Review Article

An overview of environmental chemical exposures and neurodevelopmental impairments in children

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Abstract: Children are widely viewed as the population subgroup that is most vulnerable to the toxicities that result from exposure to environmental chemicals. Their enhanced vulnerability is due to a variety of behavioral and physiologic factors. For many chemicals, the central nervous system (CNS) is the most sensitive target organ. In general, the impacts depend on a chemical's mode of action, the dose, and the stage of development at which exposure occurs. This paper surveys the toxicology of environmental chemicals, specifically the impacts on children's intellectual development. It focuses on metals (or metalloids), including mercury, lead, arsenic, fluoride, as well as on pesticides, air pollution, synthetic organic chemicals, and endocrine disruptors. The final section discusses issues germane to estimating the global burden of disease associated with exposures to neurotoxic environmental chemicals.

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Introduction

The central nervous system (CNS) is especially vulnerable to perturbation by environmental chemicals. Six of the 10 chemicals on the WHO's list of chemicals of greatest public health concern adversely affect the brain (air pollution, arsenic, dioxin- and dioxin-like compounds, lead, mercury, and pesticides), with some evidence suggesting that two of the remaining four might do so as well (cadmium, fluoride) (http://www.who.int/ipcs/assessment/public_health/chemicals_phc/en/). This review summarizes the current state of knowledge about the neurodevelopmental impacts of such chemicals. Greatest attention is paid to lead and mercury, the chemicals for which the most data on developmental neurotoxicity are available, but chemicals of more recent concern are also discussed.

Brain development is characterized by an exquisite temporal and spatial choreography of processes that must unfold properly in order to produce an organ consisting of billions of precisely located, interconnected, and specialized cells. While it is well-known that brain development is adversely affected by exposures to viruses (e.g., Zika, cytomegalovirus), bacteria (e.g., syphilis, Neisseria meningitides), and protozoa (e.g., Toxoplasma gondii, Schistosoma), evidence that exposures to environmental chemicals pose similar threats has been developed only in recent years. The stages of prenatal brain development include primary neurulation (weeks 3–4), development of the forebrain (prosencephalon) (months 2–3), neuronal proliferation (months 3–4), neuronal migration (months 3–5), and neuronal organization (later gestation and continuing postnatally). Myelination begins in mid-pregnancy and continues into young adulthood. The coordination of these complex processes is regulated by myriad signaling pathways that must work properly if a species-typical brain is to result. Although inconsequential variations occur among individuals in these processes, some variations can result in abnormalities that impair an individual's ability to carry out brain-based functions. Which aspects of CNS development a chemical perturbs

and when its effects are likely to be most deleterious depends in part on its mechanism of action and the stage of brain development at which exposure occurs. Alcohol, methylmercury, and chlorpyrifos (an organophosphate pesticide), disturb neural cell proliferation, while methylmercury and alcohol affect neural cell migration. Differentiation of neuroblasts is affected by alcohol, nicotine, methylmercury, and lead. The creation of glial cells and subsequent myelination of neurons is affected by endocrine disrupting chemicals (EDCs), alcohol, and lead. Synaptogenesis is affected by alcohol, polychlorinated biphenyls (PCBs), triethyltin, and some pesticides (e.g., parathion, permethrin), while apoptosis (the orderly process of programmed cell death) is affected by lead, alcohol, and methylmercury. Many chemicals affect neurotransmitter systems, including organophosphate pesticides, alcohol, lead, methylmercury, aluminum, and pharmaceuticals such as some anti-depressants (e.g., selective serotonin reuptake inhibitors). Exposure can therefore interfere with experience-dependent neuroplasticity, a synaptic-level process that is critical in the development of the fine structure of the CNS.

Unfortunately, the placenta and blood-brain barrier do not fully protect the fetus from exposure to all chemicals. Some, such as lead, passively diffuse across the placenta so that the concentration in fetal blood is approximately the same as in maternal blood (1). Other chemicals bioaccumulate in the fetus. For example, the concentration of methylmercury in fetal blood is approximately 70% greater than in maternal blood (2). In a nationally representative sample of pregnant U.S. women some chemicals, including PCBs, organochlorine pesticides, perfluorinated chemicals, phenols (e.g., bisphenol A), polybrominated diphenyl ethers (PBDEs) (flame retardants), phthalates (plasticizers), polycyclic aromatic hydrocarbons (PAHs) (products of the combustion of organic materials), and perchlorate, were detected in essentially every pregnant woman (3).

The toxicokinetics of chemicals in the maternal-fetal unit can be complex. For example, in addition to being exposed to the lead a woman is exposed to during her pregnancy, the fetus is also exposed to bone lead stores that reflects her past exposure. Approximately 90% of the lead in an adult's body resides in bone. To support fetal skeletal development, large quantities of calcium are mobilized from maternal bone. Because lead and calcium are both divalent cations, lead present in maternal bone is mobilized at the same time. In fact, lead that reflects maternal exposure prior to her pregnancy accounts for a substantial fraction of the lead present in umbilical cord blood (4). Even if a chemical does not cross the placenta, it can accumulate in it and impair its critical support functions (e.g., cadmium).

In adults, the blood-brain barrier, consisting of tight junctions between the endothelial cells lining cerebral microvessels, prevents larger water-soluble chemicals from entering the brain (5). This barrier is not fully developed at birth, however, and studies in nonhuman primates using radioactive tracers demonstrate that many chemicals pass more readily from the circulating blood into the brain in immature animals than in adult animals.

Certain behavioral and physiologic factors also place a developing child at greater risk than an adult to the deleterious effects of chemical exposures (6). First, certain pathways of exposure are unique to children (e.g., placental transfer, breastfeeding). It is primarily fat-soluble chemicals [e.g., dioxins, perfluorinated compounds (PFCs)] that are of concern with regard to passage into breast milk. Certain behaviors that are more common in children than adults, such as hand-to-mouth activity, oral exploration of objects, and non-nutritive ingestion (i.e., pica) bring them into more intimate contact than adults with chemicals that are present in household dust and soil (e.g., lead, PBDEs). On a body weight basis, children consume more food and breathe a greater volume of air than do adults, so they tend to experience greater exposures than adults to foodborne and airborne chemicals. The breathing zones of children and adults differ. Children spend more time near the floor where chemical concentrations in the air might be greater, for example following residential pesticide application. Dietary differences are also important. Children's relative consumption of fruit juices is typically greater than that of adults, resulting in greater exposure to pesticide residues in these products. Some micronutrient deficiencies that are more common in children (e.g., iron, calcium) can result in greater fractional absorption of chemicals that share gut binding sites with these essential metals. For example, children absorb up to 50% of ingested lead, whereas adults absorb approximately 10%. Finally, some liver detoxification pathways are not fully developed in children. The enzymes that convert lipid-soluble compounds into water-soluble metabolites that can be excreted in the urine are less effective in children, with the result that parent compounds remain in the body for a longer period following exposure.

Acute poisonings as a result of high-dose exposure to a chemical can be serious and even fatal. A broader concern is whether children's chronic, low-dose exposures to chemicals

that are commonly present in the environment compromise their everyday functioning despite not causing signs of clinical intoxication. The following sections discuss briefly what is known about the effects of chemicals or classes of chemicals on children's brain development and their risk of neurodevelopmental disorders.

Metals

Mercury

Mercury exists in three forms: elemental, inorganic, and organic. The latter forms are considered to be the most important with respect to public health and, at present, methylmercury considered to pose the greatest threat. In the general population, consumption of contaminated seafood is the major pathway of exposure to methylmercury. Inorganic mercury that is dispersed into the environment by both natural (e.g., volcanoes, forest fires) and industrial processes (e.g., combustion of fossil fuels) settles into waterbodies where it is bio-transformed, via methylation, to methylmercury by microbes in sediments. It enters the aquatic food chain and bio-concentrates in tissues as it ascends trophic levels. The concentrations of methylmercury are therefore greatest in the tissues of long-lived predatory fish (e.g., shark, swordfish, albacore tuna) and aquatic mammals (e.g., toothed whales).

Methylmercury provides a striking illustration of age-dependent vulnerability to neurotoxicity. In Minamata, Japan, women who, during pregnancy, consumed large amounts of seafood contaminated by industrial discharges of mercury, have birth to children with a distinctive constellation of neurologic signs, now called, "Congenital Minamata disease" (CMD) (7). These included growth disturbances, retention of primitive reflexes, sensory impairments, intellectual disability (ID) (10-fold increase in risk), cerebral palsy (50-fold increase in risk), and movement and coordination disorders (e.g., cerebellar ataxia, chorea, athetosis, dysarthria). Many mothers of children with CMD showed no symptoms of mercury intoxication or only mild sensory symptoms such as transient paresthesias. Neuropathological examination of individuals who were exposed at different developmental stages revealed strikingly different patterns of abnormalities (8). In individuals exposed only in adulthood, lesions were highly localized, clustering in the pre- and post-central gyri, the calcarine fissure of the occipital cortex, and the cerebellum. This is consistent with the clinical signs of mercury intoxication in adults, which include movement disorders, tremors, sensory disturbances, and constriction of the visual fields. In individuals exposed as fetuses, however, lesions were diffusely distributed, with little localization, consistent with the global developmental impairments of patients with CMD. One reason for this is that methylmercury arrests mitotic cells in metaphase, impairing the cytoskeletal proteins (microtubule assemblies) that form the mitotic spindle. As a result, cell proliferation and migration are perturbed, producing widespread abnormalities including heterotopias, reduced cell densities, anomalous cytoarchitecture, disturbances in laminar pattern of cerebral cortex, incomplete myelination, glial proliferation, and limited gyral differentiation.

The devastating neurological effects observed in poisoning episodes prompted studies to determine whether chronic low-level prenatal exposure to methylmercury produces milder signs of neurotoxicity. Numerous studies have been conducted in regions in which seafood is an important component of the diet. A large prospective study of children from the Faroe Islands showed that their performance on tests of language, attention, and memory, was inversely related to their mothers' blood- and hair-mercury concentrations during pregnancy (9). Each increase of 1 μg/g (part per million) in maternal hair-mercury was associated with a loss of one-half IQ point (10). Neuropsychological deficits were still apparent at follow-up evaluations at 14 years (11) and 22 years (12), although they were diminished in magnitude. Functional MRI studies showed dose-related alterations in patterns of activation (13). Studies of children in areas in which seafood is contaminated by the use of mercury as an amalgamator in artisanal gold mining have found substantial intellectual deficits in the most highly exposed children (14).

Some studies of fish-consuming populations have not reported mercury-associated deficits in children [e.g., (15)]. A possible explanation is that consumption of seafood is pathway of exposure not only of methylmercury but of many important macronutrients and micronutrients (e.g., protein, long-chain polyunsaturated fatty acids such as omega-3, selenium, iron, choline) that promote brain development. Failure to conduct statistical analyses that adjust for this can obscure both the toxicity of methylmercury and the benefits of the nutrients (negative confounding) (16). By careful selection of the species of fish consumed during pregnancy, nutrient intake can be maximized and methylmercury intake minimized, resulting in more favorable cognitive outcomes in children (17).

The global incidence of methylmercury-associated ID was estimated to be 225,000 cases per year (18). The incidence rate varies more than 20-fold in different regions. The highest rate is in the low-income region of the Americas (7 cases per 10,000 population) (subregion D in the WHO classification). The largest number of cases, however, is estimated to be in countries in the highly-populated Western Pacific B region (87,445 cases). As would be expected, island nations and those in which artisanal gold mining is common tended to have the highest incidence rates, most likely due to the dietary importance of seafood.

Mercury has long been used as a component of dental amalgam (50% elemental mercury by weight). Used to restore caries, amalgams can release mercury, and individuals with a larger number of amalgam fillings have somewhat higher urinary mercury concentrations. Whether the concentrations are sufficiently high to cause neurotoxicity has been controversial. Despite numerous case reports and observational studies suggesting that it is, two large randomized trials comparing the neuropsychological outcomes of children who received either dental amalgam or composite resin restorations of caries reported no differences in the outcomes of children 5 to 7 years following treatment (19,20).

Lead

Lead can produce devastating effects on the developing brain. Depending on the dose, it causes increased apoptosis, excitotoxicity, reduces cellular energy metabolism by impairing mitochondrial function, reduces heme synthesis and the oxygen-carrying capacity of red blood cells, increases oxidative stress and lipid peroxidation damaging cell membrane lipids, alters the activity of first and second messenger systems, receptor densities, and dendritic branching patterns, impairs the development and function of oligodendroglia resulting in abnormal myelin formation, disturbs neurotrophic processes including thyroid transport into brain, and alters the regulation of gene transcription (21). Severe lead poisoning can cause brain hemorrhage, edema, seizures, coma, or death. Even sub-encephalopathic children are left with a variety of difficulties. Because lead is ubiquitous in the environment, it is now recognized that intellectual impairment due to excessive exposure is a frequent rather than rare occurrence. Based on 2015 data, the Institute for Health Metrics and Evaluation estimated that in 2016, lead exposure accounted for almost 64% of the global burden of idiopathic developmental ID (https://vizhub.healthdata.org/gbd-compare/).

The blood lead concentration considered to be the "upper limit of normal" by consensus bodies such as the World Health Organization and the U.S. Centers for Disease Control and Prevention steadily dropped over the past few decades. At present, no level is considered to be safe. A set of analyses of IQ data collected in seven international prospective studies (N=1,333) provided much of the justification for this view (22). The relationships between lead exposure and child IQ, measured at age 5 to 10 years, were evaluated, adjusting for several potential confounders (e.g., maternal IQ, home environment). The best fitting model indicated that an increase in concurrent blood lead concentration from 2.4 to 30 μg/dL (the 5th and 95th percentiles of the blood lead distribution in the pooled dataset) was associated with an IQ reduction of 6.9 points. The association was non-linear, and more than half of this reduction (3.9 points), occurred in the range between 2.4 to 10 μg/dL. Although the reason why the proportional loss in IQ is greater at lower than at higher blood lead concentrations is unknown, supra-linear relationships between blood lead and other cognitive outcomes have subsequently been reported (23,24).

Many studies have reported significant inverse associations between lead exposure and success in school, i.e., lower scores on standardized tests, greater receipt of special education services and grade retention, and failure to complete qualifications (25-31). In ecologic (i.e., aggregate-level) analyses, an inverse relationship was found between preschool blood lead concentrations and SAT scores lagged by 17 years (32). In a large Swedish cohort, the impact of having a blood lead concentration of 5 versus 2.5 μg/dL was equivalent to the impact of having a mother with a primary school versus a university education (33). Surkan *et al.* (34) found that children with a blood lead concentration of 5–10 μg/dL had significantly lower reading and mathematics scores, even after adjustment for Full-Scale IQ score, suggesting that children with greater exposures did not achieve academically at a level commensurate with their ability. Quantile regression analyses of children's academic achievement scores in relation to blood lead indicate that the adverse impact is more pronounced at the lower than higher end of the test score distribution, indicating that the impact of lead is disproportionally greater on children already at academic risk (35). This might be attributable to contextual factors that influence a child's resilience or

susceptibility to lead exposure, such as nutrition, social environment, or other chemical exposures.

The effects of lead persist as greater childhood exposure is associated with reduced success in adulthood. In the large Dunedin Multidisciplinary Health and Development Study, blood lead concentration at 11 years of age was inversely related to IQ at age 38 years, even after adjustment for IQ at age 11 years (36). Furthermore, early lead exposure was inversely related to socioeconomic status in adulthood. In fact, children who were more highly exposed failed to match the socioeconomic achievements of their parents.

One aspect of lead neurotoxicity that receives little attention is the possible role of early-life exposure to lead in increasing the adverse impacts of later events and exposures or even normal aging processes. Animal studies suggest that lead exposure reduces the ability of rats to recover from an unrelated neurological insult in adulthood, such as a laser-induced stroke in the somatosensory cortex (37). Provocative studies in rodents and non-human primates show that lead exposure in infancy initiates epigenetic processes, perhaps involving altered patterns of DNA methylation, that result in adult-onset overexpression of proteins involved in neurodegenerative processes characteristic of Alzheimer's disease (viz., increased deposition of β-amyloid, increased hyper-phosphorylated tau protein) (38).

Early case-control and chelation challenge studies suggested that children diagnosed with hyperactivity had greater lead burdens [e.g., (39)]. Subsequent studies indicated that even in children who were neither clinically lead poisoned nor diagnosed with hyperactivity, a greater lead burden was associated with ADHD symptoms such as increased distractibility, reduced ability to follow directions, disorganization, daydreaming, and lack of task persistence [e.g., (40)]. A meta-analysis of 33 studies conducted between 1972 and 2010, involving more than 10,000 children, found significant effect sizes linking greater exposure and dimensional measures of both inattentive and hyperactive/impulsive symptoms (41).

It is now established that increased childhood lead exposure also increased the risk that a child meets diagnostic criteria for ADHD. In a study using NHANES 2001–2004 data, a clinician-administered diagnostic interview based on DSM-IV criteria was used to establish a diagnosis of ADHD (42). Children with a blood lead concentration in the upper tertile (>1.3 μg/dL) were 2.3 times more likely to meet criteria than were children with a concentration in the lowest tertile. This association of lead with increased risk of ADHD has been replicated in several subsequent case-control studies (43-48). The plausibility of the link is supported by the evidence that lead disrupts midbrain dopamine circuitry (striatum and fronto-striatal networks), the same circuitry that is thought to underlie ADHD (47).

Several studies in the last decade have suggested that children with greater early-life lead exposure are at increased risk of social pathologies, including criminality (48,49). If this association is true, it most likely reflects a developmental cascade, representing a possible end-state for individuals with reduced intelligence, reduced school success, behavioral impairments such as reduced impulse control and ADHD, and executive function deficits such as inability to anticipate consequences or to implement long-term plans (50). Not all children with excessive early-life lead exposure would be expected to follow this developmental trajectory, however, as there are many points along the way at which timely developmental supports might reduce the likelihood that such a cascade is fully expressed.

Neuroimaging studies have explored the associations between lead exposure history and brain structure and function in individuals from the general population. Most of the data are from the Cincinnati Prospective Lead Study in which participants were enrolled prenatally and followed into young adulthood (19–24 years of age). Volumetric imaging revealed significant inverse associations between annual mean blood lead concentration between 3 and 6 years of age and grey matter volume, particularly in the frontal regions of the brain, including the anterior cingulate cortex and the ventrolateral prefrontal cortex, areas usually considered to be related to executive functions, mood regulation, and decision-making (51). On diffusion tensor imaging, reduced fractional anisotropy and axial diffusivity were also associated with greater childhood lead exposure (52). These findings suggest impaired myelination and reduced axonal integrity in regions that regulate executive functions. Brain function in adulthood is also inversely related to childhood lead exposure. Proton magnetic resonance spectroscopy studies showed that greater childhood blood lead concentration was associated with reductions in several metabolites, including N-acetyl aspartate and creatine and phosphocreatine, in both grey and white matter (53). Functional magnetic resonance imaging (fMRI) showed that during a verb generation task, individuals with greater blood lead concentrations in childhood showed dose-dependent changes in activation pattern in the left frontal cortex and the left middle temporal gyrus (54). In another cohort, individuals with

greater lead exposure showed fMRI showed reduced activation in the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, pre-supplementary motor areas, and inferior parietal cortex on the Wisconsin Card Sorting Test and the n-back task (particularly on trials that imposed the greatest memory load) (55). These findings suggest that exposure to lead impairs the fronto-parietal working memory network.

Arsenic

Chronic exposure to arsenic impairs brain function by increasing oxidative stress, free radicals, and neuronal apoptosis, impairs neurogenesis in the hippocampus, disrupts the expression of the NMDA receptor, disrupts the hypothalamic-pituitary-adrenal axis, reduces neurotransmitter levels, interferes with the expression of thyroid hormone receptor genes, and others (56).

The neurodevelopmental effects of clinical arsenic poisoning became evident in Japan in 1955 when milk powder produced by a manufacturer was contaminated with arsenic. Infants who consumed formula made from this powder could have had an arsenic intake of as much as 5 milligrams per day, and signs of poisoning appeared after a total intake of approximately 60 milligrams. One-quarter of the infants in western prefectures of Japan were affected. As many as 130 children died, and their brains showed signs of edema, hemorrhage, and white matter degeneration. Those who survived were at an increased risk of epilepsy, severe ID, and hearing deficit (57). Neuropsychological deficits were still present 50 years later, even among those not previously recognized as having any disability (58).

For a large number of people in many areas of the world, arsenic naturally occurs at relatively high concentrations in the water used for cooking and drinking, particularly in South and East Asia. Epidemiological studies conducted in, among other countries, Bangladesh, India, China, Mexico, and the United States, have reported significant associations between chronic exposure to elevated, but not acutely toxic, concentrations of arsenic and reduced cognitive performance in children and adolescents (43,59-64).

Fluoride

Fluoride differs from most other environmental chemicals in that children are intentionally exposed to it because of its role in the prevention of caries. A large number of basic neuroscience studies raise concern, however, about the potential effects of excess exposure in developing animals. In some areas of world the natural concentration of fluoride in groundwater is high enough to cause dental and skeletal fluorosis. According to the CDC, in 1999–2004, nearly 40% of U.S. children 12–15 years of age show signs of at least mild dental fluorosis, nearly a 100% increase over the rate observed in 1986–1987 (65). A review of nearly three dozen studies conducted in China, mostly ecologic in design and comparing children from a low-exposure village to a high-exposure village, concluded that exposure to water with greater fluoride concentrations is associated with lower IQ scores (66). Such studies provide only weak evidence, however, lacking data on internal exposures (i.e., blood concentrations of fluoride in individual participants or severity of dental fluorosis). Also the villages compared likely differed not only in water fluoride concentrations, but in also in terms of other factors that might affect the distributions of their IQ scores (e.g., socioeconomic status, access to medical care, quality of schools, etc.). Recently, studies that address these limitations have been reported. In a relatively small pilot study in China, negative associations were found between fluorosis severity, reflecting lifetime exposure, and children's scores on some neuropsychological tests (67). Similar findings were reported in India (68), while in a Mexican study, children's prenatal fluoride exposure (concentration in maternal urine during pregnancy) were inversely associated with IQ scores at ages 4 and 6–12 years (69). Increased exposure to fluoride has also been linked, ecologically, to ADHD prevalence in the U.S. (70) and, in a cohort study, to increased ADHD symptoms in Mexican children (71).

Pesticides

All pesticides are neurotoxic by design insofar as they act by targeting the functioning of the insect nervous system. The toxicity of these chemicals tends not to be species-selective, however. There are many different classes of pesticides, differing in their modes of action and in their toxicities. Organochlorine pesticides (e.g., DDT) were developed in the first half of the 20th century. They are fat-soluble, accumulate in the food chain, and persist in the environment for long periods. They act by altering the electrophysiological properties of cell membranes (particularly axons), disturbing sodium and potassium ion exchange. Because of their toxicity and persistence in the

environment, their use has largely been banned or restricted in recent decades although their use continues in certain regions of the world.

Pesticides that degrade more rapidly, and therefore have shorter residence times in the environment than organochlorines, were introduced in the mid-20th century (e.g., organophosphates, carbamates). They are generally considered to be less toxic than organochlorines and are widely used on food crops, in homes, parks, schools, and golf courses. Organophosphate pesticides inhibit the activity of acetylcholinesterase, an enzyme that catalyzes the breakdown of the neurotransmitter acetylcholine, although certain OPs have adverse impacts on children's neurodevelopment at doses that do not cause acetylcholinesterase inhibition. They are thought to work by induction of inflammation, interference with C-reactive protein receptor signaling, insulin resistance, or nuclear transcription factor function. Another major class of pesticides, the pyrethroids, were developed in the 1970s. The neonicotinoids were introduced in the 1980's, although controversy quickly arose because they were implicated in colony collapse disorder, involving a massive die-off of workers in a honey bee colony with serious implications for the pollination of food crops.

In the last decades, a substantial number of studies, conducted in both cohorts presumed to have greater pesticide exposures due to the location of their residence and in general population cohorts, have reported that pesticide body burden is inversely related to children's IQ scores. In a group of children living in the agricultural Salinas Valley of California, offspring of mothers with a concentration of the dialkyl phosphate metabolites of OP greater than 50 nmol/L during pregnancy had lower IQ scores at age 7 years than the children of mothers with concentrations less than 50 nmol/L, which corresponds to the mean in U.S. women of reproductive age (72). In an urban New York City cohort, the concentration of the OP pesticide chlorpyrifos in umbilical cord blood plasma was inversely related to child IQ and working memory at age 7 years (73). In this same cohort, morphometric MRI analysis showed dose-related perturbations in the volumes of many regions of the brain (74). Recently, inverse relationships were reported in a rural, agricultural cohort between prenatal exposure to pyrethroid pesticides and children's social-emotional scores at age 1 year and language/expressive communication scores at age 2 years (75).

Several studies have reported significant associations between prenatal exposures to pesticides, based on location of residence in relation to agricultural use (76) or reported indoor use (77). In a large Finnish birth cohort study in which a biomarker of exposure was measured, greater concentrations of the DDT metabolite DDE in maternal serum from early pregnancy were associated with an increased risk of autism, particularly autism with ID, in offspring (78).

Air pollution

A rapidly developing body of literature on air pollutants indicates that greater exposures are associated with subclinical impacts on children's cognition (79). Air pollution is a complex mixture of diverse chemicals, and the composition varies widely by site. Components of the mixture include PAHs (which are produced by the incomplete combustion of organic matter), oxides of sulphur, nitrogen, and carbon, ozone, and metals. Small particles are generally considered to be the most hazardous because they can be deposited deep in the lung, reaching terminal bronchioles and alveoli.

Approximately 95% of the world's population live in areas where the concentration of outdoor fine particulate matter (less than 2.5 μm in diameter) exceeds the World Health Organization's Air Quality Guideline of 10 μg/m^3, with most areas of Africa, the Middle East, and South Asia exceeding 35 g/m^3 (www.stateofglobalair.org/air). In addition, more than one-third of the world's population is exposed to potentially hazardous indoor air pollution as a result of the combustion of biomass fuels (e.g., wood, dung, peat, crop, wastes) or coal. Because of the closed spaces and the large amount of time spent indoors, especially during the colder months, the indoor concentrations of particulate matter can be as much as 20-fold greater than outdoor concentrations.

It is only in recent years that the impacts of air pollution on the brain have been investigated, and several potential mechanisms have been identified, including oxidative stress/inflammation (viz., elevation of cytokines and reactive oxygen species), altered levels of dopamine and/or glutamate, and changes in synaptic plasticity/structure (80). Studies of children and young adults growing up in Mexico City have reported the emergence of exposure-related signs of neurodegeneration, including early stages of the development of neurofibrillary tangles (hyperphosphorylated tau protein) and neuritic plaques (beta-amyloid deposits), with 1 in 4 individuals showing later stages (Braak stages III–V) neurofibrillary

tangles by the 4th decade of life (81). They also show other abnormalities, including prefrontal white matter hyperintensities, damage to epithelial and endothelial barriers, tight junction and neural autoantibodies (82). Studies of a cohort in Spain showed that, even in the absence of morphological changes in brain, greater airborne exposure to elemental carbon and nitrogen dioxide was associated with lower functional connectivity in key brain networks (e.g., the default mode network) as well as altered activation pattern on a sensory task (83). Moreover, children attending schools in more highly polluted areas showed less favorable performance trajectories over a 12-month interval in their performance on a variety of cognitive tasks (84). A prospective study conducted in New York City found that greater prenatal exposure to PAH air pollutants was associated with lower IQ at age 5 (85) and slower processing speed, attention-deficit/hyperactivity disorder symptoms, and externalizing problems at age 7 to 9 years (86). Morphometric neuroimaging of the children indicated that these effects were mediated by disruptions of white matter in the left hemisphere. Greater postnatal exposure to PAHs was associated with disruptions of white matter in the dorsal prefrontal regions. Several studies suggest an association between various indicators of air pollution and a child's risk of either a diagnosis of an autism spectrum disorder or elements of its phenotype (87).

Synthetic organic chemicals

The research literatures on the impacts of exposure to synthetic organic chemicals are not as well-developed as those on the pollutants discussed above. These chemicals include polyhalogenated compounds such as PCBs, and PBDEs. PCBs were banned in the U.S. in the 1970's but because of their resistance to degradation, they persist in the environment. PBDEs are used as flame retardants in a wide variety of products, although some have been banned or are being phased out. Sharing many of the properties of PCBs, they accumulate and persist for long periods in the environment and in human fat tissue. A systematic review and meta-analysis of studies on children's intelligence and prenatal exposure to PBDEs at levels typical of the general population found a consistent inverse relationship (88). A 10-fold increase in PBDE exposure was associated with a decrement of nearly 4 IQ points. Compounds that are replacing PDBEs, organophosphate flame retardants, might have similar impacts on children's cognition, however (89).

PFCs are commonly used in a variety of consumer products (e.g., non-stick cookware, stain resistant fabrics, fast food packaging). To date, the evidence pertaining to the neurodevelopmental risks associated with such exposures are mixed (90).

Endocrine disruptors

Concerns have been raised about exposure during development to chemicals that alters the function(s) of the hormonal system, causing adverse effects in an organism or its progeny (91). Such chemicals are called "endocrine disrupting chemicals" (EDCs) and can mimic the effects of endogenous hormones, antagonize the effects of endogenous hormones, disrupt the synthesis and metabolism of endogenous hormones, disrupt the synthesis of hormone receptors, and alter target cell sensitivity. Hormone levels in early development are critical in organizing brain development, and perturbations can have long-lasting effects on hormonal programming. For example, adequate levels of thyroid hormone are critical for various processes of brain development, including cell migration, differentiation, and signalling. Given that congenital hypothyroidism causes ID and that even subclinical reductions in thyroid function during pregnancy are associated with IQ deficits in children (92), one can hypothesize that prenatal exposures to chemicals that affect thyroid hormone levels produce more modest impacts on children's intelligence. Increased concentrations of chemicals such as phthalates are inversely associated with total serum thyroid hormone levels in pregnant women and neonates and thyroid stimulating hormone in neonates (93). However, studies are inconsistent regarding whether the alterations that occur at levels of phthalate exposure typical in the general population affect intelligence (94,95). Some studies report that early exposure to EDCs such as phthalate influence sexually-dimorphic behaviors, that is, those that tend to differ between the sexes. For example, prenatal phthalate exposure might reduce masculine play in boys (96).

Population impact of environmental chemicals

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. The population impact of a risk factor depends not only on the magnitude of its impact on health but also on the prevalence of the risk factor. 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 U.S. 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 blood lead concentration above the detection limit. 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 U.S. children from the late 1970's 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 a 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. Environmental chemicals cause many adversities other than a reduction in intelligence, however. A full accounting of the burden of disease imposed by chemicals must include the late downstream impacts, e.g., mental health and economic success, that can reduce quality of life (98).

Conclusions

The current approach to regulating a chemical in the U.S. is to restrict its use only after it is shown unequivocally that exposure impairs human health. Unfortunately, even rudimentary toxicological data are available for only a small fraction of the approximately 80,000 chemicals in use, and most of these data pertain to rather health endpoints such as death, cancer, and birth defects rather than subtle alterations in brain development and function. It is our responsibility to future generations to reduce or, when possible, to eliminate the threats that these chemicals pose to their future well-being.

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Footnote

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