

## Review

# Prenatal Exposures to Environmental Chemicals and Children's Neurodevelopment: An Update

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This review surveys the recent literature on the neurodevelopmental impacts of chemical exposures during pregnancy. The review focuses primarily on chemicals of recent concern, including phthalates, bisphenol-A, polybrominated diphenyl ethers, and perfluorinated compounds, but also addresses chemicals with longer histories of investigation, including air pollutants, lead, methylmercury, manganese, arsenic, and organophosphate pesticides. For some chemicals of more recent concern, the available literature does not yet afford strong conclusions about neurodevelopment toxicity. In such cases, points of disagreement among studies are identified and suggestions provided for approaches to resolution of the inconsistencies, including greater standardization of methods for expressing exposure and assessing outcomes.

**Key Words:** Chemicals and drugs, Child, Neurobehavioral manifestations, Behavior

Pregnancy has long been recognized as a potentially critical window of vulnerability for exposure to a variety of chemicals. This review focuses on chemicals that are thought to perturb fetal brain development, resulting in altered postnatal behavior. These include chemicals whose risks have been known for millennia (e.g., lead), others for a few decades (e.g., methylmercury), and others for which the first data on neurotoxicity in children date only from the last few years (e.g., bisphenol A, phthalates, polybrominated diphenyl ethers, polycyclic aromatic hydrocarbons, perfluoroalkyl acids). Not surprisingly, the chemicals differ in the depth and breadth of the data available on which to base a risk assessment. Although recent advances in our understanding of chemicals such as lead and methylmercury are discussed, most of the review focuses on chemicals

of more recent concern, for which data, though sparse, have stimulated concern. As will be evident, for these chemicals it is generally not possible to draw firm inferences at present about issues such as critical dose and the period(s) of greatest vulnerability. For some of the chemicals, such as lead, perfluoroalkyl acids, organophosphate pesticides (OPs), and manganese, occupation may be a significant route of exposure. For others, the major routes involve diet and lifestyle although the exposures might act synergistically with occupational exposures to increase fetal neurotoxicity. Our understanding of such potential interactions is rudimentary at present, however.

## Phthalates

Phthalates are a group of synthetic plasticizers and solvents that are used in a wide variety of commercial products, including food packaging, polyvinyl chloride tubing, medical equipment, toys, and cosmetics. Although the mechanism of toxicity has not been established, animal studies suggest several possibilities, including perturbations of hypothalamic sexual

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differentiation, hippocampal development, midbrain dopaminergic activity, thyroid homeostasis, calcium signaling, peroxisome proliferator-activated receptors, and lipid metabolism. It is prenatal exposures to phthalates that are considered to be of greatest concern although the critical windows of vulnerability for different endpoints remain to be identified.

To date, fewer than a dozen epidemiological studies have been published evaluating phthalate exposure and child development. In prospective studies, poorer outcomes in a variety of domains have been reported to be associated with higher prenatal phthalate exposures, including neonatal neurological status [1,2], infants' scores on the Bayley scales [3,4], executive function [5], behavior problems [5], patterns of play [6], and social impairment [7]. Two cross-sectional studies reported inverse associations between the phthalate levels of school-age children and their intelligence [8] and prevalence of behaviors related to the attention deficit hyperactivity disorder (ADHD) [9].

Although these limited studies are consistent in suggesting poorer outcomes among children with higher biomarker levels of prenatal or concurrent phthalate exposure, it is impossible to draw strong inferences at this time. First, most studies included evaluation of many exposure-outcome associations, but, in general, relatively few of them reached statistical significance raising the prospect of an inflated rate of false positive findings. Second, phthalate exposure was not always expressed in the same way in the different studies. In some, specific metabolites were used in the analyses, whereas in others the sum of low- or high-molecular weight metabolites were used, making it difficult to compare the dose-response relationships across studies. Third, in some instances, studies assessed the same domain but used different instruments (e.g., neonatal behavioral assessment system vs. the neonatal intensive care unit network neurobehavioral scale). Fourth, the pattern of findings sometimes differed. For example, in some studies, it was girls' outcomes that were most strongly associated with exposure, whereas in others it was boys' outcomes. In yet others, no sex differences were found. Although multiple studies reported that children's behavior was associated with phthalate exposure, in some studies, the behavior problems were "internalizing" (i.e., anxiety, withdrawal), whereas in others they were "externalizing" (e.g., hyperactivity, aggression). Additional studies that address some of these issues are required before conclusions can be drawn about the level of risk associated with contemporary levels of exposure to phthalates.

## Bisphenol-A (BPA)

Only a few studies have evaluated the neurodevelopmental

impact of prenatal exposure to BPA, an organic compound with hormone-like properties that is used in the manufacture of plastics. In the study of Yolton et al. [1], neither urinary BPA concentration at 16 (mean 1.8 ng/mL) or 26 weeks (1.7 ng/mL) of gestation was significantly related to infants' neurological status at 5 weeks of age. Miodovnik et al. [7] reported that urinary BPA concentration in the third trimester (mean 1.2 ng/mL) was not significantly associated with the risk of social impairment at 7 to 9 years of age.

Three papers (two cohorts) have focused on child behavior as the endpoint, and the results are consistent in general, but not specific, terms. Braun et al. [10,11] measured urinary BPA at 16 weeks, 26 weeks, and at birth in pregnant women and in their children at 1, 2, and 3 years of age. The median BPA concentrations were 2.0 µg/L during pregnancy and 4.1 in the children. At 2 and 3 years of age, the children's behavior was assessed using a parent-completed questionnaire, the behavior assessment for children-2 (BASC-2). At 3 years, parents also completed the behavior rating inventory of executive function-preschool (BRIEF-P). BPA concentration measured at 16 weeks of gestation bore the strongest associations with child behavior at 2 years of age, particularly for externalizing problems (hyperactivity, aggression) and only among girls. At 3 years of age, significant associations were noted, in girls, between mean BPA concentration during gestation and ratings of some behavior problems, namely scores on the anxiety, hyperactivity, and depression scales of the BASC-2 and the emotional control and inhibition scales of the BRIEF-P. No associations were observed for boys, nor were childhood BPA concentrations associated with any of the endpoints measured. Perera et al. [12] also conducted a prospective cohort study, measuring urinary BPA in late pregnancy (34 weeks on average) and at ages 3-4 years in the children. Parents completed the child behavior checklist. In this cohort, evidence of significant adverse associations was found only in boys. Boys in the highest quartile of prenatal BPA concentration had worse scores than boys in the lower three quartiles on the emotionally reactive and aggressive behavior scales. Among girls, in contrast, higher prenatal BPA concentration was associated with better scores, with the differences reaching significance for the anxious/depressed and aggressive behavior scales. The reasons for the discrepancies between the findings of these two studies are unknown.

At present, the evidence regarding BPA neurotoxicity at levels experienced in the general population does not provide a consistent pattern in terms of sex differences in vulnerability or in the specific behavioral domains most affected.

## Polybrominated Diphenyl Ethers (PBDEs)

The evaluation of brominated flame retardants is complicated by the fact that, like polychlorinated biphenyls, there are many congeners that are likely to differ in their neurodevelopmental toxicity. As noted with respect to phthalates, studies generally have not characterized exposure in a way that permits the findings to be compared. In a cohort of Spanish newborns [13], congener concentrations were measured in cord blood and serum at 4 years of age. Statistical analyses were limited to PBDE 47 because it was the only congener that could be quantified in a sufficient number of samples. Concentration was dichotomized based on analytical rather than biological considerations (above or below the limit of quantification). No score on the McCarthy scales of children's abilities was significantly associated with either prenatal or postnatal concentration of PBDE 47. Higher postnatal concentration was significantly associated with teacher-reported ADHD symptoms and poorer social competence. In another Spanish cohort, Gascon et al. [14] evaluated the relationship between the sum of the concentrations of PBDE 47, 99, 100, 153, 154, 183, and 209 in colostrum and children's scores on the Bayley scales at 12-18 months of age. Mental development index scores, but not psychomotor development index scores, decreased with increasing PBDE concentration, and this association appeared to be due largely to congener 209.

In an inner-city cohort in New York City, Herbstman et al. [15] measured congeners 47, 99, and 100 in cord blood and assessed children's neurodevelopment at 12-48 and 72 months of age. Multivariate analyses indicated significant associations between PBDE 47 and 12-month psychomotor development index scores on the Bayley scales; PBDE 47, 99, and 100 and 24-month mental development index scores; PBDE 100 and 36-month mental development index scores; PBDE 47, 99, and 100 and 48-month full-scale and verbal intelligence quotient (IQ) scores on the Wechsler preschool and primary scale of intelligence-revised (WPPSI-R); and PBDE 100 and 72-month performance IQ scores on the WPPSI-R. In a Taiwanese cohort, Chao et al. [16] measured 14 PBDE congeners in breast milk and scores at 8-12 months of age on the Bayley scales. The sum of the concentrations of the 14 congeners (mean of 2.92 ng/g lipid) was not associated with any scores on the Bayley scales (cognitive, language, motor, social-emotional, adaptive behavior). However, PBDE 209 concentration was significantly inversely associated with score on the cognitive scale, and PBDE 196 was significantly positively associated with score on the language scale. Finally, in a cohort in California, Eskenazi et al. [17] evaluated associations between the sum of the con-

centrations of 47, 99, 100 and 153 during gestation and children's cognition, motor function, and attention at ages 5 and 7 years. The sum was associated with poorer performance on a computerized continuous performance test at age 5 and with worse ratings on parent-completed attention questionnaires at ages 5 and 7. Teacher ratings of attention and other aspects of behavior, were not associated with gestational PBDE exposure, however. Higher child PBDE concentrations at 7 years were associated with more teacher-reported attention problems, but not parent ratings of such problems. Both gestational and concurrent PBDE concentrations were significantly inversely associated with scores on the verbal comprehension index of the Wechsler intelligence scale for children-IV, with childhood PBDE concentration also inversely associated with scores on full-scale IQ, as well as the perceptual reasoning and processing speed indices.

Clearly many important issues remain to be clarified, as the findings are not consistent across studies in terms of the most vulnerable developmental domains, nor in terms of which congeners confer the greatest neurodevelopmental risk.

## Perfluorinated Compounds (PFCs)

PFCs are a group of synthetic chemicals used as surfactants, surface treatment chemicals, and processing aids for many products, including repellent coatings on carpet, textiles, leather, and paper. Exposure occurs through transfer from food packaging and preparation materials, bioaccumulation in the food chain, and household dust. Only a few studies have evaluated the potential neurotoxicity of prenatal exposures to PFCs. In the Danish national birth cohort, early pregnancy plasma perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) levels were not related to maternal report of motor or mental development through age 18 months [18] or to maternal reports of motor coordination or behavior at age 7 [19]. Similarly, in a community sample of children exposed to PFOA through contaminated water, Stein et al. [20] found that scores on a comprehensive battery of neuropsychological tests were not related to children's serum PFOA, measured several years earlier, or to a modeled estimate of prenatal exposure.

Two studies have evaluated the association between PFC exposures and ADHD in children. Using National Health and Nutrition Examination Survey data, Hoffman et al. [21] reported increased odds of parent-reported ADHD with higher serum PFC levels. In the community sample of children exposed as a result of water contamination, however, reduced odds of parent-reported ADHD were observed at the highest PFOA levels and increased odds with increasing levels of

perfluorohexane sulfonate [22]. Gump et al. [23] found higher levels of several PFCs, although not PFOA, were associated with impulsivity using a differential reinforcement of low rates of responding task among a cohort of 9-11-year old children.

The current data provides only limited evidence that higher prenatal exposures, in non-occupational cohorts, cause adverse neuropsychological outcomes in children.

## Air Pollution

The possibility that gestational exposure to higher levels of air pollution is neurotoxic to fetal brain development has been investigated by Perera and colleagues [24] in New York City, China, and Poland. In New York City, higher prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) (greater than the median air concentration of 2.26 ng/m<sup>3</sup>) was associated with an IQ deficit of 4-5 points at age 5 years [24] and greater parent-reported behavior problems at age 6-7 years [25]. In China, higher cord blood levels of PAH-DNA adducts were associated with lower neurodevelopmental scores at 2 years of age [26] but not with lower IQ scores at age 5 years except among children also exposed to environmental tobacco smoke [27]. In Poland, air PAH concentrations greater than the median during pregnancy (17.96 ng/m<sup>3</sup>) were associated with lower nonverbal reasoning scores at age 5 years [28].

In a study conducted in Guatemala, Dix-Cooper et al. [29] found that higher exposure to carbon monoxide in the third trimester, a marker of exposure to woodsmoke, was associated with poorer scores on attention, memory, and fine motor tests at age 6-7 years. Cross-sectional studies of children in Mexico City identified several possible mechanisms of neurotoxicity, including increased inflammatory processes, white matter pathology, and amyloid- $\beta$  diffuse plaques in children [30,31].

Air pollution has only recently been recognized as a risk factor for neurodevelopmental toxicity, and though the findings reported to date give cause for concern, they cannot easily be integrated in terms of critical constituent(s) of air pollution, critical doses, and most vulnerable neurodevelopmental domains.

## Lead

Despite the long history of research on lead neurotoxicity, new evidence of adverse effects at lower and lower levels of exposure continues to accumulate at a rapid pace, stimulating numerous policy revisions. In early 2012, the US Centers for Disease Control (US CDC) issued guidelines for the identification and management of elevated blood lead levels in pregnant

women [32]. It concluded that a blood lead level of 5  $\mu\text{g}/\text{dL}$  places a woman's fetus at increased risk of adverse effects and warrants follow-up testing, patient education, and nutritional, environmental, and behavioral interventions to reduce lead exposure. Also in 2012, the US CDC abandoned use of the term "level of concern" with regard to childhood lead poisoning due to the lack of evidence that any blood lead level can be considered to be "safe" [33]. As an alternative, it suggested use of a "reference" value linked to the current distribution of blood lead levels in a population. The recommendation was that the blood lead level corresponding to the 97.5th percentile of the distribution be used to identify children with an unusually high blood lead level. Currently, the blood lead level corresponding to this percentile in US children is 5  $\mu\text{g}/\text{dL}$ , but it can be expected to be lower in the future as additional measures to reduce population exposures are implemented.

This shift in the strategy used to identify children at increased risk was motivated by recent evidence that blood lead levels well below 10  $\mu\text{g}/\text{dL}$  are associated with outcomes such as reduced IQ, executive function deficits, and attention deficit hyperactivity disorder [34]. One of the more striking recent findings is that the slope of the dose-effect relationship relating blood lead level and neurodevelopment is nonlinear, specifically supra-linear, such that the rate of decline in children's scores is greater at blood lead levels below 10  $\mu\text{g}/\text{dL}$  than it is at levels greater than 10. For example, in the pooled analyses of 1,333 children enrolled in 7 international prospective studies, an increase from 2.4 to 10  $\mu\text{g}/\text{dL}$  in childhood blood lead level was associated with a decline of 3.9 points in full-scale IQ, whereas increases from 10 to 20 and from 20 to 30 were associated with declines of 1.9 and 1.1 points, respectively [35].

A birth cohort study that involved follow-up of participants at about 30 years of age reported preliminary evidence that umbilical cord blood lead level is associated with amyloid-beta levels in blood, as well as the expression of genes associated with the risk of Alzheimer's disease [36]. This is consistent with the finding, in studies in rodents and non-human primates, that early life lead exposure predisposes to neurodegeneration in adulthood via epigenetic processes [37]. Use of a variety of magnetic resonance brain imaging modalities, including morphometric [38], diffusion tensor [39], magnetic resonance (MR) spectroscopy [40], and functional MR [41] has provided evidence that prenatal or early childhood blood lead levels are associated with a variety of adverse effects on adult brain structure, organization, and function.

## Methylmercury

The primary pathway of human exposure to methylmercury is the consumption of contaminated foods, particularly seafood and rice [42]. Although the devastating impact of high prenatal exposure to methylmercury has been recognized for decades, the importance of chronic low-level exposure has been controversial due to the apparent conflict between the findings of the two largest prospective birth cohort studies, conducted in the Faroe Islands and the Seychelles Islands. Whereas reports from the Faroe Islands study have consistently identified methylmercury-associated deficits in children's neurodevelopment [43,44], reports from the Seychelles Islands have not [45,46]. Indeed, the associations found in the Seychelles study have tended to suggest that higher methylmercury exposure is associated with better child development. This discrepancy has vexed risk assessors charged with establishing exposure standards. Relying largely on the Faroe Islands study, the US Environmental Protection Agency (EPA) established a reference dose of 0.1  $\mu\text{g}/\text{kg}$  body weight/day for methylmercury intake [47], but other groups, such as the US Agency for Toxic Substances and Disease Registry, relying on the Seychelles Islands study, suggested that a higher dose, such as 0.3  $\mu\text{g}/\text{kg}/\text{body weight}/\text{day}$ , would be adequately protective for fetal neurotoxicity [48].

Recent studies have begun to provide some clarity regarding the basis for the apparent conflict of the findings of the Faroe Islands and Seychelles Islands studies. The key was the recognition that a woman's seafood consumption exposes her fetus not only to methylmercury but to nutrients that promote optimal development (e.g., omega-3 fatty acids, choline, selenium), and that a failure to consider this in the data analysis can result in an underestimate of the adverse impact of mercury. The existence of such negative confounding is illustrated by analyses of a birth cohort in Boston [49,50] and by a re-analysis of the Faroe Islands data [51]. In a new Seychellois cohort, in which biomarkers of children's nutritional status were measured, inverse associations have been found between prenatal methylmercury exposure and infant development when appropriate adjustments are made for the beneficial constituents of seafood [52].

The US EPA reference dose of 0.1  $\mu\text{g Hg}/\text{kg}/\text{day}$  corresponds to a maternal hair mercury level during pregnancy of approximately 1  $\mu\text{g}/\text{g}$  (or 5.8  $\mu\text{g}/\text{L}$  in cord blood). The point of departure for deriving this value is the lower limit of the confidence interval of the benchmark dose (BMD), the hair mercury concentration that is associated with a specified adverse effect (specifically a doubling of scores 2 or more standard deviations below the expected score). The lower limit of the BMD is then

divided by uncertainty factors to adjust for deficiencies in the database. Therefore, 1  $\mu\text{g}/\text{g}$  of hair mercury was not a level at which adverse impact was directly observed in the Faroe Islands study. In fact, few women in this cohort had biomarker levels this low (the mean was 4.27 and the inter-quartile range 2.6-7.7). However, some recent studies do provide limited evidence that prenatal exposure at levels close to the reference dose are associated with adverse neurodevelopment [49,50,53,54], including behaviors associated with ADHD disorder [55].

Worldwide, levels of methylmercury exposure vary considerably due to variability in diet. The mean concentration of hair mercury in US women of reproductive age is 0.2  $\mu\text{g}/\text{g}$  (95th percentile: 1.7) [56], and the mean concentration of mercury in blood is approximately 1  $\mu\text{g}/\text{L}$  (95th percentile: 7.1) [57]. In Japanese women, biomarker levels are approximately 10-fold higher [58,59]. In a representative sample of the population of the Republic of Korea, the geometric mean blood mercury level was 3.2  $\mu\text{g}/\text{L}$  [60]. Hair mercury levels are particularly high among individuals living in areas heavily impacted by artisanal gold mining, in which mercury is used as an amalgamator, eventually ending up in waterbodies, contaminating fish and exposing subsistence fishermen and their families [61]. These activities are being conducted in approximately 50 countries.

## Manganese

Unlike all of the other chemicals reviewed here, manganese is an essential nutrient, and the potential neurodevelopmental consequences of manganese excess have only recently come under investigation. Progress in this area of investigation has been hampered due to the absence of a clear consensus among investigators regarding the best biomarker of exposure. Studies have relied on hair manganese, blood manganese, and water manganese to represent children's exposures. Claus Henn et al. [62] reported an inverted U-shape relationship between blood manganese (mean 24.3  $\mu\text{g}/\text{L}$ , standard deviation = 4.5) and neurodevelopment in 12 month olds, such that both manganese deficiency and manganese excess were associated with lower scores. Water manganese level (mean 795  $\mu\text{g}/\text{L}$ , range 4-3,908) was reported to be inversely related, in a dose-related manner, to the IQ scores of 10-year-old Bangladeshi children [63]. Among 8-11 year old Bangladeshi children, achievement scores in mathematics were significantly lower among children with water manganese levels exceeding 400  $\mu\text{g}/\text{L}$ , but scores in language skills were not [64]. In a study conducted in Quebec, where the water manganese levels are much lower than in Bangladesh, 6-13 year-old children with higher levels of manganese in drinking water (mean 34  $\mu\text{g}/\text{L}$ , range 1-2,700) had signifi-

cantly lower IQ scores (6.2 point difference between the scores of children in the highest vs. lowest manganese quintiles) [65].

Elevated manganese exposure has also been reported to be associated with an increased risk of behavior problems in children. In a study of 8-11 year old Bangladeshi children, higher water manganese levels (mean 889  $\mu\text{g/L}$ , range 40-3,442) were associated more teacher-reported internalizing and externalizing behavior problems [66]. In a pilot study of 6-15 year-olds in Quebec, Bouchard et al. [67] found that children with higher hair manganese levels (mean 5.1  $\mu\text{g/g}$ , range 0.3-20.0) were reported by their teachers to have more oppositional and hyperactive behaviors.

A few studies have reported on the neurodevelopmental impact of children's co-exposures to manganese and other contaminants. Wright et al. [68] found interactions between manganese and arsenic such that elementary school-aged children with hair levels above the median value for both metals had significantly worse verbal skills than children with levels above the median for only one metal. Wasserman et al. [69] did not find such an interaction in their Bangladesh studies, however. Claus Henn et al. [70] reported significant interactions between manganese and lead, such that the slope of the dose-effect relationship between blood lead and infant development was steeper among children in the highest quintile of blood manganese level than it was among children with lower blood manganese levels. A similar finding was reported by Kim et al. [71] in older children.

The use of different exposure biomarkers in different studies makes it difficult to compare the findings, especially those relating to the dose-effect relationships. As a whole, the findings implicate manganese as a developmental neurotoxicant, but details of the relationships, including the critical windows of vulnerability and the most vulnerable domains, remain to be clarified.

## Arsenic

Developmental neurotoxicity has only recently been considered to be among the potential sequelae of increased arsenic exposure. Many of the studies demonstrating this association have been conducted in Bangladesh, where wellwater can be highly contaminated due to the local geology. Several studies reported on a cohort of 1,700 children for whom urinary arsenic measures from early and late gestation (approximately 80  $\mu\text{g/L}$ , range 37-230) and the post-natal years were available [72-74]. No associations were observed between arsenic levels and infant development at 7 or 18 months of age, but, at 5-years of age, concurrent urinary arsenic, urinary arsenic in late gesta-

tion, and urinary arsenic at 1.5 years, were inversely associated with verbal IQ and full-scale IQ scores, but in girls only. Each 100  $\mu\text{g/L}$  increase in urinary arsenic was associated with a 1-3 point decline in IQ score. The results of this longitudinal study illustrate the importance of extending follow-up beyond infancy, when the neurodevelopmental testing that is possible is limited in its validity and scope.

Several cross-sectional studies of older children, in which measurements or estimates of prenatal exposure were not available, have reported significant associations between children's neurodevelopment and arsenic biomarkers (e.g., urine, hair) or concentrations in environmental media (e.g., well water) [66,75-78].

## OPs

Several birth cohort studies that included neurodevelopmental follow-up at school-age provide consistent evidence that prenatal exposure to OPs is associated with reduced IQ scores in children. In two birth cohorts, the concentrations of urinary dialkyl metabolites in pregnant women were measured and found to correspond roughly to the upper half of the distribution of values in pregnant US women. Bouchard et al. [79] reported that a 10-fold increase in total urinary dialkyl phosphate metabolites was associated with a 5.6 point loss in full-scale IQ, while Engel et al. [80] reported that a 10-fold increase was associated with a loss of 1.4 points. Rauh et al. [81] measured the OP chlorpyrifos in umbilical cord blood plasma in an urban cohort and found that children's IQ scores at 7 years of age declined 1.4 points for each standard deviation increase in concentration.

Higher levels of OP metabolites have also been linked to an increased risk of ADHD [82] or parent-reported ADHD-related behaviors and performance on a continuous performance test [83]. Rauh et al. [84] conducted structural MRI studies on a subset of their New York City cohort. Children with prenatal exposures to chlorpyrifos in the upper tertile of the distribution showed evidence of white matter pathology, cortical thinning, and alterations in the usual sexual dimorphisms in brain morphology.

Though the number of studies is limited, the evidence is persuasive that prenatal exposure to OPs at levels of exposure that are prevalent in the general population is detrimental to children's neurodevelopment. Many details about the relationship remain to be clarified, but given the prevalence of prenatal exposures that have been linked to adverse outcomes, additional research on this topic is clearly warranted.

## Conclusion

For some chemicals, higher prenatal exposures have clearly and conclusively been linked to postnatal expressions of neurotoxicity. For others, it is evident that the literature is inchoate, containing study findings that, at this stage, are difficult to reconcile or integrate. For some of the chemicals, it is exceedingly challenging to characterize exposure due to short biological residence times (e.g., OPs, BPA) or the complexity of chemical class (e.g., PDBEs). The literatures on lead and arsenic illustrate the importance of conducting prospective studies that involve suitably extended follow-up, despite the substantial logistical obstacles involved in doing so, as subtle impacts might not be evident using the relatively crude assessment tools that are available for use in infancy. Moreover, as noted earlier, pregnant women are not exposed to single chemicals but to complex mixtures. It is difficult enough to characterize the neurotoxicity of exposure to single chemicals, but sooner or later, we will have to develop strategies for tackling the issue of interactions that more closely reflect real-world exposures.

The speed of any reconciliation of apparent conflicts in findings among studies would be facilitated if investigators designed studies so that the findings could be compared more easily. For some chemicals, this would involve reaching consensus on whether the best exposure measure is a biomarker or the concentration in an environmental medium (e.g., manganese, arsenic), whether exposure is expressed in terms of the individual chemical, classes of chemical (e.g., phthalates, PBDEs), and whether the most appropriate biomarker of exposure is concentration of the parent chemical or of a metabolite (e.g., OPs). Comparison among studies would also be facilitated if common endpoints were assessed at the same developmental stages, preferably using the same assessment tools and adjusting for standard sets of covariates. The value of coordinating studies in this way is illustrated by the pooled analyses that were carried out combining data from several international prospective studies of lead neurotoxicity [35]. By pursuing such coordination to the extent possible, the amount of time needed to discern coherent signals in the evidence available for a chemical or class of chemical could be reduced, permitting more timely formulation of appropriate public health measures.

## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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