20 Environmental Chemical Exposures and Intellectual Disability in Children

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Although environmental chemical exposures impair the function of many organ systems, the central nervous system (CNS) is considered to be especially vulnerable, in large part because of the potential life-long consequences of perturbations in its development. Six of the 10 chemicals identified by the WHO as being of greatest public health concern globally are known to adversely affect brain-based functions and their development (air pollution, arsenic, dioxin- and dioxin-like compounds, lead, mercury, pesticides) (http://www.who.int/ipcs/assessment/public_health/chemicals_phc/en/). Emerging data suggests that at least two others (cadmium, fluoride) might do so as well. The goal of this chapter is to describe, in brief, how exposure to an environmental chemical during a critical stage of brain development process might increase a child's risk of an intellectual disability or other developmental disorders. Many of the examples provided involve lead because the body of data available for this chemical is much more extensive than that for any other. Principles derived from the study of lead will generally apply to other chemicals, however.

One reason for the enhanced vulnerability of the developing CNS to exogenous insults is the sheer complexity of the processes it involves, which occur over a protracted period beginning shortly after conception and lasting for at least two decades. 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, highly interconnected, specialized cells. Of course, many factors other than environmental chemicals can interfere with these developmental processes during the prenatal and postnatal years. Examples of such pathogens include viruses (e.g., zika, cytomegalovirus, rubella), bacteria (e.g., syphilis, Neisseria meningitidis), and protozoa (e.g., Toxoplasma gondii, schistosoma).

In the sixteenth century, Paracelsus published what remains the most fundamental dictum of toxicology: "Solely the dose determines that a thing is not a poison." In other words, any chemical can become toxic to biological systems. Because timing is critically important for proper brain development, implying the existence of "critical windows of vulnerability," it is evident that this dictum must be amended to indicate that in addition to dose, the stage of brain development at the time of exposure is an important consideration in determining whether exposure to a chemical is neurotoxic. Nevertheless, Paracelsus' contribution provided the foundation for key toxicological concepts, including as the dose-response relationship and threshold dose. Thus,

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in evaluating the extent to which exposure to an environmental chemical poses a public health problem, it is critical to determine whether the doses incurred by members of the general population at critical times in brain development exceed the doses known to cause various forms of harm. The following section briefly describes brain development and identifies chemicals which can have deleterious impact on different aspects of the processes involved.

During prenatal life, the key stages of brain development are 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 an individual is to end up with a species-typical brain. Although minor, inconsequential variations occur among individuals in the fidelity of these processes, some variations can result in abnormalities that have substantial impact on an individual's abilities to carry out brain-based functions. Which aspects of CNS development a chemical perturbs and thus, when exposure is likely to be most deleterious, depends in part on its mechanism of action. Many chemicals affect multiple aspects of brain development. Alcohol, methylmercury, and chlorpyrifos (a pesticide) disturb neural cell proliferation, while methylmercury, alcohol, and X-irradiation 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, alcohol, and lead. Synaptogenesis is affected by alcohol, polychlorinated biphenyls, triethyltin, and the pesticides parathion and 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 pharmaceutical agents such as some anti-depressants (e.g., selective serotonin reuptake inhibitors).

One reason for the enhanced vulnerability of developing CNS is that 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 (Aylward et al., 2014). In the case of methylmercury, the concentration in fetal blood is approximately 70% greater than in maternal blood (Stern & Smith, 2003), suggesting the possibility that it is actively transported across the placenta. In a nationally representative sample of pregnant U.S. women some chemicals, including polychlorinated biphenyls, organochlorine pesticides, perfluorinated chemicals, phenols (e.g., bisphenol A), polybrominated diphenyl ethers (PBDEs, which are flame retardants), phthalates (plasticizers), polycyclic aromatic hydrocarbons (products of the combustion of organic materials), and perchlorate, were detected in 99–100% of pregnant women (Woodruff, Zota, & Schwartz, 2011).

Moreover, the toxicokinetics of chemicals in the maternal-fetal unit can be complex. For example, in addition to being exposed to whatever lead a woman is exposed to during her pregnancy, the fetus is also exposed to lead to which the woman was exposed in the past. Approximately 90% of the lead in an adult's body is stored in bones. To support the development of a fetus' skeleton, large quantities of calcium are mobilized from maternal bone during pregnancy, especially the third trimester. Lead and calcium share certain key chemical properties, viz., both are divalent cations (valence of +2). As a result, lead is mobilized from maternal bone by the same processes that mobilize calcium. In fact, lead that reflects maternal exposure that pre-dates her pregnancy accounts for a substantial fraction of the lead in a fetus's cord blood (Gulson, Mizon, Korsch, Palmer, & Donnelly, 2003). Cadmium does not cross the placenta, but it can accumulate in it and impair its critical support functions.

In adults, the blood-brain barrier, which consists of tight junctions between the endothelial

cells lining cerebral microvessels, prevents larger water-soluble chemicals from entering the brain (Zheng, Aschner, & Ghersi-Egea, 2003). 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 (Selevan, Kimmel, & Mendola, 2000). First, certain pathways of exposure are unique to children, including placental transfer and breastfeeding. It is primarily fat-soluble chemicals (e.g., dioxins, PCBs, perfluorinated compounds) that are of concern with regard to passage into breast milk. Certain behaviors that are more common in children than adults bring them into more intimate contact than adults with some chemicals. These include hand-to-mouth activity, oral exploration of objects, and non-nutritive ingestion (i.e., pica). Such behaviors can result in greater exposure to chemicals, such as lead and PBDEs, that might be present in household dust and soil. 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 hazards. Children and adults also experience different breathing zones, with children spend more time near the floor, where chemical concentrations in the air might be greater (e.g., after residential pesticide application). Differences between the diets of children and adults can also be important. Because children's relative consumption of fruit juices is typically greater than that of adults, the presence of pesticide residues on these products can pose a greater risk to them than to adults. Certain micronutrient deficiencies, such as iron and calcium, are more common in children and can result in greater fractional absorption of chemicals with which these essential metals share binding sites in the gut. 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 the early postnatal years. For example, 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 that can damage cellular processes remain present for a longer period following exposure.

Although acute poisonings as a result of a single, high-dose exposure to a chemical can be serious and even fatal, such events are, fortunately, fairly rare. A broader concern is the potential neurological impact of children's chronic, low-dose exposure to chemicals that, in some cases, are nearly ubiquitous in the environment, affecting large numbers of children. The specific concern is that although such exposures might not produce clinical signs of intoxication, they nevertheless adversely impact brain function, increasing a child's risk of reduced intellectual capacities. The following sections discuss in more detail what is known about the effects of particular chemicals or classes of chemicals on children's intellectual development.

Metals

Mercury. Mercury exists in three forms: elemental, inorganic, and organic. The latter forms are considered to be the most important from the standpoint of public health. Ethylmercury was long used as a preservative (as a component of thimerosal) in multi-use vials of vaccines, but its use has largely been discontinued in pediatric formulations because concerns were raised around 2000 about the potential toxicity of the cumulative doses young children received. The following discussion focuses largely on methylmercury.

In the general population, consumption of 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 (specifically methylated to form methylmercury) by microbes in the 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 long-lived predatory fish (e.g., whales, shark, swordfish, albacore tuna).

Methylmercury provides a striking example of age-dependence of vulnerability to neurotoxicity. Industrial discharge of mercury salts into Minamata Bay in Japan resulted in heavy contamination of the seafood in the region. Children born to women who, during pregnancy, consumed large amounts of this seafood suffered a distinctive constellation of neurologic signs that came to be called, "Congenital Minamata Disease" (CMD) (Harada, 1995). They included growth disturbances, retention of primitive reflexes, sensory impairments, intellectual disability (tenfold increase in risk), cerebral palsy (50-fold increase in risk), and movement and coordination disorders (e.g., cerebellar ataxia, chorea, athetosis, dysarthria). A special hospital was built in Minamata City solely to provide lifelong care for these children, who were unable to function independently. Many of the mothers of children with CMD manifested no symptoms of mercury intoxication or only mild sensory symptoms such as transient parathesias. Neuropathological examination of individuals who were of different ages when their mercury exposure began revealed strikingly different patterns of brain abnormalities (Choi, 1989). In individuals who had already reached adulthood at the onset of exposure, the 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 throughout gestation, however, lesions were found throughout the brain, with no apparent localization. This is consistent with the global developmental impairments characteristic of patients with CMD. One reason the impacts are diffuse rather than focal in fetuses is that exposure to 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 (islands of cells in the wrong location), reduced cell densities, anomalous cytoarchitecture, disturbance in laminar pattern of cerebral cortex, incomplete myelination, glial proliferation, and limited gyral differentiation.

The devastating neurological effects observed in poisoning episodes such as occurred in Minamata and elsewhere stimulated concern that low-level chronic prenatal exposure to methylmercury has less serious but still deleterious effects on children's brain development. Therefore, numerous studies have been conducted in cohorts from regions in which seafood is an important component of the diet. A large prospective study of children from the Faroe Islands (North Atlantic Ocean) showed that the performance of children on tests of language, attention, and memory, was inversely related to their mothers' mercury exposure during pregnancy (Grandjean et al., 1997). In this cohort, each increase of 1 μg/g (part per million) in the maternal hair-mercury was associated with, on average, a loss of about one-half of an IQ point (Bellanger et al., 2013). Neuropsychological deficits were found at follow-up evaluations of the children at 14 (Debes, Budtz-Jørgensen, Weihe, White, & Grandjean, 2006) and 22 years of age (Debes, Weihe, & Grandjean, 2016), although they were diminished in magnitude. Functional MRI studies of a subset of the cohort showed dose-related alterations in patterns of activation (White et al., 2011). Studies conducted in areas in which local seafood is heavily contaminated by the use of mercury as an amalgamator in artisanal gold mining have found substantial intellectual deficits in the children with the greatest prenatal exposure to methylmercury (Gibb & O'Leary, 2014).

Some large studies of fish-consuming populations have not found significant associations between children's prenatal methylmercury exposure and their later intellectual development (e.g., Davidson et al., 1998). One potential explanation has to do with the pathway or vehicle of exposure. Seafood is a source not only of methylmercury but also a variety of important macronutrients (e.g., protein) and micronutrients

(e.g., long-chain polyunsaturated fatty acids such as omega-3, selenium, iron, choline) that promote brain development. Failure to structure statistical analyses in such a way that adjustments are made for the fact that increased intake of these nutrients often accompanies increased intake of methylmercury can obscure the detection of both the toxicity of methylmercury and the benefits of the nutrients, i.e., produce negative confounding (Choi, Cordier, Weihe, & Grandjean, 2008). Analyses that address this issue have shown that by careful selection of the particular species of fish that are consumed, it is possible both to achieve the benefits of these nutrients and minimize exposure to methylmercury, improving the cognitive outcomes of children (e.g., Oken et al., 2005).

Bellinger, O'Leary, Rainis, and Gibb (2016) estimated that the global incidence of methylmercury-associated intellectual disability is approximately 225,000 cases per year. Based on country-specific data on exposure, the incidence rate varied more than 20-fold across different regions of the world. The highest rate of mercury-associated ID was in the low-income region of the Americas (7 cases per 10,000 population) (subregion D in the WHO classification, which includes Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, and Peru). The largest number of cases, however, was estimated to be in countries in the highly populated Western Pacific B region (87,445 cases). This includes all countries in the region except Australia, Brunei Darussalam, Japan, New Zealand, and Singapore. 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 prominence of seafood in the diet. Nearly all of the ID cases associated with methylmercury would be expected to be mild in severity.

Mercury in its elemental form has long been used in dentistry, as dental amalgam, which is used to restore caries, is 50% elemental mercury by weight. These amalgams can release mercury, and individuals with a larger number of such fillings have been shown to have somewhat higher urinary mercury concentrations. The question of whether the concentrations are sufficient to cause neurotoxicity has been controversial. Although there have been numerous case reports and observational studies suggesting that it is, two large trials comparing the neuropsychological and renal outcomes of children with substantial unmet dental needs who were randomized to receive either dental amalgam or composite resin restorations of caries, did not find evidence that children in the composite resin group performed better than the children in the amalgam group in the 5–7 year follow-up period (Bellinger et al., 2006; Lauterbach et al., 2008).

Lead. Lead can produce devastating effects on the developing brain by interfering with myriad processes. Depending on the dose, it increases apoptosis (programmed cell death), excitotoxicity (neuronal damage caused by over-activation of receptors), 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 thus damaging cell membrane lipids, alters the activity of first and second messenger systems in neurons, 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. Severe lead poisoning can cause brain hemorrhage, edema, seizures, and coma. Even children whose lead poisoning is not so severe as to cause such an encephalopathy are left with a variety of residual difficulties. In an early case series, Byers and Lord (1943) demonstrated the error of the view, widespread at the time, that children fully recover from sub-encephalopathic lead poisoning. They observed that, "after recovery from their lead poisoning, these…children made an extremely poor record in competition with their fellows," insofar as, "with one definite and a second possible exception, none of the 20 children succeeded in school" (p.479). They also noted that the children exhibited severe behavioral pathologies, including hyperactivity, reduced impulse control, and aggression (e.g., fire-setting, biting others, stealing supplies, repeatedly dancing on desks, attacking classmates). Other problem behaviors noted

included cruelty to animals and lack of response to punishment.

It is now recognized that because lead is so ubiquitous in the environment, intellectual impairment due to excessive exposure is a frequent rather than a rare occurrence. Indeed, some lead can be detected in the blood of virtually everyone. Based on 2015 data, the Institute for Health Metrics and Evaluation estimated that lead exposure accounts for 12.4% of the cases of idiopathic intellectual disability in the world, concentrating in low- and middle-income countries.

Based on the substantial amount of evidence that accrued on lead neurotoxicity over the past few decades, the blood lead concentration considered to be the "upper limit of normal" by bodies such as the World Health Organization and the U.S. Centers for Disease Control and Prevention (CDC) steadily dropped. In the 1960s a value of 60 μg/dL was considered the limit but, at present, because of the apparent absence of a threshold for the appearance of adverse effects on children's cognition and behavior, no level is considered to be "safe." A set of analyses of IQ data collected in seven prospective studies (N = 1333) conducted in several countries provided much of the justification for the present consensus (Lanphear et al., 2005). The motivation for pooling the data from these studies was to increase the precision with which the shape of the dose-effect relationship could be ascertained for blood lead concentrations <10 μg/dL. At the time of these analyses, 10 μg/dL was the U.S. CDC "action" level, at which intervention activities were triggered to reduce a child's lead exposure. The relationships between IQ, measured at age 5–10 years, and various indices of lead exposure were evaluated. A variety of statistical models were compared in terms of goodness-of-fit to the data, adjusting for 10 covariates, such as maternal IQ and home quality. A log-linear model using concurrent blood lead concentration as the exposure biomarker provided the best fit and indicated that an increase in blood lead from 2.4 to 30 μg/dL (the fifth and 95th percentiles of the blood lead distribution in the pooled dataset) was associated with an IQ reduction of 6.9 points. One of the most important findings was that the association was nonlinear, insofar as much of the total reduction, 3.9 points, occurred over the range of 2.4 to 10 μg/dL. The increase from 10 to 20 μg/dL was associated with a further reduction of 1.9 points, and the increase from 20 to 30 μg/dL with an additional reduction of 1.1 points. Although the mechanism(s) by which the proportional loss in IQ are greater at lower than at higher blood lead concentrations remain unknown, similar supra-linear relationships between blood lead and other cognitive outcomes were subsequently reported (e.g., Kordas et al., 2006; Téllez-Rojo et al., 2006).

Epidemiological studies have generally included assessment of other aspects of children's neuropsychological functioning. IQ is an apical measure, integrating children's performance in diverse verbal and nonverbal domains. If the effects of a neurotoxicant are focal, limited to only certain domains, one would expect that tests that focus more narrowly on the vulnerable domains would be more strongly related to lead biomarkers than is IQ. It is somewhat surprising, therefore, that, IQ is more consistently associated with lead biomarkers than is performance on tests that focus on more narrowly defined domains (e.g., memory, language). While this might, in part, be attributable to psychometric differences in the tests used, it might also provide some insight into the mechanism of lead-associated neurotoxicity, suggesting diffuse rather than focal neuronal and/or white matter injury, thereby producing global impairments of higher cortical functioning. It is also possible that the domains most affected vary across studies because of the joint effect of cohort differences in the timing of lead exposure and differences across domains in the timing of greatest susceptibility. The domains vulnerable to lead exposure also depend, to some extent, on cohort characteristics or context specific aspects such as genetic susceptibility, social environment, mixed chemical exposures.

Many studies have reported significant inverse associations, in the general population of children, between lead exposure and success in school, expressed as lower scores on standardized tests, receipt of special education services, grade retention, and failure to complete qualifications

(e.g., Amato et al., 2012; Delgado et al., 2017; Fergusson, Horwood, & Lynskey, 1997; Magzamen et al., 2013, 2015; Needleman, Schell, Bellinger, Leviton, & Allred, 1990). In ecologic (i.e., aggregate-level) analyses, Nevin (2009) reported an inverse relationship between preschool blood lead concentrations and SAT scores, lagged by 17 years. Evens et al. (2015) evaluated the relationship between blood lead concentration and performance on the Illinois Standard Achievement Test in a cohort of 47,168 Chicago schoolchildren. Adjusting for covariates, they found dose-dependent reductions, extending below 10 μg/dL, in both reading and math scores, with each 5 μg/dL increase in blood lead associated with an increase of 1.3 in the risk of reading and math scores defined as "failure." A nonlinear dose-response relationship was found for reading failure, with the slope steeper for blood lead concentrations less than 10 μg/dL compared to greater than 10.

In a similar study, Miranda, Kim, Reiter, Galeano, and Maxson (2009) combined a North Carolina blood lead surveillance database with a database containing scores on a reading test given to school children in the state at the end of fourth grade. In the sample of 57,678 children, blood lead concentration ranged from 1 to 16 μg/dL, with a 75th percentile of 6 μg/dL. A significant dose-response effect relationship was found between blood lead and test score, without apparent threshold. Quantile regression analyses indicated that the adverse impact was more pronounced at the lower end of the test score distribution than at the higher end, indicating that the impact of lead is disproportionally greater on children who are already at academic risk than on children who are at low academic risk. This might be attributable to contextual factors that influence a child's resilience or susceptibility to lead exposure, such as nutrition, social environment, and other chemical exposures.

Skerfving, Lofmark, Lundh, Mikoczy, and Stromberg (2015) evaluated the performance of 3176 Swedish children on an examination taken at the end of compulsory schooling (age 16 years) in relation to blood lead concentration measured when the children were in primary school (age 7–12 years). They found an inverse nonlinear association between blood lead concentration (range 0.6 to 16.2 μg/dL, 90th percentile 6 μg/dL) and school performance, with a steeper slope at concentrations below 5 μg/dL than above 5. They estimated that the adverse impact of an increase in blood lead concentration from 2.5 to 5 μg/dL was similar in magnitude to the impact of having a mother with a university versus a primary school education. Surkan et al. (2007) reported that children with a blood lead concentration of 5–10 μg/dL, compared to children with a concentration of 1–2 μg/dL, had significantly lower reading and mathematics scores, even after adjustment for Full-Scale IQ score. This suggests that the achievements of children with greater exposures were not at a level commensurate with their ability.

The effects of lead are persistent as children age, with greater childhood exposure associated with reduced success in life success. In the large Dunedin Multidisciplinary Health and Development Study, Reuben et al. (2017) found that blood lead concentration measured at 11 years of age was inversely related to IQ at age 38 years, even after adjustment for IQ at age 11 years. Furthermore, early lead exposure was inversely related to socioeconomic status at age 38, suggesting that children who were more highly exposed enjoyed lower upward social mobility and, in fact, 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 as, itself, an effect modifier that increases the adverse impacts of later events and exposures or even normal aging processes. Weiss, Clarkson, and Simon (2002) speculated that if early-life exposure to a neurotoxicant increases the annual rate of neuronal loss by less than 1%, clinical signs of neurodegeneration would appear several years earlier than they would in the absence of such an exposure. Animal studies suggest that lead exposure reduces the ability of rats to weather an unrelated neurological insult in adulthood. Rats exposed to lead early in development but not thereafter were less successful than control rats in recovering function (beam walking,

limb placing) after a laser-induced stroke in the somatosensory cortex in adulthood (Schneider & DeKamp, 2007). Early exposure to lead might also influence function in adulthood by altering the speed of aging. Provocative studies in rodents and nonhuman primates suggest that 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-phosphorylation of tau protein) (Gąssowska et al., 2016).

In the 1970s, the observations of Byers and Lord (1943) regarding the behavioral pathologies were followed up, with case-control and chelation challenge studies suggesting that children diagnosed with hyperactivity had greater lead burdens (e.g., David, Clark, & Voeller, 1972). Subsequent studies indicated that even in children who were neither clinically lead poisoned nor diagnosed with hyperactivity, a greater lead burden was associated with increased distractibility, reduced ability to follow directions, disorganization, daydreaming, and lack of task persistence (e.g., Needleman et al., 1979). 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 (Goodlad, Marcus, & Fulton, 2013).

It is now established that increased childhood lead exposure also increased the risk that a child meets diagnostic criteria for ADHD. Using data from NHANES 1999–2002, Braun, Kahn, Froehlich, Auinger, and Lanphear (2006) found that the adjusted odds ratio for parent-reported ADHD among 6–16-year old children with a blood lead concentration in the fifth quintile (>2 μg/dL) was 4.1, compared to children in the first quintile (<0.8 μg/dL). A dose-response relationship was observed, with adjusted odds ratios of 1.1, 2.1, and 2.7 for children in the second quintile, third, and fourth quintiles, respectively. Among the limitations of this study are the absence of a clinician-confirmed diagnosis of ADHD and the fact that data on important covariates, such as family history of ADHD, were not available. A study by Froehlich et al. (2009), using NHANES 2001–2004 data, addressed the first issue. The Diagnostic Interview Schedule for Children, a clinician-administered diagnostic interview based on DSM-IV, was used to confirm a diagnosis of ADHD. Children with a blood lead concentration in the upper tertile (>1.3 μg/dL) were 2.3 times more likely to meet diagnostic criteria than were children with a concentration in the lowest tertile.

This association has been replicated in several subsequent case-control studies (Choi, Kwon, Lim, Lim, & Ha, 2016; Park et al., 2016; Wang et al., 2008). Nigg et al. (2008) clarified possible behavioral mechanisms of the association between lead and ADHD symptoms. Children 8–17 years old who met rigorous criteria for the diagnosis of ADHD had a significantly higher blood lead concentration than controls, even though concentration for all participants ranged only from 0.4 to 3.5 μg/dL, mean of 1.03). A significant relationship was found between blood lead concentration and total ADHD symptoms. In this study, IQ was measured and a Stop task was administered, providing assessments of a child's ability to suppress a prepared response (stop signal reaction time) and variability of reaction time on the "go" trials (response variability, readiness, and control). Mediation analyses suggested that lead exposure might increase a child's risk of ADHD by impairing cognitive control abilities, and that the association between blood lead and IQ was mediated by the association between blood lead and hyperactivity-impulsivity, not vice versa. Nigg et al. (2008) argued that the plausibility of the link between lead and ADHD 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. Nigg, Nikolas, Knottnerus, Cavanagh, and Friderici (2010) replicated the associations between blood lead concentration and ADHD symptoms in a larger sample, including adjustment for additional covariates, and at even lower blood lead concentrations (range 0.3–2.2 μg/dL).

Several studies in the last decade have suggested that children with greater early-life lead exposure are at increased risk of social pathologies such as criminal activities (e.g., Boutwell et al., 2017; Wright et al., 2008). If this association is true, it seems most likely to reflect 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, executive function deficits such as inability to anticipate consequences or to implement long-term plans, and possible substance abuse (Bellinger, Matthews-Bellinger, & Kordas, 2016). Of course, not all children with excessive early-life lead exposure follow this developmental trajectory, as there are many points along the way at which timely developmental supports might reduce the likelihood that the cascade is fully expressed.

Neuroimaging studies have explored the associations between lead exposure history and brain structure 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 gray 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 (Cecil et al., 2008). On diffusion tensor imaging, reduced fractional anisotropy and axial diffusivity were also associated with greater childhood lead exposure (Brubaker et al., 2009). 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 gray and white matter (Cecil et al., 2011). Functional magnetic resonance (fMRI) imaging 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 (Yuan et al., 2006). 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) (Seo et al., 2015). These findings suggest that exposure to lead impairs the fronto-parietal working memory network.

Arsenic

Although arsenic is well known for its acute toxicity, chronically elevated exposure has many effects that would be expected to affect brain function. These effects include increasing oxidative stress, free radicals, and neuronal apoptosis, impaired neurogenesis in the hippocampus and disruption of the expression of the NMDA receptor, disruption of the hypothalamo-pituitary-adrenal axis, reductions in neurotransmitter levels, interference with the expression of thyroid hormone receptor genes, and others (Bellinger, 2013).

The potential consequences of clinical arsenic poisoning became evident from an episode that occurred in Japan in 1955, when milk powder produced by a manufacturer was contaminated with arsenic. Infants who consume 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 residing in the prefectures of western 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 intellectual disability, and hearing deficit (Dakeishi, Murata, & Grandjean, 2006).

Diverse neuropsychological deficits were still apparent 50 years later, even among those not previously recognized as having any disability (Yorifuji et al., 2016).

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. Studies have been conducted in several areas of South Asia (e.g., Bangladesh, West Bengal, Taiwan) to determine whether chronic exposure to elevated, but not acutely toxic, concentrations of arsenic are associated with reduced intellectual capacities of children.

Fluoride

Fluoride differs from most other environmental chemicals in that, in many areas, public health policies insure that most children are exposed to it for its assumed benefit in reducing dental caries. It is added to public water supplies and put in toothpastes and supplements. Because of its addition to water, fluoride also is present in various dietary elements, such as fruit juices, which are commonly consumed by children. A large number of basic neuroscience studies raise concern about the potential effects of excess exposure to developing animals. In some areas of world, however, the concentration of fluoride in groundwater is naturally high enough to cause observable harm (fluorosis). Depending on the dose, the signs range from small white opaque spots on the enamel of teeth to severe pitting and discoloration of teeth, as well as to 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 fluorosis, nearly a 100% increase over the rate observed in 1986–1987 (Beltran-Aguilar, Barker, & Dye, 2010). 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 they provide suggestive evidence of modest fluoride-associated reductions in children's IQ scores (Choi, Sun, Zhang, & Grandjean, 2012). For several reasons, however, such studies provide only weak evidence. The most important are the fact that only data on external exposure are available (i.e., water fluoride concentration) rather than data on internal exposures (i.e., blood concentrations of fluoride in individual participants or severity of dental fluorosis), and the likelihood that children resident in the villages being compared differ not only in the fluoride concentration in their water supplies, 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, a few studies that address at least some of these limitations have been conducted. Using dental fluorosis as the metric of exposure in a relatively small pilot study in Sichuan, China, Choi et al. (2015) found negative associations between fluorosis severity, reflecting lifetime exposure, and children's scores on some neuropsychological tests, Khan et al. (2015) found inverse associations between fluorosis severity and IQ scores in Indian children, and Bashash et al. (2017) found inverse associations between children's prenatal fluoride exposure (concentration in maternal urine during pregnancy) and their IQ scores at ages 4 and 6-to-12 years.

Pesticides

All pesticides are neurotoxic by design insofar as they act by targeting the functioning of the insect nervous system. Because the central nervous systems of insects and mammals operate on many of the same principles, the toxicity of these chemicals tends not to be species-selective. 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 twentieth 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 than organochlorines in the environment, were introduced in the mid-twentieth century (e.g., organophosphates, carbamates). The organophosphates were originally developed as nerve gas agents in Germany during WWII. 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. However, it is now known that certain OPs have adverse impacts on children's neurodevelopment at doses that do not cause acetylcholinesterase inhibition. They are thought to work by a different mechanism, which might include induction of inflammation, interference with C-reactive protein receptor signaling, insulin resistance, or nuclear transcription factor functioning. Another major class of pesticides, the pyrethroids, were developed in the 1970s. The neonicotinoids were introduced in the 1980s, 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, Bouchard et al. (2011) showed that 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. In an urban New York City cohort, Rauh et al. (2011) found an inverse association between the concentration of the OP pesticide chlorpyrifos in umbilical cord blood plasma and child IQ and working memory at age 7 years. In this same cohort, morphometric MRI analysis showed dose-related perturbations in the volumes of many regions of the brain (Rauh et al., 2012). Recently, Eskenazi et al. (2018) reported inverse relationships 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.

Air Pollution

A rapidly developing body of literature on air pollutants indicates that greater exposures are associated with subclinical impacts on children's cognition (Clifford, Lang, Chen, Anstey, & Seaton, 2016). Air pollution is a complex mixture of diverse chemicals, and the composition can vary by site. Components of the mixture include polycyclic aromatic hydrocarbons (which are produced by the incomplete combustion of organic matter), oxides of sulfur, nitrogen, and carbon, ozone, and metals. In the United States, the concentrations of particulate matter have steadily declined in recent years, although the concentration of ozone has increased (www.lung.org/our-initiatives/healthy-air/sota/key-findings). Small particles (smaller than 2.5 micrometers in diameter) are generally considered to be the most hazardous because they can be inhaled and deposited deep in the lung, reaching terminal bronchioles and alveoli.

Approximately 95% of the world's population live in areas where outdoor fine particulate matter (particles less than 2.5 microns in diameter) concentrations (dust or soot particles) exceed the World Health Organization's Air Quality Guideline of 10 $\mu g/m^3$, 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 (Allen et al., 2017). 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 fourth decade of life (Calderón-Garcidueñas et al., 2018). They also show other abnormalities, including prefrontal white matter hyperintensities, damage to epithelial and endothelial barriers, tight junction and neural autoantibodies (Calderón-Garcidueñas et al., 2016). 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 (Pujol et al., 2016). A prospective study conducted in New York City found that greater prenatal exposure to polycyclic aromatic hydrocarbon (PAH) air pollutants was associated with lower IQ at age 5 (Lovasi et al., 2014) and slower processing speed, attention-deficit/hyperactivity disorder symptoms, and externalizing problems at age 7–9 years (Peterson et al., 2015). Morphometric neuroimaging 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 (Weisskopf, Kioumourtzoglou, & Roberts, 2015).

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 polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs). PCBs were banned in the US in the 1970s but because of their resistance to degradation, they persist in the environment. PBDEs are used as flame retardants in a wide variety of products. 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 (Lam et al., 2017). A ten-fold increase in PBDE exposure was associated with a decrement of nearly 4 IQ points.

Perfluorinated compounds (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 (Liew, Goudarzi, & Oulhote, 2018).

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 (Braun, 2017). 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 signaling. Given that intellectual disability is a result of congenital hypothyroidism, and even subclinical reductions in thyroid function during pregnancy are associated with IQ deficits in children (Levie et al., 2018), it is plausible to 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 (Romano et al., in press). However, evidence that the alterations that occur at levels of phthalate exposure typical in the general population affect intelligence is presently inconsistent (Factor-Litvak et al., 2014; Nakiwala et al., 2018). Several studies have reported that early exposure to EDCs such as phthalates do, however, 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 (Swan et al., 2010).

Estimating the Population Impact of Environmental Chemicals and the Burden of Disease

An argument frequently advanced by those skeptical about the importance of environmental chemicals is that their impact on the neurodevelopment of an individual child is 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 in essence 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. Moreover, the impact of a factor at the population level depends not only on the 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 (2012) 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 care is contributed by the very large proportion of children with blood lead concentrations at the low end of the distribution (because that's where most children fall). A similar calculation of the total IQ losses among the cohort of young U.S. children from the late 1970s produced the figure of approximately 125 million points, suggesting that the public health interventions implemented to reduce population lead exposure has produced a benefit of about 100 million IQ points. Given that approximately 25 million children fall into this age range, the average IQ benefit has been about 4 points, close to the estimate of 4–5 points reached by Kaufman et al. (2014) for the gain in adult IQ.

As the research reviewed in this chapter indicates, environmental chemicals cause adversities that extend well beyond a reduction in intelligence, affecting an exposed individual's success in many aspects of future life. Although current efforts to estimate the burden of disease associated with environmental chemicals consider only IQ deficit as the sequelae (GBD 2016 Risk Factors Collaborators, 2017), a full accounting of the burden of disease imposed by environmental chemicals must include these downstream impacts that can seriously impair quality of life (Bellinger, 2018).

Conclusion

The current approach to regulating chemicals is to impose restrictions on their use only after it becomes apparent that people who are exposed to them are demonstrably harmed. In effect, this results in large-scale natural experiments on the population. The fact that children are the most vulnerable subgroup of the population makes this approach particularly unconscionable. 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 crude health endpoints such as death, cancer, and birth defects rather than brain development and function. A more protective, proactive alternative would be to require a manufacturer to provide evidence of a chemical's safety before permission is granted to introduce it into the marketplace. 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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