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Environmental chemicals and preterm birth: Biological mechanisms and the state of the science

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Abstract

Purpose of review—Preterm birth is a significant worldwide health problem of uncertain origins. The extant body of literature examining environmental contaminant exposures in relation to preterm birth is extensive but results remain ambiguous for most organic pollutants, metals and metalloids, and air pollutants. In the present review we examine recent epidemiologic studies investigating these associations, and identify recent advances and the state of the science. Additionally, we highlight biological mechanisms of action in the pathway between chemical exposures and preterm birth, including inflammation, oxidative stress, and endocrine disruption, that deserve more attention in this context.

Recent findings—Important advances have been made in the study of the environment and preterm birth, particularly in regard to exposure assessment methods, exploration of effect modification by co-morbidities and exposures, and in identification of windows of vulnerability during gestation. There is strong evidence for an association between maternal exposure to some persistent pesticides, lead, and fine particulate matter, but data on other contaminants is sparse and only suggestive trends can be noted with the current data.

Summary—Beyond replicating current findings, further work must be done to improve understanding of mechanisms underlying the associations observed between environmental chemical exposures and preterm birth. By examining windows of vulnerability, disaggregating preterm birth by phenotypes, and measuring biomarkers of mechanistic pathways in these epidemiologic studies we can improve our ability to detect associations with exposure, provide additional evidence for causality in an observational setting, and identify opportunities for intervention.

Keywords

Preterm birth; gestational age; environment; contaminants; toxicity; epidemiology

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Conflict of interest

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Human and animal rights and informed consent

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Introduction

Preterm birth (PTB) is an extensively studied perinatal outcome due to its prevalence, high societal costs, and poorly understood origins. Defined as delivery prior to 37 weeks gestation, PTB occurs in approximately 1 in 10 pregnancies worldwide and is one of the strongest predictors of neonatal mortality and morbidity (1). Furthermore, PTB may mediate numerous later life adverse health outcomes, such as neurodevelopmental delays, asthma and allergy, and metabolic disease. There are known predictors, presentations, and hypothesized mechanisms of PTB, but knowledge of concrete *causes* remains minimal. The prevalence, costliness, and ambiguity surrounding this disease has led to scientific curiosity in the potential contribution of environmental chemical factors.

Exposures to organic pollutants, metals and metalloids, and air pollutants have the potential to increase risk of PTB through multiple pathways. Some of the most important mechanisms of action that have been include inflammation, oxidative stress, and endocrine disruption, and each of these in turn has been linked to PTB. A large body of literature is devoted to this research (2-4), and, importantly, there have been recent efforts to identify the relevant biological mechanisms underlying these relationships in epidemiologic studies. By measuring biomarkers of mechanism, assessing windows of vulnerability to exposure, and examining associations with PTB phenotypes, research on environmental chemicals and PTB has advanced significantly.

The intention of this review is first to describe inflammation, oxidative stress, and endocrine disruption as three potential pathways of chemical action in the pathway to PTB (Figure 1), and to highlight recent studies that have advanced understanding of these mechanisms within the context of pregnancy (Table 1). Next, we present the state of the epidemiologic evidence examining the relationship between organic pollutants, metals and metalloids, and air pollutants. We review recent studies and discuss the major findings that support or refute an association with PTB and that point toward mechanisms.

Mechanisms of chemical action in the etiology of PTB

While rodent studies can be helpful for understanding biological processes that may be related to PTB, they offer an insufficient model, as it is very difficult to cause them to deliver preterm (5, 6). Thus, epidemiologic studies are especially valuable for studying this health outcome. This is true for studying associations with chemical exposures and for elucidating mechanisms. Beyond the utility of this model, studies of environmental chemicals and PTB that additionally investigate mechanisms can provide stronger arguments for causation in the observational setting, identify opportunities for interventions when remediating exposure is difficult or impossible, and improve the understanding of chemical toxicities in humans that may be extended to other disease. Here we examine three potential mechanistic pathways that have received some attention in the study of environmental chemicals and PTB, and deserve additional exploration in the future, including inflammation, oxidative stress, and endocrine disruption (Figure 1). Additionally, we highlight consequences of these disrupted processes in pregnancy, potentially sensitive windows of vulnerability to exposure, and phenotypic presentations of PTB that would be expected to be more strongly associated with

each pathway (e.g., spontaneous preterm labor, preterm premature rupture of the membranes [PPROM], preeclampsia, and intrauterine growth restriction [IUGR]).

Inflammation

Intrauterine bacterial infection is perhaps the best established cause of PTB (7). Inflammatory pathways are thus one of the most well-studied mechanisms in the preterm pathway. Environmental contaminants have the potential to generate circulating or tissue-specific inflammation in several ways. First, particulate matter (metallic, endotoxin, or otherwise) may be engulfed by phagocytosis and lead to activation of T helper cells and release of cytokines (8). Second, xenobiotic binding to certain receptors, such as peroxisome proliferator activated receptors, can influence cytokine production as in the example of phthalate monoesters (9, 10).Third, environmental chemicals have demonstrated capacity to cause epigenetic modification by way of DNA methylation, histone modifications, and/or perturbations in miRNA expression which can lead to changes in inflammatory responses (11). Finally, these exposures can have adjuvant effects, exemplified by phthalates (12), which can increase the inflammation response to other stimuli.

While in many cases the exact cellular processes by which chemicals create inflammation are unknown, many exposures have been associated with inflammation in epidemiologic studies (13-15). Changes in the systemic maternal or the intrauterine inflammatory milieu could have downstream consequences that precipitate PTB, e.g. by initiating a cascade of events leading to cervical ripening, rupture of the amniotic sac, or increased myometrial contractility (16). These changes—sensitive to exposures later in pregnancy—may all precipitate spontaneous PTB either by initiating preterm labor or by causing PPROM.

Oxidative Stress

Oxidative stress, which can cause or be consequence of increased inflammation, is another important mechanism that could link environmental chemical exposures to PTB. Many chemicals have the capacity to induce oxidative stress, either through: overproduction of reactive oxygen species (ROS) generated enzymatically (e.g., through upregulation of cytochrome P450 pathways) or non-enzymatically (e.g., through the Fenton reaction) (17, 18); changes in mitochondrial membrane potential and permeability (19-21); and impaired antioxidant function (22, 23). Disturbance of the delicate balance between ROS and antioxidant defenses can have numerous downstream consequences in pregnancy. Early in gestation, oxidative stress can cause impaired invasion of the spiral arterioles into the maternal myometrium, resulting in poor placentation that can lead to preeclampsia or IUGR (24). Elevated levels later in pregnancy could: activate the maternal endothelium, part of a two-stage hypothesis underlying the onset of preeclampsia (25); cause damage to the membranes resulting in premature rupture (26, 27); create signaling changes in the cervix leading to shortening and spontaneous labor (28, 29); and/or impact placental protein synthesis and nutrient transport that again lead to fetal growth restriction which can result in medically indicated PTB (30, 31).

Endocrine disruption

Hormones carefully regulate nutrient transfer in pregnancy essential for growth of the fetus as well as timing of parturition. Disrupted fetal and placental thyroid hormone signaling has been observed in cases of IUGR (32). Additionally, animal studies show that glucocorticoid administration during pregnancy leads to a clear dose-dependent decrease in size of the fetus (30), and similar associations have been observed in human populations (33). Thus, thyroid and glucocorticoid hormones (e.g., cortisol) may be involved in the pathway to PTB with presentation of IUGR. Many chemicals have been linked to thyroid hormone disruption, potentially through receptor activity, particularly polychlorinated biphenyls (PCBs) and perfluorinated compounds (34, 35). Additionally, extensive *in vitro* and animal evidence demonstrates that environmental contaminants have the potential to interfere with glucocorticoid signaling. For example, bisphenol A (BPA) and other phenols, phthalates, perfluorinated compounds, and some pesticides can inhibit enzymes involved in the metabolism of glucocorticoids, thus raising circulating levels (37). Hormonal activity, and particularly that of the hypothalamic pituitary adrenal (HPA) axis, is additionally important in the timing of delivery. Corticotropin releasing hormone (CRH) in the placenta has been hypothesized as crucial for timing of spontaneous parturition (38, 39). Progesterone, estrogen, and cortisol pathways in the mother and fetus that interact to maintain homeostasis of CRH in pregnancy may thus be sensitive targets of chemical exposure (40).

Lastly, it is important to recognize that these pathways do not operate independently. Inflammation is tightly tied to hormonal regulation in pregnancy (16), and oxidative stress and inflammation have the potential to induce one another. These mechanisms may explain in part some of the associations observed in the following sections.

Environmental chemicals and PTB

Organic pollutants

Water disinfection byproducts (DBP)—A common method to disinfect drinking water is through the process of chlorination (41, 42). The most abundant byproducts of this process are trihalomethanes (THMs) and exposure to these along with haloacetic acids (HAAs) have been studied in relation to PTB (43). Grellier and colleagues reviewed the literature on exposure to water DBP and PTB in 2010 and concluded no association (44).

Since 2010 there have been seven additional studies (45-51). Three, conducted in Europe, used a method of exposure assessment that incorporated both measurements of THMs from public drinking water sources and individual level information on personal routes of exposure including ingestion, inhalation, and dermal absorption (45-48). The study by Costet and colleagues was novel in that exposure was quantified from a biomarker of trichloroacetic acid measured in maternal urine (45). None of these studies found an association between total THM and PTB.

The remaining three studies were US based and found small positive associations with water DBP and PTB (49-51). In New York, total THM were measured from the public water source at multiple time points during pregnancy (49). Although exposure was determined

from public water source measures, this study was able to link the source with maternal residence, lending more confidence to the level of exposure being assigned to each woman. A modest association was detected between low levels of total THMs and PTB, but a null association was observed at higher levels. The remaining two studies did incorporate an individual component and used a representative water source to assign exposure, but also found similar small positive associations with some of the water DBP (51).

Persistent organic pollutants—Most of the literature examining an association between organic pollutants and PTB has focused on chemicals that persist in the environment and human body. Evidence of a relationship between persistent pesticides and PTB come from studies of populations with high levels of exposure (52, 53). A subset of studies from a recent review of environmental chemicals and PTB (54) were published since 2010 and show that overall the literature supports an association between high levels of organochlorine pesticide exposure (55-57) and PTB with weaker or null associations for the remaining persistent pollutants (54, 58-65).

Studies published since that review (54) show consistent findings of the association between persistent pesticides and PTB with high exposures associated with increased risk, whereas the relationship with lower exposures is less clear. In a study conducted in Guadeloupe where there is widespread chlordecone use and environmental contamination, authors found an association with exposure as measured by maternal blood sample at delivery and increased risk of PTB (66). However, a study conducted in Spain, where pesticide exposure was much lower, failed to show an association between 1st trimester maternal hexachlorobenzene levels and PTB (67).

Exposure to high levels of non-pesticide persistent pollutants do not show the same relationship, with generally null findings for dioxin exposure and PTB regardless of exposure burden. A chemical explosion in Seveso, Italy led to unprecedented residential dioxin exposure providing the opportunity to investigate the health effects of high levels of this chemical (68). Despite exposure to elevated levels of dioxin, an association with PTB could not be established in this cohort (68). Similarly, in a population highly exposed to perfluorooctanoic acid as a result of industrial contamination of the drinking water, no association with PTB was found.(69) In contrast, a study of flame retardants showed a dose response relationship with PTB (70). Maternal blood samples were taken at the time of delivery and an increased risk of PTB was observed with increasing levels of polybrominated diphenyl ethers.

Non-persistent organic pollutants—Investigation of organophosphate pesticides in relation to PTB has been limited and no associations with PTB have been reported (71, 72). Atrazine, another chemical used in agriculture, is applied as an herbicide, and can contaminate water supplies (73). Early studies looking at atrazine assigned exposure based on measurements from water sources and found null or weak non-significant positive associations with PTB (74, 75). Recent studies continue to use drinking water levels to assign atrazine exposure despite the ability to measure individual exposure from urine samples (76), and the evidence for atrazine being associated with increased PTB remains inconclusive (77).

Phthalates are used to increase flexibility in plastics and are also found in many personal care products. Human exposure to this group of chemicals is widespread through ingestion, dermal application, and inhalation (78). There have been conflicting findings from early studies of phthalate metabolites and PTB with one study finding a protective association (79) and another finding a harmful one (80). Since publication of these findings, there have been improvements in the assessment of phthalate exposures. In a recent nested case control study, multiple measures of nine phthalate metabolites were used to estimate exposure. In this study, the average phthalate metabolite levels from three urine samples collected from women during pregnancy (median of 10, 18, and 26 weeks gestation) was associated with increased risk of PTB (81). Further, this study examined phenotypes of PTB and observed an even stronger association between phthalate levels and spontaneous PTB. A related study characterized the variability of phthalate metabolite levels across pregnancy (82). In this study each urinary phthalate measurement was treated as a distinct exposure to assess risk of PTB in relation to different windows of susceptibility during pregnancy. Results showed the strongest association with phthalate levels measured later in pregnancy.

BPA is another chemical identified as an endocrine disrupter that is in widespread use as a component of hard plastics and epoxy resins (78). The first study to examine the relationship between BPA exposure and PTB was done using a maternal single spot urine collected during the 3rd trimester and found a modest association of BPA with PTB (84). These same investigators then used multiple measures of BPA from the same case cohort study referenced above with phthalates and found a weak and non-significant association with PTB (85).

Strengths of literature on non-persistent pollutants include several improvements in exposure assessment. Examples include the incorporation of personal information on routes of exposure of water DBP and use of multiple measurements of non-persistent chemicals like phthalates and BPA. Additionally, consideration of the timing of exposure and windows of susceptibility that may differ based on preterm phenotype aids in comparability across studies and confirmation of proposed biologic mechanisms. Limitations of the current evidence on organic pollutants and PTB include the continued use of ecological measures of exposure even when validated biomarkers exist that could quantify individual exposure. In some studies individual-level exposure was measured, but using inappropriate exposure matrices, specifically regarding non-persistent chemicals, resulting in concerns about contamination (83, 86, 87). Lastly, the consideration of combinations of related chemicals or metabolites with PTB would strengthen the literature.

Metals and metalloids

Over the past several decades, there have been many studies that have examined the association between heavy metal exposures and adverse birth outcomes. The bulk of the early literature focused on high levels of exposure (88-90) with more recent studies examining lower levels consistent with non-occupational settings.

Lead—There is convincing evidence that lead exposure in high levels is associated with PTB (88). The hypothesized mechanisms by which lead can lead to PTB fall into two

categories: 1) by influencing hormone levels (91-94) and 2) inducing the production of reactive oxygen species (92, 93). Since the elimination of lead in everyday exposures like fuel and paint, examination of lower levels of lead exposure have become more relevant (95). Studies focused on these ambient levels of exposure that still persistent in the environment have shown inconsistent results possibly as the result of differences the timing of exposure assessment or type of biologic material utilized (96, 97). In a study conducted in Mexico, exposure to lead was assessed during the 1st, 2nd, and 3rd trimester in maternal whole blood and plasma and the strongest associations with PTB were seen in early pregnancy (91). Other studies with measures of lead during early pregnancy showed similar results (92, 93). Results from studies assessing lead exposure across pregnancy show less consistent results, with the possibility of lead measurements later in pregnancy attenuating the effect (98, 99). Two studies found differences in PTB by sex of the infant, but results were opposing with one finding a stronger association in girls and the other in boys (94, 98).

Mercury—The association between mercury exposure and PTB has been mixed. A study by Taylor and colleagues conducted in the UK found weak evidence of a protective effect of blood mercury levels measured in the mother early in pregnancy (median 11 weeks) and PTB, but this association attenuated in adjusted models (100). In a study population of women who were predominantly African American or of Caribbean decent, investigators found a protective effect of higher mercury levels in maternal urine during the last trimester of pregnancy, but the estimate was imprecise (101). A slightly stronger effect was seen in cord blood measures in the same population.

Arsenic—Two of the studies reviewed looked at arsenic in drinking water and PTB. Neither used individual levels of exposure, but were consistent with prior work that has found null or weak associations with PTB (102).

Cadmium—Early studies examining maternal cadmium exposure and PTB used either an ecological study design or suffered from small sample size and showed mixed results (103-105). More recently two large cohort studies conducted in China showed an association between higher levels of cadmium exposure and increased risk of PTB (106, 107). A case-cohort study of the more restrictive outcomes of preterm low birthweight also reported this association (108). Cadmium is thought to alter zinc transport, which may trigger PTB (106, 107) and may also accumulate in the placenta where it can directly or indirectly affect the fetus (108). None of the studies that reviewed mercury or arsenic proposed a hypothesized mechanism of action.

Strengths of the current literature include taking the timing of the metal exposure into account and examining lower levels of metal exposures that are more consistent with ambient exposure. Some studies measure metal exposures in more than one type of biological sample to estimate how correlated measures are across sample type, which may have implications on the interpretation of results from future studies as well as determining the best exposure matrix for each metal.

There are still many studies that use ecological data to estimate exposure to metals and metalloids, even when individual measures have been shown to be reliable, such as arsenic

exposure measured in urine samples. Although some studies consider the timing of exposures, there are many studies that continue to compare measures taken from women at different times during pregnancy or only at delivery, which may not reflect exposure during pregnancy. This may be especially important for lead exposure which is thought to have a U-shaped curve during pregnancy with higher levels seen in the 1st and 3rd trimester (109).

Air pollutants

Criteria air pollutants—Papers published on air pollutants, including nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), carbon monoxide (CO), and particulate matter (<2.5 μm, $PM_{2.5}$; and <10um, PM_{10}) up until January 2011 were meticulously examined by Stieb and colleagues (110). Their pooled analysis using trimester-specific as well as entire pregnancy averages concluded that the most precise effect estimates were between third trimester exposures to CO and PM_{10} and PTB (110). Since that time many studies have been published on criteria air pollutants with notable improvements. Exposure assessment has been optimized by more broad application of land use regression modeling (111-113), implementation of satellite-imaging technology for the assessment of $PM_{2.5}$ exposure (114-116), and in studies of $PM_{2.5}$ exposure, examination of the individual components within the particulate fraction in attempt to identify the most harmful constituents (117-120).The study of windows of vulnerability to exposure has expanded as well, with many studies moving beyond examining trimester or month of exposure into measurement of the preconception exposures (121) or exposures in the days or hours immediately proximate to delivery (122-124). In terms of outcome assessment, some research groups have made efforts to examine phenotypes of PTB. Potentially due to ease of assessment from medical record abstraction, the focus has been on PPROM (111, 125-127). Finally, many recent studies place an emphasis on understanding effect modifiers in these relationships. These have included co-morbidities such as asthma and diabetes (117, 121, 128), demographic factors like race, education level, and socioeconomic status (120, 123), and community-level variables, e.g. urbanicity (129).

Regarding individual criteria air pollutants, the greatest advances and the largest number of studies have focused on fine particulate matter ($PM_{2.5}$). Since the review by Stieb et al., four additional reviews and meta-analyses have summarized the literature on these associations and all concluded that a positive association exists between exposure during pregnancy and PTB (130-133). The majority of papers published since that review also suggest a positive association between $PM_{2.5}$ exposure and PTB, although null and in some cases protective effects have been observed in well-designed studies (113, 114, 122, 134, 135). Differences may be due to variation in study design and population, exposure assessment methods, measurement windows, and levels of exposure.

Studies examining variation in effects by characteristics of the study population have observed the greatest effect estimates in subjects with co-morbidities like asthma and diabetes (116, 121), and who have certain demographic characteristics (low education level, non-African American, residing in large metropolitan areas) (120). Width of windows of exposure vary greatly as well. Detection of positive associations between $PM_{2.5}$ and PTB seem to suggest that exposure in the days or hours leading up to delivery may be most

relevant (123, 124, 127, 136), although this has not been evident in all studies that had the capability of assessing this window specifically (122). Exposure assessment approaches improve dramatically year to year as well, and for this exposure two recent studies have captured exposure with satellite-based predictions, which have the ability to assign exposure to small geographic areas and more accurately capture exposures where ambient air monitors are more sparse (i.e., rural areas) (114, 115). These studies had conflicting findings; however, as these methods improve they may provide more robust data on the association between $PM_{2.5}$ and PTB.

Studies of $PM_{2.5}$ also vary by exposure level, source, and composition of the particulate. In a study by the World Health Organization comparing associations in African, Asian, and Latin American countries, the only clear evidence of an association between $PM_{2.5}$ and PTB was observed in China, where the range of exposure was widest and where some of the highest levels in the world were observed (137). Though, this does not necessarily connote a stronger effect at higher levels. An analysis examining non-linear associations with exposure in attempt to identify a threshold effect observed no statistical association for $PM_{2.5}$ in linear or non-linear single pollutant models (122). Finally, an important evolution in this research is to examine sources and components of fractionated $PM_{2.5}$. One study identified power plants as important sources of $PM_{2.5}$ exposure, and illustrated that proximity to these plants specifically was associated with increased risk of preterm delivery (138). Additionally, two studies examining compounds present in $PM_{2.5}$ fractions suggested that elemental carbon and SO_4 specifically were associated with increased risk of PTB (111, 119). Additional research studies designed to capture these elements combined will help improve the understanding of the role of exposure to $PM_{2.5}$ in the etiology of PTB.

Associations with PM_{10} specifically are difficult to assess because not all studies examine both PM_{10} and $PM_{2.5}$ fractions separately, thus many studies measuring PM_{10} alone may be capturing effects of the smaller particulate fraction. Previously Stieb et al. concluded that there was an association between PM_{10} and PTB, but more recent studies are ambiguous. Of the studies that do report an association with PM_{10}, only one measured $PM_{2.5}$ concurrently (123), and noted that the strongest associations were with exposure very close to the time of delivery. Notably, two studies examined these associations within natural experiments. Balsa and colleagues examined pregnancy outcomes among individuals residing near an active volcano, and observed strong associations with PM_{10} levels measured in the third trimester (139). On the other hand, however, a study of elevated air pollution levels occurring during the Beijing Olympic games observed no association between ambient PM_{10} concentrations and PTB (140).

Studies of other criteria air pollutants are less conclusive, despite having made similar advancements by way of examining more specific exposure windows, non-linearity of associations, and multi-pollutant models. In regard to NO_2, positive (111, 116, 117, 120, 122, 123, 129, 141-145) and null (112, 113, 127, 128, 135, 137, 140, 146-154) associations seem to be evenly mixed. Studies that have observed positive associations point toward the second trimester or the time period immediately preceding delivery as sensitive windows of exposure (122, 129, 143). Also, evidence suggests that an association may exist only in urban populations or at a certain threshold of exposure (122, 129). Additionally, one study

showed an association was between NO_2 and PTB in a single-pollutant model, but when $PM_{2.5}$ was added to the model the association between PTB and NO_2 became null (117). Findings for O_3, CO, and SO_2 also remain inconclusive.

Polycyclic aromatic hydrocarbons (PAHs) and volatile organic compounds (VOCs)—Fewer studies examine PAHs or VOCs because they are not as tightly regulated by the EPA and hence are not commonly captured by air monitors. PAHs are released during combustion processes from vehicles and industrial facilities, and they are also found in tobacco smoke and grilled meats and vegetables (155). Thus, exposure occurs commonly through inhalation pathways but ambient monitors likely capture a smaller percentage of exposure compared to other air pollutants. Studies examining ambient PAH exposure in relation to PTB have identified significant associations between total PAHs as well as individual congeners, particularly with levels measured in the end of gestation (156, 157). Additionally, a study measuring PAH concentrations in cord blood identified higher levels in pregnancies with adverse birth outcomes, including PTB (158). While this research is suggestive, additional studies are necessary and would benefit from utilizing urinary biomarkers which capture total exposure through inhalation and ingestion pathways. Similarly, exposure to some VOCs in pregnancy, e.g. benzene or toluene, show some evidence of an association with PTB but the data remains very limited (143, 151, 159-161).

Environmental tobacco smoke—Lastly, environmental tobacco smoke has been examined in several studies in relation to PTB. The association between PTB and maternal smoking has been established (162), however the risk associated with indirect exposure is less clear. A meta-analysis published in 2010 showed a slight positive association with PTB that was not statistically significant in adjusted models (163). A more recent meta-analysis concluded otherwise, specifying that passive smoking in either the workplace or at home was associated with preterm delivery (164). Of the largest of these studies published in recent years (>10,000 subjects), two report positive associations with PTB, particularly delivery <32 weeks gestation (165, 166) and one had null findings (167).

In 2008, Slama et al. addressed the overarching limitations of studies examining air pollutant exposures in relation to PTB and identified major research needs (168). Many of these needs remain, including the need to better understand mechanisms underlying these observed associations, addressing co-exposure to multiple pollutants, and working from a unified methodological framework to improve comparability between studies (169). Toward this end, Pereira and colleagues are implementing a series of studies with the same design to assess the relationship between gestational exposures to $PM_{2.5}$ and PTB in different regions of the world (125, 126, 170). The International Collaboration on Air Pollution and Pregnancy Outcomes is designed with the same aim, to unify methodologies across research studies to identify the relationship between ambient air pollutant exposures and adverse pregnancy outcomes (171). These collaborative research efforts will be extremely informative in the coming years.

Conclusions

Although numerous studies have been published on the relationship between environmental chemical exposures and PTB, few individual compounds have sufficient evidence to conclude an association. The data suggest a strong association between PTB and fine particulate matter ($PM_{2.5}$), lead, and dichlorodiphenyltrichloroethane (DDT) exposures in pregnancy—compounds for which there have also been the largest number of publications. However, for other chemicals the overall findings are ambiguous. This is due both to small numbers of studies for some compounds as well as conflicting results. Future work on other compounds where there is strong evidence but not enough data—e.g., polycyclic aromatic hydrocarbons—is warranted.

Of the studies reviewed, many of the common limitations of environmental epidemiology studies exist. These include limited exposure assessment metrics (e.g., using a spot urine sample to assess non-persistent chemical exposures), small sample sizes and/or small numbers of cases, and failure to account for key confounders and/or co-exposures. We posit that, although there has been some concerted effort in this direction, an additional limitation to this literature is the infrequent attention to mechanistic pathways underlying the relationships of interest. It would behoove future studies to focus on disentangling these mechanisms through one or more approaches. First, by examining windows of vulnerability during gestation, investigators can examine time points of exposure that may be reflective of specific pathways to delivery. The greatest progress in this arena has been made in the study of particulate matter, where investigators have leveraged the wealth of information available from ambient air monitors to examine acute exposures (i.e., the hours or days leading up to delivery) in relation to PTB (123, 124, 127, 136). Identifying this sensitive window of exposure provides stronger evidence of a relationship between $PM_{2.5}$ and PTB by highlighting a biologically plausible pathway (e.g., acute $PM_{2.5}$ exposure causes oxidative stress or inflammation, which leads to membrane damage and PPROM). A second approach to identifying mechanism may be through examining associations with specific presentations of PTB, as opposed to looking at the 37-week cutoff alone, or at other cutoffs based on gestational age that may not necessarily be homogenous by mechanism. Again progress has been made here in the realm of air pollution research by groups who have focused their efforts on examining associations with PPROM (125-127), and also to some extent in the study of non-persistent organic pollutants such as BPA and phthalates (172, 173). Examining associations with phenotypes of PTB based on presentation enables both greater ability to detect effects and also identifies mechanisms that may be targeted for interventions. Finally, and most ideally, biomarkers of mechanistic intermediates can be measured concurrently with exposure to provide supportive evidence of causality if indeed an association with exposure exists.

Worth mentioning is the study published by Ferguson, McElrath, and Meeker in which mechanism is investigated under all three of these approaches (174). In that study phthalate exposure biomarkers were measured at four time points during pregnancy (*windows of vulnerability*); associations were examined with phenotypes of PTB (*presentation phenotypes*); and indices of mechanistic intermediates were measured under multiple hypothesized pathways, including inflammation, oxidative stress, and endocrine disruption

(*biomarkers of mechanism*). In that study the authors established an association between some phthalate metabolites and specifically spontaneous PTB, with associations that were greatest in magnitude with exposure measured late in pregnancy (172). Additionally, they demonstrated that urinary phthalate metabolites were associated with oxidative stress biomarkers, particularly 8-isoprostane, and that 8-isoprostane concentrations during pregnancy were associated with spontaneous preterm delivery (175, 176). Finally, the authors developed and applied novel mediation methods and showed that, statistically, oxidative stress, as indicated by 8-isoprostane, may account for upwards of 50% of the association between some phthalate metabolites and PTB (177).

These additional steps beyond the analysis of association between exposure and outcome provide greater weight to the analysis and can provide feedback into the obstetrics community to further understanding of the complex pregnancy outcome that is PTB. Additional studies with this type of framework are necessary for establishing more concrete connections with environmental chemical exposures. By examining windows of vulnerability, presentation phenotypes, and biomarkers of mechanism, we may also reduce variability in published associations and have a greater chance at replicating study findings. This work will strengthen the evidence supporting associations between environmental chemical exposures and PTB, and help us to identify opportunities for remediating exposures or implementing interventions to prevent this serious public health problem.

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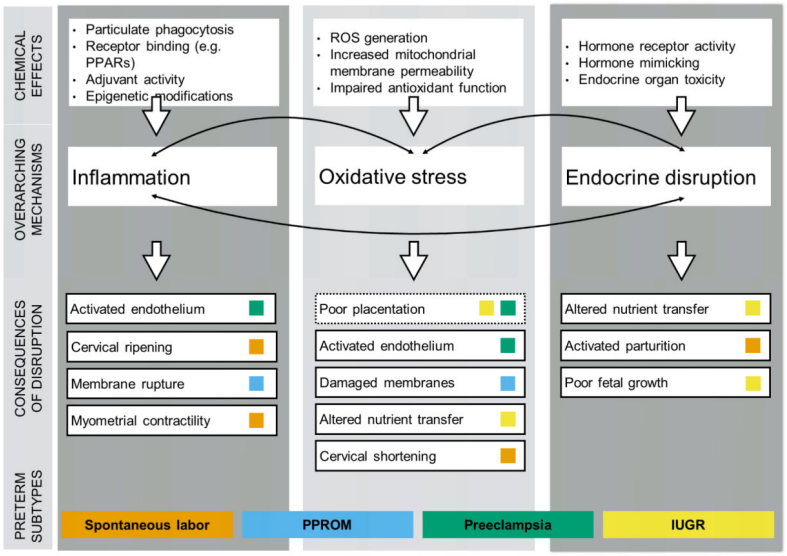

Figure 1. Potential mechanisms of environmental chemical action in the path to preterm birth

Note: Under ‘Consequences of disruption’, dashed borders represent biological changes that may be sensitive to exposures early in pregnancy, while solid borders reflect middle to late pregnancy windows of susceptibility. Abbreviations: Peroxisome proliferator activated receptors (PPARs); Reactive oxygen species (ROS); Preterm premature rupture of the membranes (PPROM); Intrauterine growth restriction (IUGR).

Table 1

Epidemiologic studies of environmental chemical exposures and preterm birth published since 2010.

CLASS	CHEMICAL	REFERENCES	MAJOR FINDINGS	MAJOR FINDINGS ON MECHANISM
Organic pollutants	*Water disinfection byproducts*	Horton 2011 (51); *Kogevinas 2016 (46); Kumar 2014 (49); Patelarou 2011 (47); Rivera-Nunez 2013 (50); Villanueva 2011 (48).	*A systematic review and meta-analysis by Grellier in 2010 showed no association between water disinfection byproducts and PTB. Individual studies published after this review largely show null results with a few reporting small positive associations.*	*In a large mother-child cohort (n=14,005 mothers) conducted in Europe between 2002-2010, no association was seen with total trihalomethanes, chloroform, or brominated trihalomethanes; route of exposure (ingestion, inhalation, absorption); or trimester of pregnancy and PTB.*
	Persistent pollutants	Arbuckle 2012 (58); Basterrechea 2014 (67); Bergonzi 2011 (56); Chen 2012 (19); Darrow 2013 (178); Hamm 2010 (60); Kadhel 2014 (66); Pathak 2009 (57); Peltier 2015 (70); *Savitz 2012 (61); *Wesselink 2014 (68); Whitworth 2012 (63); Wojtyniak 2010 (55); Wu 2010 (64); Wu 2012 (65).	*A recent prospective cohort study of women (n=818) exposed to chlordecone adds to past evidence that high levels of organochlorine pesticides are associated with PTB (Kadhel 2014). There are fewer studies on non-pesticide persistent compounds with mixed results. A large highly exposed population-based cohort (n=11,737 pregnancies) found no association with perflourooctonoic acid and PTB (Savitz 2012). A study of the highest know levels of residential dioxin exposure (n=617 women) also showed no association. Peltier 2015 identified an association with PBDEs and PTB.*	*A case-control study examining the relationship between PBDEs showed a dose-response relationship with increased risk of PTB with increasing levels of PBDEs in maternal plasma (Peltier 2015).*
	Non-persistent pollutants	Albouy-Llaty 2016 (179); *Cantonwine 2010b (180); *Ferguson 2014a (174); Ferguson 2014b (172); Forand 2012 (159); Rinsky 2012 (77); Ruckart 2014 (181); Sathyanarayana 2010 (72).	*Few studies exist for individual non-persistent pollutants. The first study to examine longitudinal measure of phthalate metabolites during pregnancy found an association with these chemicals and PTB (Ferguson, 2014a). The association between bisphenol A and non-persistent pesticides and herbicides and PTB is less clear.*	*Ferguson 2014a utilized longitudinally collected phthalate metabolite measures during pregnancy (cases=132, controls = 352) and found an association with spontaneous PTB, particularly when restricted to exposure later in pregnancy. Behnia 2014 found an increased risk of PPROM with amniotic fluid BPA levels.*
Metals and Metalloids	*Lead, Arsenic, Mercury, Cadmium*	Bashore 2014 (101); Cantonwine 2010a (182); Huang 2016 (108); Myers 2010 (102); Perkins 2014 (98); Shi 2015 (183); Taylor 2015 (93); Taylor 2016 (100); Vigeh 2011 (92); Wang 2016 (106); Yang 2016 (107); Zhang 2015 (94); Zhu 2010 (99).	*Exposure to lead was consistently associated with an increase in PTB. The most recently published study of lead exposure and PTB in a cohort of 4,285 pregnant women also shows an increased risk of PTB with prenatal lead exposure (Taylor 2015). Studies of other metals show mixed results and are inconclusive.*	*Cantonwine 2010 measured lead in each trimester during pregnancy in 235 women and found an association first trimester lead exposure and PTB. Vigeh 2011 (n=348) also found an association with PTB and 1st trimester lead exposure.*

CLASS	CHEMICAL	REFERENCES	MAJOR FINDINGS	MAJOR FINDINGS ON MECHANISM
Air pollutants	*Criteria pollutants (NO_2, O_3, CO, SO, PM_{10}, $PM_{2.5}$)*	Arroyo 2016 (146); Baker 2014 (147); Balsa 2016 (139); Candela 2013 (141); Capobussi 2016 (142); Dadvand 2015 (111); Dibben 2015 (148); Estarlich 2016 (143); Gray 2014 (134); Ha 2015 (138); Hao 2016 (120); Huang 2015 (140); Johnson 2016 (135); *Laurent 2016 (117); Lavigne 2016 (116); Le 2012 (184); Lee 2013 (185); *Li 2016 (122); Lin 2015 (128); Mendola 2016 (121); Olsson 2012 (144); Olsson 2013 (150); Olsson 2015 (149); Padula 2014 (123); Panasevich 2016 (112); Pereira 2016a (186); Poirier 2015 (151); Qian 2016 (152); Schifano 2016 (187); Stieb 2016 (113); Symanski 2015 (188); Transande 2013 (145); van den Hooven 2012 (154); *Wallace 2015 (127).	*A large number of recent studies support an association between PTB and O_3, CO, PM_{10}, but not NO_2, or SO. Work to investigate effect modification has identified an important role of co-morbidities (e.g., asthma), community level variables (e.g., urbanicity), and demographic factors.*	*A study by Li 2016 in Australia identified non-linear associations between PTB and acute exposures in the days before delivery to NO2, SO2, and CO. Wallace 2015 demonstrated associations between acute exposure to CO and SO2 with PROM, and between chronic exposure to O3 and PROM.*
	$PM_{2.5}$ only	Chang 2012 (189); DeFranco 2016 (190); Fleischer 2014 (137); *Hyder 2014 (114); Kloog 2012 (115); Pereira 2014a (125); Pereira 2014b (118); Rappazzo 2014 (124); *Rappazzo 2015 (119); Symanski 2014 (136).	*Advances in exposure assessment enabled measurement of exposure using satellite monitoring data. Hyder 2014 utilized this approach and found no association between $PM_{2.5}$ and PTB in two US states (N~800,000). Recent reviews, however, conclude an association between exposure and PTB (130-133).*	*Rappazzo 2015 identified differences in association with PTB by week of gestation in which exposure was measured and by components of PM in 3 US states (N~1.75 million). Wallace 2015 identified associations between exposure hours before delivery and increased odds of PROM (N~225,000).*
	Polycyclic aromatic hydrocarbons	Guo 2012 (158); Padula 2014b (156); Porter 2014 (160); Wilhelm 2011 (157).	*Very few studies exist and none utilized personal air monitoring or biomarkers of PAH exposure. The largest study utilizing land use regression models (N~10,000 cases, N~100,000 controls) observed positive associations between non-traffic related PAH and PTB (Wilhelm 2011).*	*Padula 2014b observed positive associations between exposure during the last six weeks of pregnancy and very early PTB (<27 weeks) in California (N~43,000).*
	Volatile organic compounds	Estarlich 2016 (143); Forand 2012 (159); Ghosh 2013 (161); Poirier 2015 (151); Porter 2015 (160); Wilhelm 2011(157).	*Very few studies exist, particularly by individual compound (e.g., only one study examined trichloroethylene). The largest study by Wilhelm 2011 observed positive associations with benzene.*	*Using land use regression models, Estarlich 2016 observed that benzene exposure in the third trimester was associated with PTB in a cohort study in Spain (N=2,409).*
	Environmental tobacco smoke	Arffin 2012 (191); Crane 2011 (165); Ghosh 2013 (161); Ion	*Recent meta-analyses by Salmasi 2010 (163) and Cui 2016 (164)*	*Qiu 2014 observed increased odds of very PTB birth (<32 weeks gestation)*

CLASS	CHEMICAL	REFERENCES	MAJOR FINDINGS	MAJOR FINDINGS ON MECHANISM
		2015 (167); Luo 2012 (192); *Qiu 2014 (166).	*showed mixed results.*	*in association with passive smoking sustained for the duration of pregnancy in a large prospective study in China (N~10,000). No differences observed by trimester, but associations were strongest among very PTB without PPROM.*

*Denotes study of importance. For criteria air pollutants and $PM_{2.5}$, references are provided for papers published since the most recent comprehensive review by Stieb et al. (110). Abbreviations: PTB, preterm birth; PPROM, preterm premature rupture of the membranes; PBDEs, polybrominated diphenyl ethers.