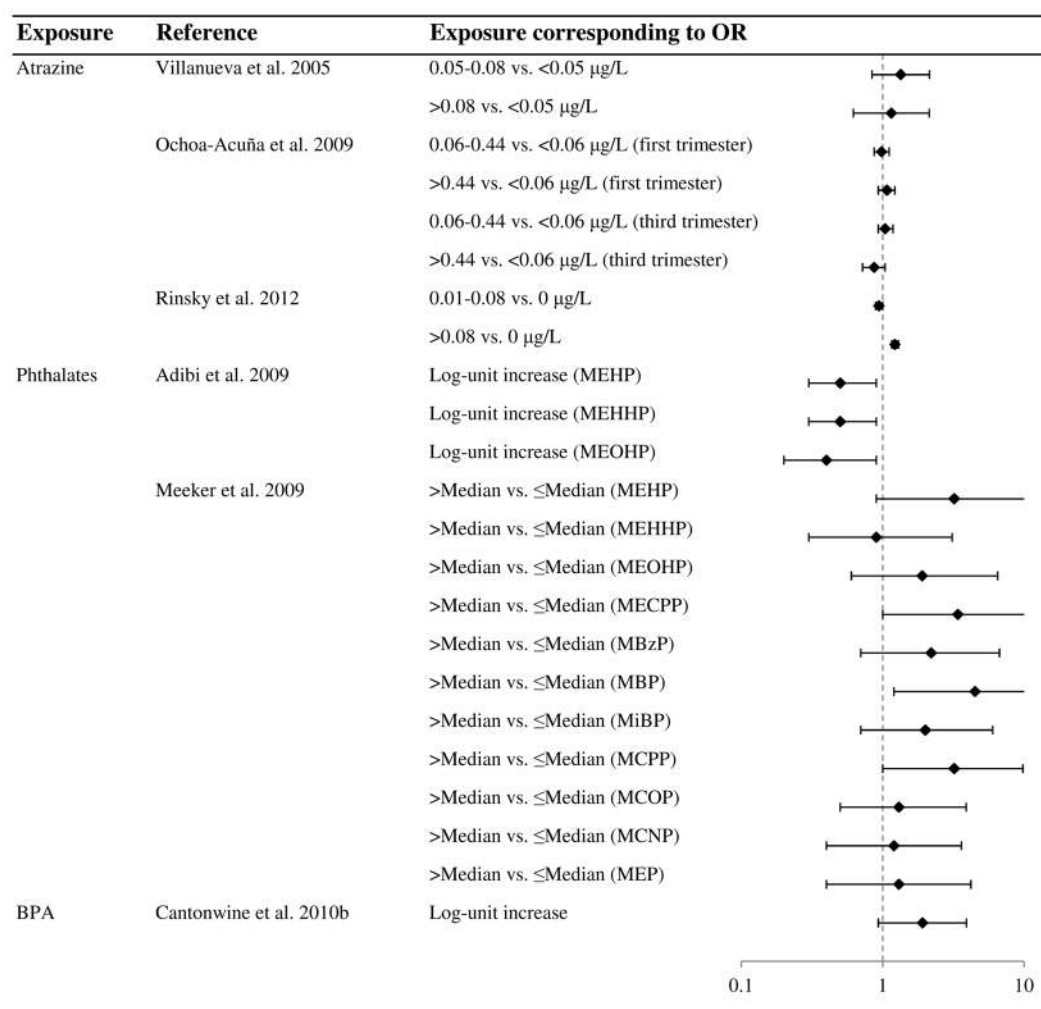
**Figure 3.**

Odds ratios and 95% confidence intervals for studies of atmospheric pollutants in relation to preterm birth

*Note.* Abbreviations: Polycyclic aromatic hydrocarbons (PAHs);interquartile range (IQR).



**Figure 4.**  
Odds ratios and 95% confidence intervals for studies of metals and metalloids in relation to preterm birth

**Figure 5.**

Odds ratios and 95% confidence intervals for other environmental contaminants in relation to preterm birth

*Note.* Adjusted odds ratios are presented where available. Abbreviations: Mono(2-ethylhexyl) phthalate (MEHP); mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP); mono(2-ethyl-5-oxohexyl) phthalate (MEOHP); mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); monobenzyl phthalate (MBzP); mono-*n*-butyl phthalate (MBP); mono-isobutyl phthalate (MiBP); mono(3-carboxypropyl) phthalate (MCCP); monocarboxyisooctyl phthalate (MCOP); monocarboxyisononyl phthalate (MCNP); monoethyl phthalate (MEP); bisphenol-A (BPA).

Table 1

Studies of persistent organic pollutants in relation to preterm birth

Study					Exposure		
Reference	Design	Location	Sample size	Timing	Assessment	Chemical	Level
Saxena et al. 1981	Case-control	Lucknow, India	n=40 preterm=15	Delivery	Maternal blood and placental tissue	<i>p,p'</i> -DDT <i>p,p'</i> -DDE <i>p,p'</i> -DDD HCB Lindane Aldrin	4.5±4.1 ppb 12.6±7.0 ppb 6.9±7.9 ppb 52.2±18.2 ppb 18.9±8.80 ppb 11.1±7.30 ppb
Procianny and Schvarzman 1981	Case-control	Sao Paulo, Brazil	n=54 preterm=24	Delivery	Maternal and cord blood	<i>p,p'</i> -DDT	10.5±10.6 µg/L
Wassermann et al. 1982	Case-control	Jerusalem, Israel	n=27 preterm=17	3 <sup>rd</sup> trimester to delivery	Maternal serum	<i>p,p'</i> -DDE <i>p,p'</i> -DDT <i>p,p'</i> -DDE <i>p,p'</i> -DDD ΣPCBs HCB	20.0±13.6 µg/L 2.9±3.0 ppb 10.7±6.1 ppb 3.3±2.2 ppb 19.3±10.3 ppb 4.3±4.8 ppb
Berkowitz et al. 1996	Case-control	New York, NY	n=40 preterm=20	1 <sup>st</sup> trimester	Maternal serum	Dieldrin Heptachlor <i>p,p'</i> -DDE	1.1±1.4 ppb 3.0±4.2 ppb 1.35 ng/mL <sup>†</sup>
Longnecker et al. 2001	Cohort	11 US cities	n=2,380 preterm=361	3 <sup>rd</sup> trimester	Maternal serum	ΣPCBs <i>p,p'</i> -DDE	1.70 ng/mL <sup>†</sup> 25.0 µg/L <sup>†</sup>
Ribas-Fitó et al. 2002	Cohort	Flix, Spain	n=72 preterm=4	Delivery	Maternal and cord serum	<i>p,p'</i> -DDE ΣPCBs HCB β-HCH	0.85 ng/mL <sup>†</sup> 0.27 ng/mL <sup>†</sup> 1.13 ng/mL <sup>†</sup> 0.54 ng/mL <sup>†</sup>
Torres-Arreola et al. 2003	Case-cohort	Mexico City, Mexico	n=233 preterm=100	Delivery	Maternal serum	<i>p,p'</i> -DDE HCB β-HCH	153 ng/g lipid <sup>†</sup> 45.8 ng/g lipid <sup>†</sup> 54.3 ng/g lipid <sup>†</sup>
Farhang et al. 2005	Cohort	San Francisco, CA	n=420 preterm=33	2 <sup>nd</sup> trimester to delivery	Maternal serum	DDT	11 µg/L <sup>†</sup>

Study							Exposure	
Reference	Design	Location	Sample size	Timing	Assessment	Chemical	Level	
Longnecker et al. 2005	Cohort	11 US cities	n=1,034 preterm=132	3 <sup>rd</sup> trimester	Maternal serum	DDE	43 µg/L <sup>†</sup>	
Apelberg et al. 2007	Cross-sectional	Baltimore, MD	n=293 preterm=38	Delivery	Cord serum	ΣPCBs	2.80 µg/L <sup>†</sup>	
Fei et al. 2007	Cohort	Denmark	n=1,400 preterm=53	1 <sup>st</sup> trimester, 2 <sup>nd</sup> trimester, and delivery	<b>Maternal</b> and cord plasma	PFOA	1.6 ng/mL <sup>†</sup>	
						PFOS	5 ng/mL <sup>†</sup>	
						PFOA	5.6±2.5 ng/mL	
Wood et al. 2007	Case-control	Alberta, Canada	n=78 preterm=26	1 day postpartum	Maternal serum	PFOS	35.3±13.0 ng/mL	
						DDE	69.3 ng/g lipid <sup>†</sup>	
Nolan et al. 2009	Cross-sectional	Washington County, Ohio	n=1,555 preterm=200	Entire pregnancy	Drinking water	PFOA	0.0–5.7 µg/L <sup>†</sup>	
Pathak et al. 2009	Case-control	Delhi, India	n=46 preterm=23	Delivery	<b>Maternal</b> and cord blood	<i>p,p'</i> -DDT	1.66±1.18 ng/mL	
						<i>p,p'</i> -DDE	3.70±2.63 ng/mL	
						ΣHCH	8.59±8.11 ng/mL	
Hamm et al. 2010	Cohort	Alberta, Canada	n=252 preterm=21	2 <sup>nd</sup> trimester	Maternal serum	PFOA	1.3±2.9 ng/mL <sup>‡</sup>	
						PFOS	7.4±2.0 ng/mL <sup>‡</sup>	
						PFHxS	1.1±3.0 ng/mL <sup>‡</sup>	

Study							Study	
Reference	Design	Location	Sample size	Timing	Assessment	Chemical	Level	
Wojtyniak et al. 2010	Cohort	Greenland	n=572 preterm=28	Entire pregnancy	Maternal serum	<i>p,p'</i> -DDE	274±2.9 ng/g lipid <sup>‡</sup>	
		Kharkiv, Ukraine	n=611 preterm=12			PCB-153	105±2.8 ng/g lipid <sup>‡</sup>	
						<i>p,p'</i> -DDE	653±1.8 ng/g lipid <sup>‡</sup>	
		Warsaw, Poland	n=258 preterm=12			PCB-153	25.7±1.9 ng/g lipid <sup>‡</sup>	
						<i>p,p'</i> -DDE	357±1.9 ng/g lipid <sup>‡</sup>	
Bergonzi et al. 2011	Cohort	Brescia, Italy	n=70 preterm=4	Delivery	<b>Maternal serum</b> and adipose tissue, cord serum, placental tissue	PCB-153	9.0±2.1 ng/g lipid <sup>‡</sup>	
						<i>p,p'</i> -DDE	124 ng/g lipid <sup>‡</sup>	
						ΣPCBs	229 ng/g lipid <sup>‡</sup>	
Chen et al. 2012	Cohort	Taipei and New Taipei, Taiwan	n=429 preterm~40	Delivery	Cord blood	HCB	20 ng/g lipid <sup>‡</sup>	
						PFOA	1.84±2.23 ng/mL <sup>‡</sup>	

Study						
Reference	Design	Location	Sample size	Timing	Assessment	Chemical Level
Atbuckle et al. 2012	Cohort	Ottawa, Canada	n=100 preterm=3	Delivery	Cord serum	PFOA 5.94±1.95 ng/mL <sup>‡</sup>
						PFOA 2.36±4.74 ng/mL <sup>‡</sup>
						PFOA 10.3±3.07 ng/mL <sup>‡</sup>
						PFOA 1.47 ng/mL <sup>‡</sup>
						PFOA 4.44 ng/mL <sup>‡</sup>
Savitz et al. 2012a	Cohort	Ohio and West Virginia	n=11,737 preterm=1,843	Entire pregnancy	Modeling of maternal serum concentrations	PFOA 0.36 ng/mL <sup>‡</sup>
						PFOA 0.58 ng/mL <sup>‡</sup>
						PFOA 6.0–15.9 ng/mL <sup>†</sup>
						PFOA 7.7 ng/mL <sup>†</sup>
						PFOA 13.4 ng/mL <sup>†</sup>
Savitz et al. 2012b Study I	Cohort	Ohio and West Virginia	n=7,308 preterm=3,613	Early pregnancy	Modeling of maternal serum concentrations	PFOA 2.2 ng/mL <sup>†</sup>
						PFOA 13.0 ng/mL <sup>†</sup>
						PFOA 9.76±5.05 ng/mL
						PFOA 2.2 ng/mL <sup>†</sup>
						PFOA 13.0 ng/mL <sup>†</sup>
Savitz et al. 2012b Study II	Cohort	Ohio and West Virginia	n=4,547 preterm=405	Early pregnancy	Modeling of maternal serum concentrations with data on residential history	PFOA 2.2 ng/mL <sup>†</sup>
						PFOA 13.0 ng/mL <sup>†</sup>
						PFOA 9.76±5.05 ng/mL
						PFOA 2.2 ng/mL <sup>†</sup>
						PFOA 13.0 ng/mL <sup>†</sup>
Whitworth et al. 2012	Cohort	Norway	n=901 preterm=35	2 <sup>nd</sup> trimester	Maternal plasma	PFOA 2.2 ng/mL <sup>†</sup>
						PFOA 13.0 ng/mL <sup>†</sup>
						PFOA 9.76±5.05 ng/mL
						PFOA 2.2 ng/mL <sup>†</sup>
						PFOA 13.0 ng/mL <sup>†</sup>
Wu et al. 2012	Cohort	Guiyu and Chaonan, China	n=167 cases=8	Delivery	Maternal serum	PFOA 2.2 ng/mL <sup>†</sup>
						PFOA 13.0 ng/mL <sup>†</sup>
						PFOA 9.76±5.05 ng/mL
						PFOA 2.2 ng/mL <sup>†</sup>
						PFOA 13.0 ng/mL <sup>†</sup>

*Note.* Levels represent means±standard deviations, medians (<sup>†</sup>), or geometric means±geometric standard deviations (<sup>‡</sup>) of chemicals measured in all subjects pooled or in controls alone where pooled information was not available. If exposure was assessed in multiple matrices, levels from the bolded matrix are presented. Ranges represent minimum to maximum median levels from study subgroups where overall medians not presented. For drinking water levels averages that included values below the limit of detection were preferentially presented. See Figure 1 for results. Abbreviations: Dichlorodiphenyltrichloroethane (DDT); dichlorodiphenyldichloroethylene (DDE); polychlorinated biphenyls (PCBs); hexachlorobenzene (HCB); hexachlorohexane (HCH); perfluorooctane sulfonic acid (PFOS); perfluorohexane sulfonate (PFHxS); perfluorooctanoic acid (PFOA); perfluorodecanoic acid (PFDA); perfluoroundecanoic acid (PFNA); perfluorododecanoic acid (PFDoA); perfluorotridecanoic acid (PFTeA); perfluorotetradecanoic acid (PFTeA); perfluoropentadecanoic acid (PFPeA); perfluorohexadecanoic acid (PFHxS); brominated diphenyl ether (BDE); parts per billion (ppb).

Table 2

Studies of drinking water contaminants in relation to preterm birth

Study		Exposure						
Reference	Design	Location	Sample size	Timing	Assessment	Chemical	Level	
Kramer et al. 1992	Case-control	Iowa	n=2,052 preterm=342	Entire pregnancy	Drinking water	Chloroform	1 µg/L <sup>†</sup>	
Bove et al. 1995	Cross-sectional	New Jersey	n=80,938 preterm=7,167	Entire pregnancy	Drinking water	TCE	55 ppb	
						PCE	14 ppb	
						TTHMs	144 ppb	
Savitz et al. 1995	Case-control	North Carolina	n=577 preterm=244	3 <sup>rd</sup> trimester	Drinking water	TTHMs	Not reported	
Gallagher et al. 1998	Cohort	Denver, CO	n=1,893 preterm=68	3 <sup>rd</sup> trimester	Drinking water	TTHMs	Not reported	
Dodds et al. 1999	Cohort	Nova Scotia, Canada	n=49,842 preterm=3,173	3 <sup>rd</sup> trimester	Drinking water	TTHMs	Not reported	
Sonnenfeld et al. 2001	Cross-sectional	Camp Lejeune, NC	n=11,798 preterm=832	Entire pregnancy	Drinking water	PCE	Not reported	
Wright et al. 2003	Cross-sectional	Massachusetts	n=56,513 preterm=3,173	Entire pregnancy	Drinking water	TTHMs	25.5–34.8 µg/L <sup>†</sup>	
Wright et al. 2004	Cross-sectional	Massachusetts	n=196,000 preterm=11,580	3 <sup>rd</sup> trimester	Drinking water	TTHMs	38.2±27.0 µg/L	
Aschengrau et al. 2008	Cohort	Massachusetts	n=2,125 preterm=96	Conception	Drinking water	HAA5	31.4±13.6 µg/L	
						PCE	0.9 g/month per residence	
Lewis et al. 2007	Case-control	Massachusetts	n=37,498 preterm=2,813	1 <sup>st</sup> –3 <sup>rd</sup> trimester and pregnancy average	Drinking water	TTHMs	Not reported	
Yang et al. 2007	Cohort	Taiwan	n=90,848 preterm=2,818	Entire pregnancy	Drinking water	TTHMs	Not reported	
Hoffman et al. 2008	Cohort	3 US sites	n=2,039 preterm=185	2 <sup>nd</sup> trimester	Drinking water	TTHMs	42.4±32.4 µg/L	
						HAA5	20.0±17.3 µg/L	
						TOX	119±79.8 µg/L	
Forand et al. 2011	Cross-sectional	New York	n=1,090 preterm=93	Delivery	Indoor air	TCE	0.18–140 µg/m <sup>3</sup>	
						PCE	0.1–24 µg/m <sup>3</sup>	
Horton et al. 2011	Cohort	US site with brominated DBP contamination	n=3,946 preterm=438	2 <sup>nd</sup> trimester	Drinking water	TTHMs	60.4±20.7 µg/L	
						HAA5	21.5±5.9 µg/L	

Study		Exposure				
Reference	Design	Location	Sample size	Timing	Assessment	Chemical Level
Patelarou et al. 2011	Cohort	US site with chlorinated DBP contamination	n=27,177 preterm=2,201		TOX	186±35.1 µg/L
					TTHMs	63.3±23.1 µg/L
					HAAs	33.2±12.1 µg/L
					TOX	171±37.3 µg/L
Villanueva et al. 2011	Cohort	Crete, Greece	n=1,359 preterm=156	Each trimester and pregnancy average	Drinking water	3.71±5.75 µg/L
					TTHMs	5.9–114.7 µg/L
Costet et al. 2012	Case-control	Brittany, France	n=513 preterm=114	1 <sup>st</sup> trimester	Maternal urine	0.03 mg/L <sup>†</sup>
				3 <sup>rd</sup> trimester	Drinking water	41.6±16.1 µg/L

*Note.* Levels represent means±standard deviations, medians (<sup>†</sup>), or geometric means±geometric standard deviations (<sup>‡</sup>) of chemicals measured in all subjects pooled or in controls alone where pooled information was not available. Ranges represent medians across multiple seasons for Wright et al. (2003), range of indoor air concentrations observed for Forand et al. (2011), and medians across multiple sites for Villanueva et al. (2011). Table adapted in part from Grellier et al. (2010). Exposures estimated from drinking water levels were often combined with modeling of data on maternal water consumption and household use. In some studies levels for individual THM or HAA were presented, however they are not included here for the sake of brevity. See Figure 2 for results. Abbreviations: Trichloroethylene (TCE); tetrachloroethylene (PCE); total trihalomethanes (TTHMs); haloacetic acids (HAAs); total organic halides (TOX); trichloroacetic acid (TCAA); parts per billion (ppb).

Table 3

Studies of atmospheric pollutants in relation to preterm birth

Study						Exposure		
Reference	Design	Location	Sample size	Timing	Assessment	Chemical	Level	
Vassilev et al. 2001	Cross-sectional	New Jersey	n=214,493 preterm=13,989	Entire pregnancy	Ambient air monitoring	Polycyclic organic matter	0.49 $\mu\text{g}/\text{m}^3$	
Choi et al. 2008	Cohort	New York, NY	n=351 Dominicans preterm=8 n=205 African Americans preterm=12	3 <sup>rd</sup> trimester	Personal air monitoring	$\Sigma$ PAHs	3.15 $\pm$ 3.42 $\text{ng}/\text{m}^3$	
Singh et al. 2008	Case-control	Lucknow, India	n=60 preterm=29	Delivery	Placenta	$\Sigma$ PAHs	3.32 $\pm$ 3.38 $\text{ng}/\text{m}^3$	
						Naphthalene	250 $\pm$ 47.6 ppb	
						Acenaphthylene	58.7 $\pm$ 42.5 ppb	
						Phenanthrene	378 $\pm$ 79.5 ppb	
						Anthracene	25.8 $\pm$ 8.08 ppb	
						Fluoranthene	209 $\pm$ 21.9 ppb	
						Pyrene	296 $\pm$ 91.6 ppb	
						Benzo(f)fluoranthene	29.9 $\pm$ 22.3 ppb	
						Benzo(b)fluoranthene	23.8 $\pm$ 7.01 ppb	
						Benzo(a)pyrene	8.83 $\pm$ 5.84 ppb	
						Dibenzo(a,h)anthracene	22.0 $\pm$ 17.1 ppb	
Maroziene and Grazuleviciene 2009	Cross-sectional	Kaunas, Lithuania	n=3,988 preterm=203	Entire pregnancy	Ambient air monitoring	Formaldehyde	3.14 $\pm$ 2.36 $\mu\text{g}/\text{m}^3$	
Llop et al. 2010	Cohort	Valencia, Spain	n=785 preterm=47	Each trimester	Ambient air monitoring	Benzene	2.2 $\pm$ 0.6 $\mu\text{g}/\text{m}^3$	
Wilhelm et al. 2011	Cohort	Los Angeles, CA	n=112,915 preterm=10,265	Each trimester and pregnancy average	Ambient air monitoring	Naphthalene	182 $\pm$ 34.6 $\mu\text{g}/\text{m}^3$	
						Benzo(a)pyrene	0.13 $\pm$ 0.05 $\mu\text{g}/\text{m}^3$	
						Benzo(g,h,i)perylene	0.32 $\pm$ 0.08 $\mu\text{g}/\text{m}^3$	
						$\Sigma$ PAHs	221 $\pm$ 38.6 $\mu\text{g}/\text{m}^3$	
						Benzene	0.66 $\pm$ 0.16 $\mu\text{g}/\text{m}^3$	

Note. Levels represent means $\pm$ standard deviations or standard errors or medians ( $\bar{x}$ ) of chemicals measured for all subjects pooled or in controls alone where pooled information was not available. See Figure 3 for results. Abbreviations: Polycyclic aromatic hydrocarbons (PAHs).

Table 4

Studies of metals and metalloids in relation to preterm birth

Study		Exposure					
Reference	Design	Location	Sample size	Timing	Assessment	Metal/metalloid	Level
Fagher et al. 1993	Case-control	Sweden	n=30 preterm=17	Delivery	Maternal blood, placenta, myometrium	Lead	11.2±2.9 ug/L
		Cadmium				1.1±1.7 ug/L	
		Lead				37.9±17.2 ug/L	
Landgren 1996	Cross-sectional	Poland	n=38,718	Entire pregnancy	Ground concentration in municipality	Cadmium	1.8±1.3 ug/L
		Sweden				Lead	151 µg/m <sup>3</sup>
						Cadmium	1.6 µg/m <sup>3</sup>
Torres-Sanchez et al. 1999	Case-cohort	Mexico City, Mexico	n=459 preterm=161	Delivery	Cord blood	Arsenic	93 µg/m <sup>3</sup>
						Mercury	0.02 µg/m <sup>3</sup>
						Lead	10.6±7.13 µg/dL
Ahmad et al. 2001	Cross-sectional	Katiachar, Bangladesh	n=96 preterm=27.1 per 1,000 live births	Entire pregnancy	Drinking water	Arsenic	<0.02 mg/L
							0.24 mg/L
Sowers et al. 2002	Cohort	Camden, NJ	n=705 preterm=72	1 <sup>st</sup> trimester	Maternal blood	Lead	1.22±0.04 µg/dL
		2 <sup>nd</sup> trimester		1.08±0.05 µg/dL			
		3 <sup>rd</sup> trimester		1.10±0.03 µg/dL			
Falcon et al. 2003	Cohort	Murcia, Spain	n=89 cases=18	Delivery	Placenta	Lead	1.32±0.03 µg/dL
		Delivery		103±49.5 ng/g			
Yang et al. 2003	Cohort	TaiwanTaiwan	n=14,387 unexposed preterm=494	Entire pregnancy	Drinking water	Arsenic	<0.9 ppb
Zhang et al. 2004	Cohort	Da-Ye, China	n=3,872 exposed preterm=145	Delivery	Maternal and cord blood, placenta		>0.9 ppb
			n=44 preterm=7			Cadmium	2.10±2.10 µg/L <sup>†</sup>
Mukherjee et al. 2005	Cross-sectional	Murshidabad, Bangladesh	n=18 preterm=2	Entire pregnancy	Drinking water	Arsenic	<3 µ/L

Study	Exposure							
	Reference	Design	Location	Sample size	Timing	Assessment	Metal/metalloid	Level
				<i>n</i> =21 preterm=8				284–400 µ/L
				<i>n</i> =44 preterm=12				401–1474 µ/L
Jelliffe-Pawlowski et al. 2006	Cross-sectional	California	<i>n</i> =262 preterm=30	Entire pregnancy	Maternal blood	Lead	Not reported	
Xue et al. 2007	Cohort	5 communities in Michigan	<i>n</i> =1,024 preterm=101	15 <sup>th</sup> –27 <sup>th</sup> week gestation	Maternal hair	Mercury	0.29 µg/g	
Cantonwine et al. 2010a	Cohort	Mexico City, Mexico	<i>n</i> =235 preterm=22	1 <sup>st</sup> trimester 2 <sup>nd</sup> trimester 3 <sup>rd</sup> trimester	<b>Maternal blood</b> and plasma, cord blood	Lead	7.2±5.2 µg/dL 6.3±4.3 µg/dL 6.8±4.5 µg/dL	
Myers et al. 2010	Cross-sectional	Inner Mongolia, China	<i>n</i> =9,890 preterm=289	Entire pregnancy	Drinking water	Arsenic	37.6±0.7 µg/L	
Vigeh et al. 2011	Cohort	Tehran, Iran	<i>n</i> =348 preterm=44	1 <sup>st</sup> trimester	Maternal blood	Lead	3.8±2.0 µg/dL	
Zhu et al. 2010	Cohort	New York	<i>n</i> =43,288 preterm=3,519	Entire pregnancy	Maternal blood	Lead	2.1 µg/dL	

*Note.* Levels represent means±standard deviations or geometric means±geometric standard deviations (†) of chemicals measured in samples of all subjects pooled or in controls alone where pooled information was not available. If exposure was assessed in multiple matrices, levels from the bolded matrix are presented. For Torres-Sanchez et al. (1999) levels are for primiparous births. For Sowers et al. (2002) preterm birth is defined as <36 weeks gestation. For Zhang et al. (2004) preterm birth is defined as <37 weeks gestation. For Myers et al. (2010) levels are taken from Ning et al. (2007). See Figure 4 for results.

Table 5

Studies of other environmental contaminants in relation to preterm birth

Study						Exposure		
Reference	Design	Location	Sample size	Timing	Assessment	Chemical	Level	
Eskenazi et al. 2004	Cohort	Salinas Valley, CA	n=488 preterm=32	Entire pregnancy	Maternal urine	DAPs	136 nmol/L <sup>†</sup>	
						MDA	0.2 µg/L <sup>†</sup>	
						PNP	0.5 µg/L <sup>†</sup>	
						TCPy	3.3 µg/L <sup>†</sup>	
Villanueva et al. 2005	Cross-sectional	Finistère, France	n=3,510 preterm=137	Entire pregnancy	Drinking water	Atrazine	0.036 µg/L	
Adibi et al. 2009	Cohort	4 US cities	n=283 preterm=14	3 <sup>rd</sup> trimester	Maternal urine	MEHP	3.6 ng/mL	
						MEHHP	11.9 ng/mL	
						MEOHP	10.9 ng/mL	
Meeker et al. 2009	Case-control	Mexico City, Mexico	n=60 preterm=30	3 <sup>rd</sup> trimester	Maternal urine	MEHP	1.90 µg/L	
						MEHHP	13.6 µg/L	
						MEOHP	10.4 µg/L	
						MECPP	29.7 µg/L	
						MBzP	2.30 µg/L	
						MBP	38.1 µg/L	
						MtBP	1.9 µg/L	
						MCP	1.1 µg/L	
						MCOP	Not calculated	
						MCNP	Not calculated	
						MEP	112 µg/L	
Ochoa-Acuña et al. 2009	Cohort	Indiana	n=24,154 preterm=1,777	First and last months of pregnancy	Drinking water	Atrazine	0.011–0.996 µg/L <sup>†</sup>	
Cantonwine et al. 2010b	Case-control	Mexico City, Mexico	n=60 preterm=30	3 <sup>rd</sup> trimester	Maternal urine	BPA	1.52 µg/L	
Rinsky et al. 2012	Cross-sectional	Kentucky	n=71,768 preterm=8,915	Entire pregnancy	Drinking water	Atrazine	0.11±0.49 µg/L <sup>‡</sup>	

Note. Levels represent geometric means±geometric standard deviations, medians or median ranges in multiple groups measured (<sup>†</sup>), or means±standard deviations (<sup>‡</sup>) of chemicals measured in maternal urine or drinking water of all subjects pooled or in controls alone where pooled information was not available. For Cantonwine et al. (2010b) preterm birth is defined as ≤37 weeks gestation. For Rinsky et al. (2012) mean includes values below the detection limit. For Eskenazi et al. (2004) levels of selected pesticide-specific metabolites are presented. See Figure 5 for results. Abbreviations: Dialkyl

phosphates (DAPs); malathion dicarboxylic acid (MDA; malathion metabolite); 4-nitrophenol (PNP; parathion metabolite); 3,5,6-trichloro-2-pyridinol (TCPy; chlorpyrifos metabolite); mono(2-ethylhexyl) phthalate (MEHP); mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP); mono(2-ethyl-5-oxohexyl) phthalate (MEOHP); mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); monobenzyl phthalate (MBzP); mono-*n*-butyl phthalate (MBP); mono-*isobutyl* phthalate (MiBP); mono(3-carboxypropyl) phthalate (MCPP); monocarboxyisooctyl phthalate (MCOP); monocarboxyisononyl phthalate (MCNP); monoethyl phthalate (MEP); bisphenol-A (BPA).