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Neonatology and the Environment: Impact of Early Exposure to Airborne Environmental Toxicants on Infant and Child Neurodevelopment

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Abstract

Environmental contaminants pose a threat to infant neurodevelopment. In this current paper, we discuss evidence for the potentially harmful impact of fetal and early childhood exposure to polycyclic aromatic hydrocarbons (PAHs), environmental tobacco smoke (ETS), and organophosphorus (OP) insecticides. We focus on effects resulting from chronic and low-level exposure during the prenatal period and early childhood, when the brain is still undergoing rapid developmental changes.

Introduction

Researchers in the field of children's environmental health science have a particular interest in making the world a safer place for pregnant women, the developing fetus and young children. Achieving this goal requires strategic collaboration between researchers, health care providers and families. By working with vulnerable newborn infants, neonatologists play an important role in raising awareness and reducing exposures to a wide variety of known and suspected neurodevelopmental toxicants that are widely present in consumer products, food, the home, and wider community. Our intention in this paper is to expand neonatologists' awareness of the adverse developmental effects of environmental toxicants present in ambient and indoor air.

Epidemiologic literature has long documented the adverse health outcomes associated with exposures to environmental toxicants for the developing infant and young child [1,2]. Increased vulnerability to environmental toxicants among infants and children can be attributed to several factors ; 1) children experience greater exposures by eating, drinking and breathing more per pound of body weight than adults; 2) children's metabolic systems are immature and the ability to metabolize, detoxify and excrete many toxicants is different from adult systems; 3) children's rapidly growing developmental processes are easily disrupted; and 4) children have more years of life remaining over which to develop chronic diseases. The developing central nervous system (CNS) is particularly more vulnerable to environmental insults than the adult CNS because the maturation of neural tissue involves more developmental processes than those required for other tissues.

Extensive laboratory and clinical studies demonstrate the unique vulnerability of the developing brain to environmental agents including lead, mercury, polychlorinated biphenyls, alcohol and nicotine, at exposure levels that have no lasting effects in adults [3]. An extensive and accessible literature exists on the child health hazards associated with exposure to lead and (methyl) mercury, for which the adverse neurodevelopmental impacts are well documented [4]. However, clinicians may be less familiar with the more recent research on several other widespread airborne toxicants including polycyclic aromatic hydrocarbons (PAHs), environmental tobacco smoke (ETS), and organophosphorus (OP) insecticides. PAH exposures are known to be heavily concentrated in urban areas; OP insecticide exposure may be more prevalent in some agricultural areas; and ETS, despite decades of public health effort to limit tobacco use, remains a common exposure in all geographical regions. Here we review evidence for the potentially harmful impact of fetal and early childhood exposure to these compounds.

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are chemical compounds released into air following incomplete combustion and/or pyrolysis of organic material [5]. Major sources of PAHs in urban ambient air include fossil fuel combustion by motor vehicles, residential heating units, power plants and industrial activities. In the United States and Europe, diesel and gasoline-powered motor vehicles contribute 46–90% of the mass of individual PAHs in ambient airborne particles in urban areas [6]. Environmental tobacco smoke is the major source of PAH in indoor air. Human exposure to PAHs in air occurs through both inhalation and dermal absorption.

PAHs are human mutagens and carcinogens [5], and are potentially significant reproductive and developmental toxicants [7,8]. Our research and that of others indicate that PAHs are transferred from mother to fetus during pregnancy, with the fetal dose approximately 10-fold lower than maternal levels [9]. Accordingly, PAH-DNA adducts have been detected in multiple fetal organs following prenatal exposures [9]. Our prior research showed that mean levels in cord blood (0.24 per 10^8 nucleotides, n=268) and maternal blood (0.22 per 10^8 nucleotides, n=268) at delivery are comparable, despite the 10-fold lower transplacental dose, suggesting greater fetal susceptibility to DNA damage from PAHs or a less efficient DNA repair system [10]. Prenatal exposure to PAHs may critically affect epigenetic programming and immune, metabolic and neurologic functions with consequences manifesting throughout the life span [11]. Furthermore, experimental and epidemiologic studies suggest that the fetal brain and nervous system may be particularly sensitive to PAH exposure [12].

Gestational and early childhood exposures to PAHs have been associated with a cascade of effects on infant growth and neurodevelopment. Decrements in growth may be due to anti-estrogenic effects, induction of P450 enzymes, DNA damage resulting in activation of apoptotic pathways, or binding [7]. In humans, associations between PAH or PAH-DNA damage and adverse effects on fetal growth have been observed in several studies [8,13]. Notably, in two parallel prospective cohort studies of women and newborns in Krakow, Poland and New York City (NYC), a wide range of prenatal PAH exposures were associated with significantly reduced birth weight and preterm birth [14]. In the NYC cohort, these children were followed until age 5 [15], and evidence suggests a continued adverse impact of high PAH exposure on child development. After adjustment for potential confounders, Full-Scale and Verbal IQ scores on the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) of the high and low-exposed PAH groups differed by 4.31 (95% CI: −7.41 to −1.21) points and 4.67 (95% CI: −7.73 to −1.61) points, respectively [15]. The observed decrement in Full-Scale IQ is similar to that reported for children with lifetime

average blood lead concentrations between 5 and 9.9 microg/dL, compared with children who had lifetime average blood lead concentrations < 5 microg/dL, (difference of −4.9 IQ points) [16]. Verbal and Full-Scale IQ measured during the preschool period on the WPPSI have been shown to be predictive of subsequent elementary school performance in a range of populations. Given this evidence for adverse effects of PAHs on fetal growth, and the frequently reported associations of fetal growth problems with subsequent developmental deficits, exposed children are now thought to be at high risk for developmental problems in early life.

Organophosphorus Insecticides—The Case of Chlorpyrifos

Organophosphorus (OP) insecticides including chlorpyrifos (CPF) constitute one of the dominant classes of contemporary pesticides used in agricultural settings throughout the US and worldwide (www.chlorpyrifos.com). Insect and mammalian OP toxicity is attributed to the inhibition of acetylcholinesterase (AChE) and subsequent cholinergic hyperstimulation [17]. New evidence in mammals suggests additional pathogenic effects of CPF target events specific to the developing brain [18]. CPF disrupts the basic cellular machinery controlling neuronal maturation and the formation and activity of synapses, effects that are independent of AChE [19]. CPF also disrupts neuronal maturation by impairing the proliferation and differentiation of neural progenitor cells and by disrupting the formation of axons and synapses. Disturbances in these early neurodevelopmental events may impair later performance on a range of cognitive and behavioral tasks [20].

Epidemiologic studies demonstrate that in utero or early childhood exposure to low levels of OP insecticides, including CPF, adversely affect fetal growth and neurodevelopment [21–24]. In a New York City minority cohort (African Americans and Dominicans), CPF-exposed infants were significantly more likely to be born small-for-gestational age (<10^{th} %) (p=0.02), with lower mean birth weight, smaller head circumference, and shorter birth length than comparable infants with lower exposure [25,26]. This suggests growth-restriction in early pregnancy, curtailing the rate of cell division/organ size, resulting in symmetrically small infants, similar to effects of maternal antenatal smoking. In a birth cohort study of mothers and children living in agricultural communities in California, higher prenatal urinary OP metabolite concentrations were associated with an increase in abnormal infant reflexes in 3 day-old infants [24].

Emerging literature also supports the adverse and persistent effects of prenatal exposure to OP insecticide on child neurodevelopment. Developmental problems were more common among 4–5-year-old children in a Mexican agricultural community using large quantities of OP and organochlorine pesticides, as compared to children from a nearby community with less pesticide usage [27]. Exposed children showed disturbances in stamina, hand-eye coordination, drawing ability, and short-term recall, but the study did not include any validation of exposure using biomarkers. More recent studies of agricultural OP insecticide exposures, using biological measures of exposure, have also documented developmental deficits in exposed children. Ruckart et al. [28] studied development in young children following illegal applications of methyl parathion in their homes, and found associations with poorer performance on short-term memory and attention tasks. Parents of exposed children also reported more child behavioral and motor problems than parents of unexposed children. Young et al. [24] reported associations between prenatal maternal exposure to OP insecticides and deviant neonatal reflexes at three days of age. Ecuadorian children exposed to multiple pesticides as a result of maternal floriculture employment showed significantly lower scores on the Stanford-Binet copying test [29]. In the same study, postnatal OP insecticide exposure (measured by increased total excretion of dimethyl and diethyl metabolites of OPs) was associated with increased simple reaction time. A California study

of farm family children in the Salinas Valley also showed that prenatal agricultural exposures to CPF and other OPs were associated with significant neurobehavioral deficits [30]. The total amount of OP metabolites in prenatal maternal urine related inversely to scores on the Bayley MDI at 2 years [30].

Our own work has shown significant inverse associations of umbilical cord CPF levels with birth outcomes and subsequent neurodevelopment [31]. By 3 years of age, children most highly exposed to CPF (levels greater than 6.17 picograms/gram plasma in cord blood) scored significantly lower on the Psychomotor and Mental Indices of the Bayley Scales of Infant Development, 2nd Ed (BSID-II) [32]. In addition, children most highly exposed to CPF were almost 10 times as likely to show attentional problems and 5 times as likely to show symptoms of attention deficit hyperactivity disorder (ADHD) on the Child Behavior Checklist (CBCL) at 3 years as compared to children with lower prenatal exposure [32]. This was the first report of attentional and hyperactive effects in CPF-exposed children, but there are numerous reports of similar behavior problems associated with other neurotoxicants, including tobacco smoke [33]. Furthermore, a recent study in rats showed that CPF exposure produces deficits in expression of the D4-dopamine receptor [34], the same subtype previously implicated in genetic association studies of ADHD. Whether or not the ADHD-type deficits observed in children exposed to pesticides are identical (anatomically or functionally) with ADHD as identified by DSM-IV diagnosis in the general population is unknown; nor is there any data yet concerning the persistence of such symptoms into middle childhood among children who were exposed prenatally or in early childhood. Since ADHD is now one of the most commonly reported childhood behavior disorders, with prevalence estimates in school-age children ranging from 2–18% in community samples [35], this is an important area of investigation.

Environmental Tobacco Smoke

Across the United States, 10 million children under the age of 6 years are exposed to residential ETS [36], including exposures in the homes of relatives and caregivers. Elevated cotinine levels (a biomarker of ETS exposure) have been reported in 70–80% of inner-city newborns and children [37]. Notably, exposure to ETS is often higher among low-income and minority groups, because smoking rates are generally higher in these populations [38].

Cigarette smoke contains over 4,700 chemical compounds, including nicotine (a toxic alkaloid that accounts for the addictive properties of tobacco), carbon monoxide, > 60 known carcinogens, (i.e., polynuclear aromatic hydrocarbons, aromatic amines, nitrosamines, tar, benzo(a)pyrene, vinyl chloride), co-carcinogens (i.e., catechol, phenol, cresol), ciliotoxins and pulmonary irritants, and radioactive compounds [39]. As mentioned previously, cigarette smoke is also a significant source of exposure to PAHs. Cigarette smoke may be broken down into two categories: mainstream smoke (MS) and environmental tobacco smoke (ETS). MS is inhaled directly by the smoker from the cigarette, while ETS is emitted by the burning cigarette. The chemical compositions of both types of smoke are qualitatively similar, however, the temperature at which MS is formed is much higher than that at which ETS is formed. Consequently, ETS contains larger quantities of many organic chemical compounds than does MS.

The multiple biological mechanisms activated by ETS exposure can produce a range of disturbances in growth and development. ETS has been associated with a range of adverse effects on the feto-placental unit [40] including placental abruption, increased risk of miscarriage, reduced birth weight, reduced birth length, preterm birth, and fetal growth restriction [41], as well as deficits in early cognitive functioning [33,42]. The adverse impact of fetal exposure to ETS may be caused by any of the diverse mechanisms exerted by the

many ETS constituents, such as alteration of receptor-mediated cell signaling in the brain, anti-estrogenic effects or induction of P450 enzymes [43].

Animal models support the biological plausibility of a direct programming effect of tobacco smoke on the developing fetal brain, establishing ETS as a regionally and cellularly selective developmental neurotoxicant [44]. ETS affects fetal brain development in the same manner as exposure through direct maternal routes. Nicotine, inhaled by the mother, crosses the placenta resulting in fetal blood concentrations potentially higher than in the mother. Nicotine then binds with and stimulates nicotinic cholinergic receptors, mimicking the effects of acetylcholine neurotransmission. Nicotine may then affect processes such as cell replication, differentiation, growth, death, and sensitivity to future stimulation [45]. The critical period for damage to the CNS corresponds to the second and third trimester in humans, when nicotinic receptors maximally influence neurodevelopment. No effects have been noted when exposure is limited to the first trimester. Nicotine likely impairs neural development at doses well below those required for fetal growth restriction [46] so that longer-term impairment might be expected even in the absence of reduced birth weight.

A clinical illustration of this biological model involves the observation that, infants exposed to tobacco smoke (active maternal smoking) *in utero* are at higher risk for sudden infant death syndrome (SIDS) than unexposed infants [47]. These infants show reduced physiological capacity to compensate for challenges (physiological stressors) that lead to decreases in blood pressure [48]. This is manifested by altered patterns of heart rate and heart rate variability in response to blood pressure challenge in the first few days of life. The hypothesized mechanism is that prenatal toxic exposures lead to a defect in brainstem mechanisms that insure proper integration of cardiac, vascular, and respiratory activity. Fetal and early infant patterns of autonomic dysregulation appear to be relatively stable over time, and are associated with response to novelty at four months, infant difficultness, inability to adapt, reactivity and attention problems at 12 months of age [49]. This work has important implications for subsequent problems in processing frequently encountered stimuli, such as might be seen in attentional problems, impulsivity, or other learning problems.

Studies of the long-term cognitive effects of active versus passive prenatal smoking on children's neurobehavioral functioning indicate that ETS has smaller effects, suggesting a continuum of effects with possible dose-response characteristics [38,42]. Despite the dilution of effects in ETS exposure, certain toxic chemical constituents of tobacco smoke are higher in ETS as compared to MS, possibly boosting their neurotoxic effects. The magnitude of the ETS effect on early cognitive development at 2 years of age is comparable to that of low-level lead exposure [50], ranging from 3.4 to 6.6 IQ points, depending on pre- or postnatal exposure, dietary factors and length of follow-up.

Conclusion

In summary, recent studies strongly suggest that the developing nervous system is particularly vulnerable to insult from low levels of exposure to environmental toxicants in ambient and indoor air. For health care providers such as neonatologists working with already vulnerable infant populations, special consideration of the impact of these toxicants on fetal growth and development is warranted.

Environmental PAHs at levels encountered in the air of New York City, largely as a result of fossil fuel combustion, can adversely affect child IQ. These results are worrisome since IQ is an important predictor of subsequent academic performance. Although PAH exposure remains widespread in urban environments worldwide, airborne PAH concentrations can be

reduced through currently available pollution controls, greater energy efficiency, the use of alternative energy sources, and regulatory intervention to remove polluting sources.

Evidence is accumulating that the adverse consequences of early exposures to the OP pesticide CPF are serious and persistent, including a range of attentional, sensorimotor, impulse control and memory-related functions with implications for learning and school performance in children. Further, these early low-dose exposures are well below the level known to be associated with the toxic consequences of acetylcholinesterase inhibition, suggesting the presence of additional pathways and pathophysiological mechanisms. Although CPF was banned for indoor residential use by the Environmental Protection Agency in 2001, it is still widely used in agriculture in the U.S. and abroad and exposures remain ubiquitous.

Recent studies also strongly suggest that a range of exposures to tobacco smoke, both active and passive, are harmful to the developing nervous system, establishing a link between ETS exposure and neurobehavioral abnormalities in both infants and children. Smoking may well be the most important modifiable cause of poor outcomes of pregnancy among women in the U.S., with serious implications for subsequent child neurobehavioral development. Even a small increase in developmental risk associated with ETS exposure may be sufficient to move significant numbers of children into the developmentally delayed range of functioning, requiring early intervention services or special education classes in the early school years. Although educational problems are multiply determined, residential exposure to ETS does appear to be a source of significant, highly prevalent, and largely preventable risk for impaired neurodevelopmental outcomes in this population.

Taken together, the many emerging studies of the hazards associated with early exposure to neurotoxic chemicals should sound the alarm for clinicians, researchers, and public health policy makers alike. Further studies are needed to determine the extent of potential damage to the fetus and the young child, and to better understand whether longer-term effects are reversible. As the results of recent work become more accessible to the health care community outside the field of environmental science research, there may be new opportunities for prevention and the design of interventions to redress these worrisome outcomes.

Objectives

After completing this article, readers should be able to:

1. Discuss the relevance of environmental exposures for infant and child neurodevelopment in the United States.
2. Identify the specific neurodevelopmental consequences of prenatal exposure to common airborne pollutants.

Abbreviations

AChE	Acetylcholinesterase
ADHD	Attention deficit hyperactivity disorder
ATSDR	Agency for Toxic Substances and Disease Registry
BSID-II	Bayley Scales of Infant Development, 2nd edition
CBCL	Child Behavior Checklist

CNS	Central Nervous System
CPF	Chlorpyrifos
DNA	Deoxyribonucleic acid
DSM-IV	Diagnostic and Statistic Manual of Mental Disorders, 4th edition
ETS	Environmental tobacco smoke
IQ	Intelligence quotient
MS	Mainstream smoke
NYC	New York City
OP	Organophosphorus
PAH	Polycyclic aromatic hydrocarbon
SIDS	Sudden infant death syndrome
WHO	World Health Organization
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

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