Chapter 7
Neurodevelopment and Neurobehavioral Disorders in Relation to Developmental Exposures

Youssef Oulhote and David C. Bellinger

Abstract The environment is now known to be an important determinant of child health, with increasing evidence that some chemicals are particularly toxic to the human brain. More than 140,000 new chemicals have been synthesized since 1950. In this chapter, we review the most studied neurotoxicants for their associations with neurodevelopment and the potential mechanisms of action. We describe the societal effects of such contaminants, and discuss the main challenges facing studies investigating potential neurodevelopmental effects of chemicals. Finally, we provide future directions for the next generation of developmental neuroepidemiology studies.

Keywords Neurodevelopment · Children · Chemicals · Neurotoxicants · Review

Neurodevelopmental disorders are a group of conditions characterized by impairments of social skills or intelligence due to perturbed growth and development of the brain, with onset in the developmental period. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), they include

Y. Oulhote (✉)
Department of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts Amherst, Amherst, MA, USA

Department of Environmental Health, Harvard T. H. Chan School of Public Health, Boston, MA, USA
e-mail: youlhote@umass.edu

D. C. Bellinger
Department of Environmental Health, Harvard T. H. Chan School of Public Health, Boston, MA, USA

Department of Neurology, Harvard Medical School, Boston, MA, USA

Boston Children's Hospital, Boston, MA, USA
e-mail: David.Bellinger@childrens.harvard.edu

R. Kishi, P. Grandjean (eds.), *Health Impacts of Developmental Exposure to Environmental Chemicals*, Current Topics in Environmental Health and Preventive Medicine, https://doi.org/10.1007/978-981-15-0520-1_7

intellectual disability (intellectual developmental disorder), communication disorders, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), specific learning disorders, and motor disorders [1]. They are among the most common chronic disorders in children worldwide. For instance, in 2016 9.4% of US children 2–17 years of age had at one time been diagnosed with ADHD [2]. The prevalence of children aged 3–17 years who had ever been diagnosed with a developmental disability increased from 5.8% to 7% between 2014 and 2016 [3], whereas the prevalence of ever receiving an ASD in children aged 3–17 years reached 2.5% in 2016 [4].

Although the conditions included among neurodevelopmental disorders are heterogeneous, these disorders are thought to be developmental, with early onset and involving a multitude of potential risk factors. The environment is now known to be an important determinant of child health, with increasing evidence that some chemicals are particularly toxic to the human brain. More than 140,000 new chemicals and pesticides have been synthesized since 1950, with about 5000 that are produced in high volume, and many have become ubiquitous in the environment [5]. The fetal period is a critical window of development, and in utero exposure to environmental chemicals has a significant influence on fetal growth and development, with consequences for birth outcomes, child development, and cognitive and behavioral functions [6, 7]. For instance, over 200 chemicals used in commerce or industry are known to be neurotoxic to humans [6]. Disruptions caused by exposure to these toxic chemicals may have far-reaching consequences with a considerable impact in regard to long-term complications including developmental delays, effects on socio-emotional adjustment, educational success, and quality of life [8–10]. In this chapter, we describe the accumulated evidence in regard to specific chemicals of interest, the potential mechanisms of action through which exposure to these chemicals affects child neurodevelopment, and the societal impacts of these neurotoxicants. We will finally discuss challenges arising when studying effects, and propose future research needs and directions.

7.1 Main Findings in Regard to Neurodevelopment and Developmental Chemical's Exposure

7.1.1 Trace Elements: Lead, Manganese, Mercury, and Arsenic

There is a compelling evidence that trace metals adversely affect neurodevelopment and increase risk of neurodevelopmental disorders. Lead (Pb) is the most studied environmental toxicant, and its neurotoxic effects have been known and well described for centuries. For instance, Dioscorides, the well-known Greek physician and botanist once said: "Lead makes the mind give away". Thus, Pb is considered a paradigm metal to study. Exposure to high concentrations of Pb has been linked to

effects on the central nervous system, such as deficits in concentration, memory, cognition, and behavior [6, 10]. Epidemiological research has linked Pb exposure during childhood to deficits in cognitive skills and IQ, behavioral problems, and attention hyperactivity disorder (ADHD) [11–14]. Prenatal and early postnatal Pb poisoning and long-term exposure to Pb at low levels has also been associated to an increased risk of aggressive behaviors [15]. Recent studies also showed a link between early-life exposure to Pb and criminal behavior later in life [16]. Overall, Pb exposure unequivocally affects the developing brain, and its effects have been shown for a variety of cognitive and behavioral domains.

Although manganese (Mn) is an essential element, high exposure to Mn has been associated with behavioral problems, decreased cognitive function, and frontal lobe abnormalities [17]. The health implications for fetuses and infants are a concern given the high accumulation of Mn in tissue during development [18]. Indeed, maternal levels of Mn increase markedly during pregnancy, peaking in the third trimester [19]. Both prenatal and postnatal exposure to Mn has been linked to neurodevelopmental effects. In Bangladesh, greater exposure to manganese from drinking water was associated with reduced mathematics achievement scores in school children [20], whereas in Quebec, greater hair concentrations of Mn were associated with hyperactivity [21], reduced memory [22], and attention functions [23]. Other studies from Mexico and Brazil showed reduced intelligence quotient and impaired olfactory function [24, 25].

Arsenic (As) has also received much attention as a neurotoxicant, largely based on studies conducted in Bangladesh. Currently, the permitted concentration of arsenic in water is 10 μg/L (10 ppb); yet, an estimated 100 million people worldwide are exposed to excessive amounts of arsenic via drinking water [26]. As, including inorganic and methylated arsenicals, accumulates in many parts of the brain [27]. Studies of children from Bangladesh showed an inverse association between cognitive function and As levels in water [28, 29]. A recent meta-analysis on the associations between arsenic exposure and IQ concluded that a 50% increase in arsenic levels was associated with a 0.4% decrease in IQ in children [30]. Interestingly, studies on As exposure and neurodevelopment showed differential effects between boys and girls with a higher susceptibility among girls.

Mercury (Hg) is a trace metal of known toxicity. It naturally occurs in several physical and chemical forms, including metallic mercury, inorganic, and organic mercury (e.g., methylmercury, MeHg), with varying toxic effects [31]. Hg can have neurotoxic effects on the human central nervous system, particularly during fetal development. A number of prospective cohort studies assessed the neurodevelopmental effects of chronic low and moderate prenatal MeHg exposure from maternal fish consumption. The most influential studies were conducted in the Faroe Islands and were used by the EPA to establish guidelines for mercury toxicity [6, 32–34].

Although the individual toxicity of these trace elements is now well established, the neurotoxic effects of metals may occur in an interactive way, and several metals may have synergistic effects. However, to date few studies have investigated the independent and joint toxicity of metals within a mixture.

7.1.2 Polychlorinated Biphenyls (PCBs) and Brominated Flame Retardants (PBDEs)

Polychlorinated biphenyls (PCBs) are ubiquitous neurotoxicants used for various industrial applications as coolants and lubricants in electrical equipment because of their general chemical inertness and heat stability [35]. PCBs were manufactured as a mixture of congeners and banned from production and use in the late 1970s. The major exposure route for humans is through food, whereas inhalation and dermal routes are predominant in occupational settings [36]. There is a large body of scientific evidence showing neurodevelopmental effects of early exposure to PCBs. Recent systematic reviews showed that prenatal or early postnatal exposure to PCBs was associated with adverse cognitive and behavior outcomes in most studies, although null associations were also reported [37, 38]. Additionally, a few studies found associations between developmental exposure to PCBs and autism [39, 40].

Polybrominated diphenyl ethers (PBDEs) and their hydroxylated forms have been widely studied for their neurotoxicity. PBDE additives are not fixed in the polymer product through chemical binding, and can thus leak into the environment [41]. Like PCBs, they persist in the environment with relatively long half-lives. Human exposure is mainly due to ingestion of house dust, consumption of fish and other animal products, and breastfeeding for infants [42]. Higher maternal concentrations of PBDEs were associated with impaired cognitive and motor function, increased attention problems, anxious behavior, increased withdrawal, and altered response to frustration [43–46]. Additionally, early-life PBDE exposures were associated with decreased IQ and psychomotor development [47].

7.1.3 Pesticides

There is a strong scientific evidence that exposure to pesticides produces human health effects, including impairment of the central nervous system. Pesticides are widely used in both developed and developing countries, especially with the expansion of free-trade agreements and the focus of many developing countries on agricultural exports. This trend makes extensive pesticides use one of the major environmental health issues in low- and middle-income countries. The most prevalent chemical families of pesticides are organophosphates, organochlorines, and pyrethroids, with organophosphates being the most frequently used. Overall, research points to deleterious effects of pesticides on cognitive and behavioral development in children. Findings from prospective birth cohorts such as the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) point to a multitude of effects of organophosphates, including decreased IQ [48–50], impaired mental development, and pervasive developmental disorder at 24 months of age [51]. A study in New York City found a possible link between prenatal indoor pesticide use and abnormal neonatal reflexes [52]. Other studies from Brittany,

France reported associations between prenatal pesticides exposure in an agricultural area and cranial growth in a prospective birth cohort of 3421 pregnant women [53]. Prenatal exposure to organochlorine pesticides (DDT and its metabolite DDE) was also associated with reduced psychomotor development index scores and significant reduction in the general cognitive index and neurodevelopmental delays [54–56]. However, many studies that investigated the associations between DDE exposure and cognitive and behavioral development reported null findings [57–60]. Unlike DDT, pyrethroids are rapidly metabolized and have short half-lives in humans (hours to days) [61], and very few studies investigated their associations with child neurodevelopment. Oulhote et al. found a positive association between concurrent exposure of some pyrethroid metabolites and child difficulties scores in a cross-sectional study in Canada [62]. Although a French study found no association between prenatal urinary pyrethroid metabolites and 6 year olds' performance on WISC Verbal Comprehension or Working Memory [63], studies from China and Mexico reported that prenatal pyrethroid exposures were associated with lower cognitive scores in 1-year infants [64] and children 2–3 years of age [65]. Further, studies from France and the USA showed adverse effects of pyrethroids exposure on behavioral outcomes in children [66, 67].

7.1.4 Plasticizers

Studies investigating the associations between developmental exposure to plasticizers such as phthalates and bisphenol A (BPA) are still in their infancy but have shown some evidence of associations with both cognitive and behavioral outcomes. Developmental exposure to phthalates was shown to be associated with ADHD behaviors, autistic traits, reduced mental and psychomotor development, and reduced IQ [68–71]. BPA was also reported to be associated with more internalizing and externalizing behaviors, increased risk of ADHD, and executive function [72–75]. Most of these studies point to sexually dimorphic effects of these compounds on child neurodevelopment, with boys being more vulnerable [76]. Other studies showed no association between neither phthalates nor BPA with child neurodevelopment [71, 77].

7.1.5 Perchlorate

Perchlorate is used in a variety of industrial products including missile fuel, fireworks, and fertilizers, and industrial contamination of drinking water occurs in several areas [78]. Exposure to perchlorate is widespread and exposure from contaminated food and drinking water is ubiquitous [79]. Perchlorate can block iodide uptake into the thyroid gland, and result in decreased production and secretion of thyroid hormone, therefore potentially perturbing proper brain development

that is dependent on thyroid function. One study investigated potential neurodevelopmental effects of gestational exposure to perchlorate in the UK and Italy. Findings from this study showed that higher maternal perchlorate levels in hypothyroid/hypothyroxinemic pregnant women were associated with adverse effects on offspring cognitive development [80].

7.2 Potential Mechanisms of Action

Traditionally, mechanisms of neurotoxicity have been identified as pathways leading to neuronal cell death, neuropathology, or neural injury. However, recent research highlights alternative mechanisms that result in more subtle but serious changes in cognition and behavior. These mechanisms include neuroendocrine and immune system pathways, in addition to inflammation and epigenetic mechanisms.

Early-life inflammation induced by exposure to chemicals, especially metals, has been suggested as a potential mechanism for the observed neurodevelopmental effects [81, 82]. For instance, chronic low-level lead exposure may trigger chronic inflammation and lead to adverse changes in inflammatory markers such as CRP [83]. Lead is also known to interfere with the *N*-methyl-D-aspartate receptor, which is essential for hippocampus-mediated learning and memory [84, 85], and to disrupt neurotransmission by inhibiting neuronal voltage-gated calcium channels and intracellular calcium dynamics [86]. Methylmercury also induces impairment in intracellular calcium homeostasis, in addition to alteration of glutamate homeostasis and oxidative stress [87]. Methylmercury perturbs cell proliferation and migration, producing widespread abnormalities including heterotopias, reduced cell densities, incomplete myelination, glial proliferation, and limited gyral differentiation [12]. The effects of Mn on behavior and cognitive abilities in children may be related to effects on the dopaminergic system during development. Mn accumulates in neurons, astrocytes, and oligodendrocytes, inhibits ATP synthesis in mitochondria, and interferes with the dopaminergic system [88, 89]. Arsenic has been shown to impact the synaptic activity of neurons localized to the hippocampus [26]. These effects may be attributable to alterations in synapse-related gene expression. Experimental studies showed that exposure to arsenic throughout gestation increased DNA methylation on two genes involved in neural plasticity in rat cortex and hippocampus [90]. Hypomethylation of these genes in both regions was observed later after 4 months of cumulative exposure to arsenic. Arsenic also interferes with glucocorticoid, cholinergic, and glutamatergic signaling, leading to hippocampal-related deficits [91–93].

Many pesticides, including organophosphates (OPs), carbamates, pyrethroids, and organochlorines (OCs), are designed to attack insects' central nervous system by interfering with chemical neurotransmission or ion channels. They specifically work by targeting enzymes that regulate neurotransmitters, such as acetylcholine, which is released by motor neurons [94]. For instance, both OPs and carbamates have a common target of toxicity, the inhibition of acetylcholinesterase, whose

physiological role is hydrolyzing acetylcholine, a major neurotransmitter in the central and peripheral nervous system [95, 96]. Pyrethroids bind to the sodium channel and slow its activation, as well as the rate of inactivation, leading to a stable hyperexcitable state, and inhibit Gamma aminobutyric $acid_A$-gated chloride channels, leading to the choreoathetosis, salivation, and seizures seen in occupational exposures [96]. Finally, OCs such as DDT interfere with the sodium channels in the axonal membrane, by a mechanism like that of pyrethroids, prolonging the depolarizing (negative) afterpotential of the action potential, thus producing a period of increased neuronal excitability [97].

PCBs exert their neurotoxicity through a variety of mechanisms including thyroid disruption, interference with sex steroids, and aryl hydrocarbon receptor (AhR) activity, especially for dioxin-like PCBs [98–100]. Thyroid and sex steroid hormones are critical for proper brain development, and subtle perturbations of these systems have been shown to be associated with both cognitive and behavioral problems. PBDEs act on the developing brain mainly through a reduction in circulating thyroid hormones; however, direct effects on the developing brain have also been reported. Thyroid hormones are known to play a role in brain development, and a large body of experimental and human studies showed decreased levels of thyroxine (T4) and triiodothyronine (T3), and increased likelihood of hypothyroidism in relation to higher levels of PBDEs [101, 102]. These effects on the thyroid hormone levels are explained by an enhanced metabolism and excretion of T4 as a result of exposure to PBDEs and interactions of PBDEs (or their metabolites) with the thyroid hormone transport systems or with thyroid receptors [103]. In addition to their effect on the thyroid system, PBDEs exert effects by inducing oxidative stress in human neuroblastoma cells and hippocampal neurons, interfering with calcium homeostasis, and causing DNA damage and apoptotic cell death [104–107].

Plasticizers are endocrine-disrupting chemicals that can mimic the effects of endogenous hormones or disrupt the synthesis, metabolism, or uptake of endogenous hormones. For instance, phthalates may interfere with the action or metabolism of androgens and thyroid hormones, with subsequent anti-androgenic effects [108]. Increased concentrations of phthalates were inversely associated with total serum thyroid hormone levels in pregnant women and neonates and thyroid stimulating hormone in neonates [109]. Additionally, phthalate exposure may exert neurotoxic effects by increasing oxidative stress and via epigenetic re-programming of the fetus and placenta [76]. BPA may interfere with thyroid-specific gene expression, and affect androgen/estrogen concentrations by inhibiting key enzymes involved in gonadal hormone synthesis and metabolism [110]. These hormones play a substantial role in brain development [111].

Although perchlorate has not been extensively studied in relation to neurodevelopment, its effect on the thyroid gland through blocking the uptake of iodine is well studied. Low-level exposure to perchlorate has been shown to be positively associated with TSH and negatively associated with free T_4 [112, 113]. Thyroid hormones are essential for proper brain development, and it is therefore hypothesized that the effects of perchlorate on thyroid function may lead to potential neurodevelopmental

consequences [114, 115]. These effects may be stronger in children of women with low iodine status [116].

It is important to mention that these potential mechanisms of action are not mutually exclusive and many chemicals, such as metals, can exhibit endocrine-disrupting properties or increase oxidative stress and inflammation, mediated by epigenetic and neuroendocrine mechanisms.

7.3 Societal Impact of Environmental Chemicals

An argument frequently advanced by those skeptical about the importance of the neurodevelopmental impact of environmental chemicals is that the effect on an individual child is relatively modest, failing to reach the level of clinical significance. This argument fails to consider the issue in the context of population health. Effect estimates from epidemiologic data are population average effects and should be interpreted in the context of a population and not at the individual level. Some individuals will be resistant and some will be more sensitive. It is critical to view the issue of children's exposures to environmental chemicals in the context of population health and not just the health of an individual child. Moreover, the impact of a factor at the population level depends not only on the magnitude of its impact on health, or its effect size, but also on the distribution of the factor or, in the case of a dichotomous factor, its incidence or prevalence. In a set of comparative analyses of pediatric disease and events, such as brain tumors, congenital heart disease, traumatic brain injury, iron deficiency, and lead exposure, Bellinger [97] estimated the total number of IQ points lost among US children younger than 5 years of age associated with each disease or event. The estimate for the loss associated with lead exposure was nearly 23 million IQ points, exceeded only by preterm birth. Among the reasons for this is the absence of a threshold for its inverse relationship with IQ and the fact that virtually every child has a quantifiable blood lead concentration. As a result, and in contrast to most other diseases and events, every child contributes to the total IQ loss in the population that is associated with lead exposure. In fact, the greatest contribution to the total loss is contributed by the very large proportion of children with blood lead concentrations at the lower end of the distribution. A similar calculation using the blood lead distribution of young US children from the late 1970s indicated that, at that time, the total loss of IQ points attributable to lead was approximately 125 million points, suggesting that the measures taken to reduce population lead exposure since that time produced savings of about 100 million IQ points in the current cohort of children. With approximately 25 million children in this age range, the average IQ benefit has been approximately 4 points. Analyzing temporal trends in the IQ scores of US adults over the period in which population blood lead concentrations declined, Kaufman et al. [117] estimated that the mean IQ has increased by 4–5 points.

An even more critical point with regard to the societal impact of environmental chemicals is that a reduction in a child's IQ is only the "tip of the iceberg" in terms of their neurodevelopmental impacts. IQ is easily measured and widely recognized outcome, but it is merely a marker for a range of other neuropsychological and behavioral adversities that have a substantial impact on an individual's future health and well-being. A full account of the burden of disease imposed by environmental chemicals must include these downstream impacts on mental health and economic success that can seriously impair quality of life [12].

This perspective is not captured by the method traditionally used to estimate global burden of diseases and risk factors. Current efforts to estimate the burden of disease associated with environmental chemicals consider only a clinically significant IQ deficit as the sequelae of chemicals such as lead [118], i.e., an IQ score <70, the criterion for identifying mild intellectual disability. As the research reviewed in this chapter illustrates, a reduction in IQ is only the "tip of the iceberg" in terms of the neurodevelopmental impacts of chemicals, which, as described, include deficits in specific neurodevelopmental domains such as executive functions, attention, language, and memory, and mental health disorders such as ADHD and, perhaps, autism spectrum disorders. IQ has the virtue of being easily measured, but an IQ deficit likely is only an indication of the likely presence of a range of other neuropsychological and behavioral adversities that subsequently unfold as a "developmental cascade" and have a substantial impact on an individual's future health and well-being [119].

Another dimension of the societal impact of many environmental chemicals is that the non-random distribution of exposures perpetuates health disparities. In the case of lead, for example, poor and minority children tend to incur greater exposures due to the siting of point sources and the presence of greater lead hazards in the housing available to them. Compounding this problem is the fact that, at any given blood lead concentration, the adverse effects of lead are greater on children already at increased risk of poor outcomes due to the presence of other risk factors. In quantile regression analyses of the associations between blood lead concentration and reading scores, Miranda et al. [120] showed that lead exposure stretched out the left-hand tail of the performance distribution, such that the decrease per μg/dL increase in blood lead concentration was greater among poorer readers than among better readers. One effect would be to aggravate the disparities between the educational outcomes of poor children and their more advantaged peers and, as a study in New Zealand showed, reduce upward social mobility, limiting the socioeconomic success that is achieved in adulthood [121]. The origins of such environmental injustices can be located in the social and economic forces of modern society. One factor contributing to their persistence is the lack of voice affected communities have in influencing those with the power and the means to implement remedies. This was illustrated by the episode of lead contaminated water in Flint, Michigan. It took 18 months after citizens began to complain about the poor quality of their drinking water before government officials acknowledged the problem and began to address it.

7.4 Challenges and Future Directions in Studying Environmental Neurotoxicants

In the following section, we discuss some of the main challenges in investigating the potential neurotoxicity of chemicals. As summarized earlier, many chemicals have been shown to exert neurodevelopmental effects, and the body of literature keeps growing as new compounds are introduced into the market. The multiplicity of environmental neurotoxicants calls for a general framework that considers the cumulative effect of the mixtures, in addition to their potential interactive effects, while including other effect modifiers (i.e., Sociomics). It will also be important that the field adopt novel causal inference approaches that are widely used in clinical, pharmaco-epidemiology, social epidemiology, and econometrics. Finally, the complexity of child development calls for holistic approaches that consider all the facets of development and the multilayers of potential interactions, hence the need to consider broader definitions of the environment beyond just chemicals exposures.

7.4.1 The Issue of Chemical Mixtures and Cumulative Effects

Perhaps one of the most important issues for the field is the development of methods to account for the cumulative effects of chemical mixtures. Although the general population experiences exposure to multiple chemicals from many different sources at various doses, most studies in environmental epidemiology consider each chemical separately when assessing the adverse health effects of environmental exposures. This single pollutant approach suffers from several pitfalls including: (1) the risk of false positives in the case of multiple hypotheses testing; (2) confounding from correlated exposures; and (3) the lack of insights on the cumulative or synergistic effects of multiple exposures. These all weaken the inferences that can be drawn about the relationships between chemicals and neurodevelopmental outcomes. In recent years, several statistical methods have been proposed to address these issues. These methods include environmental-wide association studies (EWAS) [122], penalized regression methods (i.e., least angle selection and shrinkage operator [LASSO]) [123], Ridge regression [124], and elastic net regularization [125], dimension reduction methods, and exposure-response surface methodology such as generalized additive models and Bayesian kernel regression methods (i.e., BKMR) [126]. A recent study by Agier and colleagues used simulation to demonstrate feasibility of some established and emerging methods for handling multiple correlated exposures [127]. While promising, these methods underperformed when the goal was identification of individual exposures with an impact on the phenotype of interest. Many exhibited high false discovery proportions as the number of correlated exposures increased. Moreover, results from a recent NIEHS workshop showed that none of the tested approaches appeared to outperform the others [128], and most of these methods performed poorly in the context of

complex mixtures [127]. More importantly, most of the methods (e.g., elastic net, LASSO) focus on the issues of correlated exposures while ignoring the threats arising from model misspecification (e.g., interactions, non-linearities). The most promising of these methods appears to be the BKMR. This method relaxes a priori parametric assumptions and allows for the investigation of cumulative effects and potential interactions between chemicals. However, one challenge is that such methods provide conditional estimates that are not applicable in simulating public health interventions since they do not provide marginal estimates of the exposures of interest. A new family of methods is emerging that takes advantage of the developments of machine learning, and specifically, ensemble learning techniques (i.e., stacked generalization). Machine-learning methods have shown great potential for quantifying the role of environmental exposures in regard to their effects on human health [129]. Typically, machine-learning approaches consist of algorithms that find variables (exposures) that are predictive of an outcome (phenotype) in two steps. In the first step, an algorithm "learns" the variables that are associated with the outcome. The algorithm is then tested in an independent dataset to estimate the predictive capability or generalizability of the algorithm [130]. Ensemble techniques reduce the variance and avoid overfitting by combining predictions from numerous "similar" algorithms. Although these methods are in their infancy, several of them have shown promising results in the context of chemical mixtures [131, 132], while others have been used in other contexts and could be leveraged to infer causal estimates of complex mixtures [133]. These methods allow for incorporation of multiple correlated exposures, estimation of both individual and cumulative effects at the population level, and screening of potential interactions. Moreover, these ensemble learning methods allow for more flexibility since they relax a priori assumptions regarding the functional forms and presence of interactions, which means that one can include all the exposures without specifying interactions or functional forms (e.g., non-linearities) and the approach will identify the models that yield the best predictions.

7.4.2 Incorporating Causal Inference Methods When Studying Neurotoxicants

For obvious ethical reasons, it is often impossible to conduct randomized controlled trials in the field of environmental epidemiology. Therefore, most studies investigating potential neurodevelopmental effects of chemicals rely on observational studies. Additionally, other issues arise when studying environmental chemicals that make causal inferences difficult. First, exposure to the chemical of interest is typically ubiquitous, and all individuals in the study are exposed at a detectable level, leading to continuous exposures, making emulation of RCTs nearly impossible. Second, environmental epidemiology relies on measurements of biomarkers to investigate the exposure-outcome relationship; such reliance on biomarkers makes it difficult to

insure "consistency" and "positivity," two major assumptions necessary for inferring causal effects. "The positivity assumption states that there is a nonzero probability of receiving every level of exposure for every combination of values of exposure and confounders that occur among individuals in the population" [134]. In other words, within each level of the exposure, one will need individuals with all levels of all confounders. This is obviously extremely difficult in studying continuous exposures unless a cohort includes millions of participants or exposures are categorized. The consistency assumption is the ability to hypothetically assign a certain level of exposure to a person exposed to a different level. This opens to the issue of defining what intervention could hypothetically lower the measured biomarker level to a specific desired level in an individual, or what other methodologists call "well-defined interventions" [135]. This calls for the identification of what kind of interventions can directly change the concentrations of a neurotoxicant in the tissue of interest (or circulating blood levels that are also just proxies of the level of neurotoxicant in the target tissue) [136]. This is obviously impossible outside of a few cases (e.g., chelation treatment for lead). Many physiological parameters will influence the measures of circulating levels of a neurotoxicant, and therefore impact the relationship between the external intervention (on which we can intervene) and the biomarker concentrations. This will likely violate the consistency assumption thereby impeding valid causal estimates. However, it is worth mentioning that this issue of consistency can be challenged in terms of scientific discovery. Not all studies aim at emulating an intervention when studying health effects of chemicals, therefore, the knowledge acquired from establishing causal links between a biomarker of exposure and neurodevelopment is still valuable and will likely lead to measures that can reduce external exposures at the population level. For more details on this debate, reader can refer to papers by Judea Pearl, Miguel Hernan, and others [135, 137, 138].

There is also a new body of methods that have been proposed recently to tackle some of the issues arising when inferring causality from observational data. One of the promising methods that can be used is Mendelian randomization analysis [139], which uses genetic variants as instrumental variables for exposures of interest. It is a useful method for assessing causal relationships because the allocation of alleles is random; therefore, genotypes are not expected to be associated with measured or unmeasured confounders. The use of single nucleotide polymorphisms (SNPs) that are associated with exposure levels but not with the outcome of interest (except through the exposure) represents an appropriate approach to examine the causal relationship between pollutant exposures and children's developmental outcomes. The metabolism and excretion of many xenobiotic substances has been linked to many SNPs (e.g., pesticides and paraoxonase or cytochrome P450). Using these SNPs to construct allelic scores robustly related to the exposures as instrumental variables may help to identify causal effects of environmental exposures on neurodevelopmental test scores. One limitation of such approaches is the lack of instrumental variables (SNPs) that are specific to a class of chemicals, but research on this field should yield valid instruments in the coming years. One study used two SNPs in the 10q24.32 region (near AS3MT) that show independent associations with arsenic metabolism efficiency to investigate the causal relationship between arsenic

metabolism efficiency and skin lesion risk [140]. Another issue that arises when using such methods is that they rely on very large sample sizes, and this will depend on the strength of the association between the SNP (or the allelic score combining many SNPs) and the biomarker of exposure. The stronger the association, the smaller the sample size that is needed.

Additional methods that can be leveraged are econometric methods that rely on quasi-experimental designs. Some of these methods leverage natural experiments to emulate randomized controlled trials. We recently leveraged the fact that undergrad students at Harvard University are randomly assigned to dormitories to infer causal estimates of high temperatures on cognitive functions among students during a heat wave [141]. A recent study from the National Bureau of Economic Research showed causal effects of air pollution on dementia by capitalizing on quasi-random variation in pollution exposure due to the EPA's 2005 designation of nonattainment counties for $PM_{2.5}$ [142]. Closer to our field, some mesalamine medications used to treat inflammatory bowel disease have dibutyl-phthalate (DBP) in their coating, whereas other mesalamine formulations do not. This difference and the fact that the type of medication depends mainly on the prescribing physician and not on other potential confounders have been leveraged to study the potential effect of DBP on semen quality [143]. Creativity in exploiting such random events will be a very useful approach in solving some of the most challenging issues in environmental neuroepidemiology studies.

7.4.3 Measurement Error in Exposures

Perhaps one of the most critical issues in the field of environmental epidemiology is the error in measuring both exposures and outcomes. Exposure and outcome misclassification can seriously affect estimates from studies investigating neurodevelopmental effects of chemicals. Non-differential exposure misclassification is a common problem, especially for endocrine-disrupting chemicals with short half-lives that tend to vary widely within individual. Under such conditions, an individual's true exposure will be difficult to establish because of the low precision of the measurement. When error is not related to the outcome of interest, this will often, but not always, bias the association towards the null. Several studies have used multiple samples to characterize exposure to short half-life compounds, yielding a better characterization. However, this will require a large number of samples, increasing costs in terms of follow-up and analyses [144]. Other researchers proposed using calibration and Bayesian methods to account for non-differential misclassification errors, but these are very rarely used [145]. Construction of latent functions based on measurements of a chemical in multiple matrices represents a hypothetical true measure of exposure and could tackle this issue by modeling the shared variance from these multiple measures instead of a single concentration. This approach was used in studies to examine neurodevelopmental effects of mercury and PFASs [23, 33, 146]. Other researchers propose sensitivity analyses to explore the impact of such biases, allowing for inference of interval estimates.

7.4.4 Holistic Approaches to Study Child Development

Child neurodevelopment is a dynamic process with a complex structure of determinants and feedback loops. Present studies of developmental neurotoxicants are still in their infancy in terms of addressing such complexity and future studies may benefit from incorporating it both in the study design and analyses stages. Currently, there is a strong need for a comprehensive approach that puts epidemiological studies of neurotoxicants within a developmental framework, particularly across the lifespan.

Context information matters and is a key to understanding effects of neurotoxicants on child development. For instance, many non-environmental cofactors play a key role beyond their main effects and can be effect modifiers of the associations between neurotoxicants and neurodevelopment. Many confounders can potentially play an effect modification role. Additionally, every factor that is impacting child neurodevelopment and not associated with the exposure may modify neurotoxicant's effect. An important example is the stimulating home environment. While it is very important to take this variable into account, it is not acting as a confounder in most of the studies, but mainly as a strong predictor of the neurodevelopmental outcome. It is therefore very useful to test for its modification effect. Another important example is some nutritional factors that co-occur with environmental exposures. Recently, a few studies showed that folic acid supplementation may blunt the deleterious effects of pesticides and air pollutants on autism [147, 148]. Selenium has also been shown to play an important modifying role in the association between mercury and neurodevelopment [149]. Both these examples of effect modifiers including stimulation and nutritional factors show up when investigating effect modification by socioeconomic status.

These contextual factors may be of an utmost interest in areas of the globe in which many environmental, nutritional, and social factors co-act to yield a high burden of developmental disabilities. For instance, around a third of children in low- and middle-income countries are not developmentally on track [150]. The interplay between nutritional deficiencies, lack of child stimulation due to education policies and early childcare, and a high burden of environmental exposures may explain a significant part of the observed delay in children's neurodevelopment in these countries. These issues cannot be tackled separately, hence the need for holistic approaches to study neurotoxicants, in addition to an urgent need to develop specific and tailored frameworks that can incorporate these complexities. Transposition of western models to the LMIC realities may likely fail if local dynamics and holistic approaches to environmental health are not considered.

References

1. Harris JC. New classification for neurodevelopmental disorders in DSM-5. Curr Opin Psychiatry. 2014;27(2):95–7.
2. Danielson ML, Bitsko RH, Ghandour RM, Holbrook JR, Kogan MD, Blumberg SJ. Prevalence of parent-reported ADHD diagnosis and associated treatment among U.S. children and adolescents, 2016. J Clin Child Adolesc Psychol. 2018;47(2):199–212.

3. Zablotsky B, Black LI, Blumberg SJ. Estimated prevalence of children with diagnosed developmental disabilities in the United States, 2014-2016. NCHS Data Brief. 2017;291:1–8.
4. Kogan MD, Vladutiu CJ, Schieve LA, Ghandour RM, Blumberg SJ, Zablotsky B, et al. The prevalence of parent-reported autism spectrum disorder among US children. Pediatrics. 2018;142(6):e20174161.
5. Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu NN, et al. The Lancet Commission on pollution and health. Lancet. 2017;391(10119):462–512.
6. Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity. Lancet Neurol. 2014;13(3):330–8.
7. Mattison DR. Environmental exposures and development. Curr Opin Pediatr. 2010;22(2):208–18.
8. Zwicker JG, Harris SR. Quality of life of formerly preterm and very low birth weight infants from preschool age to adulthood: a systematic review. Pediatrics. 2008;121(2):e366–76.
9. Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, Costeloe KL, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the epicure studies. BMJ. 2012;68:345.
10. Rauh VA, Margolis AE. Research Review: environmental exposures, neurodevelopment and child mental health – new paradigms for the study of brain and behavioral effects. J Child Psychol Psychiatry. 2016;57(7):775–93.
11. Bellinger D, Leviton A, Allred E, Rabinowitz M. Pre- and postnatal lead exposure and behavior problems in school-aged children. Environ Res. 1994;66(1):12–30.
12. Bellinger DC. Environmental chemical exposures and neurodevelopmental impairments in children. Pediatr Med. 2018;2018:1.
13. Chen A, Cai B, Dietrich KN, Radcliffe J, Rogan WJ. Lead exposure, IQ, and behavior in urban 5- to 7-year-olds: does lead affect behavior only by lowering IQ? Pediatrics. 2007;119(3):e650–e8.
14. Eubig PA, Aguiar A, Schantz SL. Lead and PCBs as risk factors for attention deficit/hyperactivity disorder. Environ Health Perspect. 2010;118(12):1654–67.
15. Nkomo P, Naicker N, Mathee A, Galpin J, Richter LM, Norris SA. The association between environmental lead exposure with aggressive behavior, and dimensionality of direct and indirect aggression during mid-adolescence: Birth to Twenty Plus Cohort. Sci Total Environ. 2018;612:472–9.
16. Wright JP, Dietrich KN, Ris MD, Hornung RW, Wessel SD, Lanphear BP, et al. Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. PLoS Med. 2008;5(5):e101.
17. Guilarte TR. Manganese neurotoxicity: new perspectives from behavioral, neuroimaging, and neuropathological studies in humans and non-human primates. Front Aging Neurosci. 2013;5:23.
18. Fechter LD. Distribution of manganese in development. Neurotoxicology. 1999;20(2-3):197–201.
19. Takser L, Lafond J, Bouchard M, St-Amour G, Mergler D. Manganese levels during pregnancy and at birth: relation to environmental factors and smoking in a Southwest Quebec population. Environ Res. 2004;95(2):119–25.
20. Khan K, Wasserman GA, Liu X, Ahmed E, Parvez F, Slavkovich V, et al. Manganese exposure from drinking water and children's academic achievement. Neurotoxicology. 2012;33(1):91–7.
21. Bouchard M, Laforest F, Vandelac L, Bellinger D, Mergler D. Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water. Environ Health Perspect. 2007;115(1):122–7.
22. Carvalho CF, Oulhote Y, Martorelli M, Carvalho CO, Menezes-Filho JA, Argollo N, et al. Environmental manganese exposure and associations with memory, executive functions, and hyperactivity in Brazilian children. Neurotoxicology. 2018;69:253–9.
23. Oulhote Y, Mergler D, Barbeau B, Bellinger DC, Bouffard T, Brodeur ME, et al. Neurobehavioral function in school-age children exposed to manganese in drinking water. Environ Health Perspect. 2014;122(12):1343–50.

24. Ortiz-Romo N, Drucker-Colín R, Guarneros M, Alcaraz-Zubeldia M, Hudson R. Nonoccupational environmental exposure to manganese is linked to deficits in peripheral and central olfactory function. Chem Senses. 2013;38(9):783–91.
25. Carvalho CF, Menezes-Filho JA, de Matos VP, Bessa JR, Coelho-Santos J, Viana GF, et al. Elevated airborne manganese and low executive function in school-aged children in Brazil. Neurotoxicology. 2014;45:301–8.
26. Tyler CR, Allan AM. The effects of arsenic exposure on neurological and cognitive dysfunction in human and rodent studies: a review. Curr Environ Health Rep. 2014;1(2):132–47.
27. Sanchez-Pena LC, Petrosyan P, Morales M, Gonzalez NB, Gutierrez-Ospina G, Del Razo LM, et al. Arsenic species, AS3MT amount, and AS3MT gene expression in different brain regions of mouse exposed to arsenite. Environ Res. 2010;110(5):428–34.
28. Wasserman GA, Liu X, Parvez F, Ahsan H, Factor-Litvak P, van Geen A, et al. Water arsenic exposure and children's intellectual function in Araihazar, Bangladesh. Environ Health Perspect. 2004;112(13):1329–33.
29. Wasserman GA, Liu X, Parvez F, Factor-Litvak P, Kline J, Siddique AB, et al. Child intelligence and reductions in water arsenic and manganese: a two-year follow-up study in Bangladesh. Environ Health Perspect. 2016;124(7):1114–20.
30. Rodriguez-Barranco M, Lacasana M, Aguilar-Garduno C, Alguacil J, Gil F, Gonzalez-Alzaga B, et al. Association of arsenic, cadmium and manganese exposure with neurodevelopment and behavioural disorders in children: a systematic review and meta-analysis. Sci Total Environ. 2013;454-455:562–77.
31. Moneim AEA. Mercury-induced neurotoxicity and neuroprotective effects of berberine. Neural Regen Res. 2015;10(6):881–2.
32. Debes F, Budtz-Jorgensen E, Weihe P, White RF, Grandjean P. Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. Neurotoxicol Teratol. 2006;28(5):536–47.
33. Oulhote Y, Debes F, Vestergaard S, Weihe P, Grandjean P. Aerobic fitness and neurocognitive function scores in young faroese adults and potential modification by prenatal methylmercury exposure. Environ Health Perspect. 2017;125(4):677–83.
34. Grandjean P, White RF. Effects of methylmercury exposure on neurodevelopment. JAMA. 1999;281(10):896.
35. Hopf NB, Ruder AM, Succop P. Background levels of polychlorinated biphenyls in the U.S. population. Sci Total Environ. 2009;407(24):6109–19.
36. Faroon O, Ruiz P. Polychlorinated biphenyls: new evidence from the last decade. Toxicol Ind Health. 2016;32(11):1825–47.
37. Berghuis SA, Bos AF, Sauer PJJ, Roze E. Developmental neurotoxicity of persistent organic pollutants: an update on childhood outcome. Arch Toxicol. 2015;89(5):687–709.
38. Vrijheid M, Casas M, Gascon M, Valvi D, Nieuwenhuijsen M. Environmental pollutants and child health—a review of recent concerns. Int J Hyg Environ Health. 2016;219(4):331–42.
39. Lyall K, Schmidt RJ, Hertz-Picciotto I. Maternal lifestyle and environmental risk factors for autism spectrum disorders. Int J Epidemiol. 2014;43(2):443–64.
40. Rossignol DA, Genuis SJ, Frye RE. Environmental toxicants and autism spectrum disorders: a systematic review. Transl Psychiatry. 2014;4:e360.
41. Costa LG, Giordano G. Developmental neurotoxicity of polybrominated diphenyl ether (PBDE) flame retardants. Neurotoxicology. 2007;28(6):1047–67.
42. Hendriks H, Westerink R. Neurotoxicity and risk assessment of brominated and alternative flame retardants. Neurotoxicol Teratol. 2015;52(Pt B):248–69.
43. Herbstman JB, Sjödin A, Kurzon M, Lederman SA, Jones RS, Rauh V, et al. Prenatal exposure to PBDEs and neurodevelopment. Environ Health Perspect. 2010;118(5):712–9.
44. Hudson-Hanley B, Irvin V, Flay B, MacDonald M, Kile ML. Prenatal PBDE exposure and neurodevelopment in children 7 years old or younger: a systematic review and meta-analysis. Curr Epidemiol Rep. 2018;5(1):46–59.
45. Sagiv SK, Kogut K, Gaspar FW, Gunier RB, Harley KG, Parra K, et al. Prenatal and childhood polybrominated diphenyl ether (PBDE) exposure and attention and executive function at 9–12 years of age. Neurotoxicol Teratol. 2015;52:151–61.

46. Oulhote Y, Tremblay E, Arbuckle TE, Fraser WD, Lemelin JP, Seguin JR, et al. Prenatal exposure to polybrominated diphenyl ethers and predisposition to frustration at 7 months: results from the MIREC study. Environ Int. 2018;119:79–88.
47. Herbstman JB, Mall JK. Developmental exposure to polybrominated diphenyl ethers and neurodevelopment. Curr Environ Health Rep. 2014;1(2):101–12.
48. Bouchard MF, Chevrier J, Harley KG, Kogut K, Vedar M, Calderon N, et al. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. Environ Health Perspect. 2011;119(8):1189–95.
49. Engel Stephanie M, Wetmur J, Chen J, Zhu C, Barr Dana B, Canfield Richard L, et al. Prenatal exposure to organophosphates, paraoxonase 1, and cognitive development in childhood. Environ Health Perspect. 2011;119(8):1182–8.
50. Rauh V, Arunajadai S, Horton M, Perera F, Hoepner L, Barr Dana B, et al. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. Environ Health Perspect. 2011;119(8):1196–201.
51. Eskenazi B, Marks AR, Bradman A, Harley K, Barr DB, Johnson C, et al. Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. Environ Health Perspect. 2007;115(5):792–8.
52. Engel SM, Berkowitz GS, Barr DB, Teitelbaum SL, Siskind J, Meisel SJ, et al. Prenatal organophosphate metabolite and organochlorine levels and performance on the Brazelton Neonatal Behavioral Assessment Scale in a multiethnic pregnancy cohort. Am J Epidemiol. 2007;165(12):1397–404.
53. Petit C, Chevrier C, Durand G, Monfort C, Rouget F, Garlantezec R, et al. Impact on fetal growth of prenatal exposure to pesticides due to agricultural activities: a prospective cohort study in Brittany, France. Environ Health. 2010;9:71.
54. Torres-Sanchez L, Rothenberg SJ, Schnaas L, Cebrian ME, Osorio E, Del Carmen HM, et al. In utero p,p′-DDE exposure and infant neurodevelopment: a perinatal cohort in Mexico. Environ Health Perspect. 2007;115(3):435–9.
55. Torres-Sánchez L, Schnaas L, Rothenberg SJ, Cebrián ME, Osorio-Valencia E, Hernández MDC, et al. Prenatal p,p′-DDE exposure and neurodevelopment among children 3.5-5 years of age. Environ Health Perspect. 2013;121(2):263–8.
56. Eskenazi B, Marks AR, Bradman A, Fenster L, Johnson C, Barr DB, et al. In utero exposure to dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) and neurodevelopment among young Mexican American children. Pediatrics. 2006;118(1):233–41.
57. Eskenazi B, An S, Rauch SA, Coker ES, Maphula A, Obida M, et al. Prenatal exposure to DDT and pyrethroids for malaria control and child neurodevelopment: The VHEMBE Cohort, South Africa. Environ Health Perspect. 2018;126(4):047004.
58. Gaspar FW, Harley KG, Kogut K, Chevrier J, Mora AM, Sjodin A, et al. Prenatal DDT and DDE exposure and child IQ in the CHAMACOS cohort. Environ Int. 2015;85:206–12.
59. Pan IJ, Daniels JL, Goldman BD, Herring AH, Siega-Riz AM, Rogan WJ. Lactational exposure to polychlorinated biphenyls, dichlorodiphenyltrichloroethane, and dichlorodiphenyldichloroethylene and infant neurodevelopment: an analysis of the pregnancy, infection, and nutrition babies study. Environ Health Perspect. 2009;117(3):488–94.
60. Jusko TA, Klebanoff MA, Brock JW, Longnecker MP. In-utero exposure to dichlorodiphenyltrichloroethane and cognitive development among infants and school-aged children. Epidemiology. 2012;23(5):689–98.
61. Barlow SM, Sullivan FM, Lines J. Risk assessment of the use of deltamethrin on bednets for the prevention of malaria. Food Chem Toxicol. 2001;39(5):407–22.
62. Oulhote Y, Bouchard MF. Urinary metabolites of organophosphate and pyrethroid pesticides and behavioral problems in Canadian children. Environ Health Perspect. 2013;121(11-12):1378–84.
63. Viel JF, Warembourg C, Le Maner-Idrissi G, Lacroix A, Limon G, Rouget F, et al. Pyrethroid insecticide exposure and cognitive developmental disabilities in children: The PELAGIE Mother-Child Cohort. Environ Int. 2015;82:69–75.

64. Xue Z, Li X, Su Q, Xu L, Zhang P, Kong Z, et al. Effect of synthetic pyrethroid pesticide exposure during pregnancy on the growth and development of infants. Asia Pac J Public Health. 2013;25(4 Suppl):72s–9s.
65. Watkins DJ, Fortenberry GZ, Sánchez BN, Barr DB, Panuwet P, Schnaas L, et al. Urinary 3-phenoxybenzoic acid (3-PBA) levels among pregnant women in Mexico City: distribution and relationships with child neurodevelopment. Environ Res. 2016;147:307–13.
66. Viel JF, Rouget F, Warembourg C, Monfort C, Limon G, Cordier S, et al. Behavioural disorders in 6-year-old children and pyrethroid insecticide exposure: The PELAGIE Mother-Child Cohort. Occup Environ Med. 2017;74(4):275–81.
67. Furlong MA, Barr DB, Wolff MS, Engel SM. Prenatal exposure to pyrethroid pesticides and childhood behavior and executive functioning. Neurotoxicology. 2017;62:231–8.
68. Factor-Litvak P, Insel B, Calafat AM, Liu X, Perera F, Rauh VA, et al. Persistent associations between maternal prenatal exposure to phthalates on child IQ at age 7 years. PLoS One. 2014;9(12):e114003.
69. Arbuckle TE, Davis K, Boylan K, Fisher M, Fu J. Bisphenol A, phthalates and lead and learning and behavioral problems in Canadian children 6–11 years of age: CHMS 2007–2009. Neurotoxicology. 2016;54:89–98.
70. Kim BN, Cho SC, Kim Y, Shin MS, Yoo HJ, Kim JW, et al. Phthalates exposure and attention-deficit/hyperactivity disorder in school-age children. Biol Psychiatry. 2009;66(10):958–63.
71. Miodovnik A, Engel SM, Zhu C, Ye X, Soorya LV, Silva MJ, et al. Endocrine disruptors and childhood social impairment. Neurotoxicology. 2011;32(2):261–7.
72. Harley KG, Gunier RB, Kogut K, Johnson C, Bradman A, Calafat AM, et al. Prenatal and early childhood bisphenol A concentrations and behavior in school-aged children. Environ Res. 2013;126:43–50.
73. Roen EL, Wang Y, Calafat AM, Wang S, Margolis A, Herbstman J, et al. Bisphenol A exposure and behavioral problems among inner city children at 7–9 years of age. Environ Res. 2015;142:739–45.
74. Evans SF, Kobrosly RW, Barrett ES, Thurston SW, Calafat AM, Weiss B, et al. Prenatal bisphenol A exposure and maternally reported behavior in boys and girls. Neurotoxicology. 2014;45:91–9.
75. Casas M, Forns J, Martinez D, Avella-Garcia C, Valvi D, Ballesteros-Gomez A, et al. Exposure to bisphenol A during pregnancy and child neuropsychological development in the INMA-Sabadell cohort. Environ Res. 2015;142:671–9.
76. Braun JM. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. Nat Rev Endocrinol. 2016;13:161.
77. Braun JM, Kalkbrenner AE, Just AC, Yolton K, Calafat AM, Sjodin A, et al. Gestational exposure to endocrine-disrupting chemicals and reciprocal social, repetitive, and stereotypic behaviors in 4- and 5-year-old children: The HOME Study. Environ Health Perspect. 2014;122(5):513–20.
78. Steinmaus CM. Perchlorate in water supplies: sources, exposures, and health effects. Curr Environ Health Rep. 2016;3(2):136–43.
79. Blount BC, Valentin-Blasini L. Biomonitoring as a method for assessing exposure to perchlorate. Thyroid. 2007;17(9):837–41.
80. Taylor PN, Okosieme OE, Murphy R, Hales C, Chiusano E, Maina A, et al. Maternal perchlorate levels in women with borderline thyroid function during pregnancy and the cognitive development of their offspring: data from the controlled antenatal thyroid study. J Clin Endocrinol Metabol. 2014;99(11):4291–8.
81. Fry RC, Navasumrit P, Valiathan C, Svensson JP, Hogan BJ, Luo M, et al. Activation of inflammation/NF-kappaB signaling in infants born to arsenic-exposed mothers. PLoS Genet. 2007;3(11):e207.
82. Dietert RR. Misregulated inflammation as an outcome of early-life exposure to endocrine-disrupting chemicals. Rev Environ Health. 2012;27(2-3):117–31.
83. Sirivarasai J, Wananukul W, Kaojarern S, Chanprasertyothin S, Thongmung N, Ratanachaiwong W, et al. Association between inflammatory marker, environmental lead exposure, and glutathione S-transferase gene. Biomed Res Int. 2013;2013:474963.

84. Morris RG, Anderson E, Lynch GS, Baudry M. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature. 1986;319(6056):774–6.
85. Toscano CD, Guilarte TR. Lead neurotoxicity: from exposure to molecular effects. Brain Res. 2005;49(3):529–54.
86. Neal AP, Guilarte TR. Mechanisms of lead and manganese neurotoxicity. Toxicol Res. 2013;2(2):99–114.
87. Farina M, Rocha JBT, Aschner M. Mechanisms of methylmercury-induced neurotoxicity: evidence from experimental studies. Life Sci. 2011;89(15-16):555–63.
88. Gavin CE, Gunter KK, Gunter TE. Mn2+ sequestration by mitochondria and inhibition of oxidative phosphorylation. Toxicol Appl Pharmacol. 1992;115(1):1–5.
89. Burton NC, Guilarte TR. Manganese neurotoxicity: lessons learned from longitudinal studies in nonhuman primates. Environ Health Perspect. 2009;117(3):325–32.
90. Martinez L, Jimenez V, Garcia-Sepulveda C, Ceballos F, Delgado JM, Nino-Moreno P, et al. Impact of early developmental arsenic exposure on promotor CpG-island methylation of genes involved in neuronal plasticity. Neurochem Int. 2011;58(5):574–81.
91. Martinez-Finley EJ, Ali AM, Allan AM. Learning deficits in C57BL/6J mice following perinatal arsenic exposure: consequence of lower corticosterone receptor levels? Pharmacol Biochem Behav. 2009;94(2):271–7.
92. Rodriguez VM, Carrizales L, Mendoza MS, Fajardo OR, Giordano M. Effects of sodium arsenite exposure on development and behavior in the rat. Neurotoxicol Teratol. 2002;24(6):743–50.
93. Kruger K, Binding N, Straub H, Musshoff U. Effects of arsenite on long-term potentiation in hippocampal slices from young and adult rats. Toxicol Lett. 2006;165(2):167–73.
94. Gilden RC, Huffling K, Sattler B. Pesticides and health risks. JOGNN. 2010;39(1):103–10.
95. Costa LG. Interactions of neurotoxicants with neurotransmitter systems. Toxicology. 1988;49(2):359–66.
96. Costa LG, Giordano G, Guizzetti M, Vitalone A. Neurotoxicity of pesticides: a brief review. Front Biosci. 2008;13:1240–9.
97. Vijverberg HP, van der Zalm JM, van der Bercken J. Similar mode of action of pyrethroids and DDT on sodium channel gating in myelinated nerves. Nature. 1982;295(5850):601–3.
98. Tilson HA, Kodavanti PR. The neurotoxicity of polychlorinated biphenyls. Neurotoxicology. 1998;19(4-5):517–25.
99. Schantz SL. Developmental neurotoxicity of PCBs in humans: what do we know and where do we go from here? Neurotoxicol Teratol. 1996;18(3):217–27.
100. Ribas-Fitó N, Sala M, Kogevinas M, Sunyer J. Polychlorinated biphenyls (PCBs) and neurological development in children: a systematic review. J Epidemiol Community Health. 2001;55(8):537–46.
101. Oulhote Y, Chevrier J, Bouchard MF. Exposure to polybrominated diphenyl ethers (PBDEs) and hypothyroidism in Canadian women. J Clin Endocrinol Metab. 2016;101(2):590–8.
102. Chevrier J, Harley KG, Bradman A, Gharbi M, Sjodin A, Eskenazi B. Polybrominated diphenyl ether (PBDE) flame retardants and thyroid hormone during pregnancy. Environ Health Perspect. 2010;118(10):1444–9.
103. Costa LG, de Laat R, Tagliaferri S, Pellacani C. A mechanistic view of polybrominated diphenyl ether (PBDE) developmental neurotoxicity. Toxicol Lett. 2014;230(2):282–94.
104. Blanco J, Mulero M, Lopez M, Domingo JL, Sanchez DJ. BDE-99 deregulates BDNF, Bcl-2 and the mRNA expression of thyroid receptor isoforms in rat cerebellar granular neurons. Toxicology. 2011;290(2-3):305–11.
105. Tagliaferri S, Caglieri A, Goldoni M, Pinelli S, Alinovi R, Poli D, et al. Low concentrations of the brominated flame retardants BDE-47 and BDE-99 induce synergistic oxidative stress-mediated neurotoxicity in human neuroblastoma cells. Toxicol In Vitro. 2010;24(1):116–22.
106. Madia F, Giordano G, Fattori V, Vitalone A, Branchi I, Capone F, et al. Differential in vitro neurotoxicity of the flame retardant PBDE-99 and of the PCB Aroclor 1254 in human astrocytoma cells. Toxicol Lett. 2004;154(1-2):11–21.

107. Mariussen E, Fonnum F. Neurochemical targets and behavioral effects of organohalogen compounds: an update. Crit Rev Toxicol. 2006;36(3):253–89.
108. Talsness CE, Andrade AJM, Kuriyama SN, Taylor JA, vom Saal FS. Components of plastic: experimental studies in animals and relevance for human health. Philos Trans R Soc London Ser B. 2009;364(1526):2079–96.
109. Romano ME, Eliot MN, Zoeller RT, Hoofnagle AN, Calafat AM, Karagas MR, et al. Maternal urinary phthalate metabolites during pregnancy and thyroid hormone concentrations in maternal and cord sera: The HOME Study. Int J Hyg Environ Health. 2018;221(4):623–31.
110. Zhang X, Chang H, Wiseman S, He Y, Higley E, Jones P, et al. Bisphenol A disrupts steroidogenesis in human H295R cells. Toxicol Sci. 2011;121(2):320–7.
111. Gentilcore D, Porreca I, Rizzo F, Ganbaatar E, Carchia E, Mallardo M, et al. Bisphenol A interferes with thyroid specific gene expression. Toxicology. 2013;304:21–31.
112. Blount BC, Pirkle JL, Osterloh JD, Valentin-Blasini L, Caldwell KL. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. Environ Health Perspect. 2006;114(12):1865–71.
113. Charatcharoenwitthaya N, Ongphiphadhanakul B, Pearce EN, Somprasit C, Chanthasenanont A, He X, et al. The association between perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant Thai women. J Clin Endocrinol Metabol. 2014;99(7): 2365–71.
114. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med. 1999;341(8):549–55.
115. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. Clin Endocrinol. 2010;72(6):825–9.
116. Trumbo PR. Perchlorate consumption, iodine status, and thyroid function. Nutr Rev. 2010;68(1):62–6.
117. Kaufman AS, Zhou X, Reynolds MR, Kaufman NL, Green GP, Weiss LG. The possible societal impact of the decrease in U.S. blood lead levels on adult IQ. Environ Res. 2014;132:413–20.
118. Collaborators GDaIIaP. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1211–59.
119. Bellinger DC, Matthews-Bellinger JA, Kordas K. A developmental perspective on early-life exposure to neurotoxicants. Environ Int. 2016;94:103–12.
120. Miranda ML, Kim D, Reiter J, Overstreet Galeano MA, Maxson P. Environmental contributors to the achievement gap. Neurotoxicology. 2009;30(6):1019–24.
121. Reuben A, Caspi A, Belsky DW, Broadbent J, Harrington H, Sugden K, et al. Association of childhood blood lead levels with cognitive function and socioeconomic status at age 38 years and with IQ change and socioeconomic mobility between childhood and adulthood. JAMA. 2017;317(12):1244–51.
122. Patel CJ, Bhattacharya J, Butte AJ. An environment-wide association study (EWAS) on type 2 diabetes mellitus. PLoS One. 2010;5(5):e10746.
123. Tibshirani R. Regression shrinkage and selection via the lasso. J R Stat Soc Ser B. 1996;58(1):267–88.
124. Hoerl AE, Kennard RW. Ridge regression: biased estimation for nonorthogonal problems. Technometrics. 1970;12(1):55–67.
125. Zou H, Hastie T. Regularization and variable selection via the elastic net. J R Stat Soc. 2005;67(2):301–20.
126. Bobb JF, Valeri L, Claus Henn B, Christiani DC, Wright RO, Mazumdar M, et al. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. Biostatistics. 2014;16(3):493–508.

127. Agier L, Portengen L, Chadeau-Hyam M, Basagana X, Giorgis-Allemand L, Siroux V, et al. A systematic comparison of linear regression-based statistical methods to assess exposome-health associations. Environ Health Perspect. 2016;124(12):1848–56.
128. Taylor KW, Joubert BR, Braun JM, Dilworth C, Gennings C, Hauser R, et al. Statistical approaches for assessing health effects of environmental chemical mixtures in epidemiology: lessons from an innovative workshop. Environ Health Perspect. 2016;124(12):A227–a9.
129. Sun Z, Tao Y, Li S, Ferguson KK, Meeker JD, Park SK, et al. Statistical strategies for constructing health risk models with multiple pollutants and their interactions: possible choices and comparisons. Environ Health. 2013;12(1):85.
130. Patel CJ. Analytic complexity and challenges in identifying mixtures of exposures associated with phenotypes in the exposome era. Curr Epidemiol Rep. 2017;4:22–30.
131. Oulhote Y, Bind M-A, Coull B, Patel CJ, Grandjean P. Combining ensemble learning techniques and G-computation to investigate chemical mixtures in environmental epidemiology studies. bioRxiv:147413. 2017.
132. Park SK, Zhao Z, Mukherjee B. Construction of environmental risk score beyond standard linear models using machine learning methods: application to metal mixtures, oxidative stress and cardiovascular disease in NHANES. Environ Health. 2017;16(1):102.
133. Kennedy EH, Ma Z, McHugh MD, Small DS. Nonparametric methods for doubly robust estimation of continuous treatment effects. Philos Trans R Soc B. 2017;79(4):1229–45.
134. Cole SR, Frangakis CE. Commentary: the consistency statement in causal inference: a definition or an assumption? Epidemiology. 2009;20(1):3–5.
135. Hernan MA, Taubman SL. Does obesity shorten life? The importance of well-defined interventions to answer causal questions. Int J Obes. 2008;32(Suppl 3):S8–14.
136. Weisskopf MG, Webster TF. Trade-offs of personal versus more proxy exposure measures in environmental epidemiology. Epidemiology. 2017;28(5):635–43.
137. Rehkopf DH, Glymour MM, Osypuk TL. The consistency assumption for causal inference in social epidemiology: when a rose is not a rose. Curr Epidemiol Rep. 2016;3(1):63–71.
138. Pearl J. On the consistency rule in causal inference: axiom, definition, assumption, or theorem? Epidemiology. 2010;21(6):872–5.
139. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Hum Mol Genet. 2014;23(R1):R89–98.
140. Pierce BL, Tong L, Argos M, Gao J, Jasmine F, Roy S, et al. Arsenic metabolism efficiency has a causal role in arsenic toxicity: Mendelian randomization and gene-environment interaction. Int J Epidemiol. 2014;42(6):1862–72.
141. Cedeño Laurent JG, Williams A, Oulhote Y, Zanobetti A, Allen JG, Spengler JD. Reduced cognitive function during a heat wave among residents of non-air-conditioned buildings: an observational study of young adults in the summer of 2016. PLoS Med. 2018;15(7):e1002605.
142. Kelly C. Bishop JDK, Nicolai V. Kuminoff. Hazed and confused: the effect of air pollution on dementia. NBER Working Paper No 24970. 2018.
143. Nassan FL, Coull BA, Skakkebaek NE, Williams MA, Dadd R, Mínguez-Alarcón L, et al. A crossover–crossback prospective study of dibutyl-phthalate exposure from mesalamine medications and semen quality in men with inflammatory bowel disease. Environ Int. 2016;95:120–30.
144. Philippat C, Botton J, Calafat AM, Ye X, Charles M-A, Slama R, et al. Prenatal exposure to phenols and growth in boys. Epidemiology. 2014;25(5):625–35.
145. MacLehose RF, Olshan AF, Herring AH, Honein MA, Shaw GM, Romitti PA, et al. Bayesian methods for correcting misclassification: an example from birth defects epidemiology. Epidemiology. 2009;20(1):27–35.
146. Oulhote Y, Steuerwald U, Debes F, Weihe P, Grandjean P. Behavioral difficulties in 7-year old children in relation to developmental exposure to perfluorinated alkyl substances. Environ Int. 2016;97:237–45.

147. Schmidt RJ, Kogan V, Shelton JF, Delwiche L, Hansen RL, Ozonoff S, et al. Combined prenatal pesticide exposure and folic acid intake in relation to autism spectrum disorder. Environ Health Perspect. 2017;125(9):097007.
148. Goodrich AJ, Volk HE, Tancredi DJ, McConnell R, Lurmann FW, Hansen RL, et al. Joint effects of prenatal air pollutant exposure and maternal folic acid supplementation on risk of autism spectrum disorder. Autism Res. 2018;11(1):69–80.
149. Lemire M, Fillion M, Frenette B, Mayer A, Philibert A, Passos CJ, et al. Selenium and mercury in the Brazilian Amazon: opposing influences on age-related cataracts. Environ Health Perspect. 2010;118(11):1584–9.
150. McCoy DC, Peet ED, Ezzati M, Danaei G, Black MM, Sudfeld CR, et al. Early childhood developmental status in low- and middle-income countries: national, regional, and global prevalence estimates using predictive modeling. PLoS Med. 2016;13(6):e1002034.