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Special vulnerability of children to environmental exposures

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Abstract

Fetal life and childhood are the periods most vulnerable to the harmful effects of exposure to environmental insults. This is because, during these periods, there is rapid cell division, organs are being formed, and growth is rapid. Thus, disruption of these processes may result in life-long abnormalities. Of particular concern are exposures that alter cognitive function and behavior, but exposures that alter growth, development, and reproductive and immune system function and that may increase risk of development of diseases like cancer later in life are also especially important. Exposure to environmental chemicals as well as infectious agents occurs via air, food, water, and absorption through the skin. Therefore, the environment in which fetal and childhood development occurs is very important. Unfortunately, poverty is a major risk factor for both exposures and childhood and later-life disease resulting from exposures to both environmental chemicals and infectious agents. It is very important to protect children because they are the future generation.

Keywords: children; cognitive function; environmental chemicals; environmental exposures.

Introduction

Most chronic non-communicable diseases have their origins in childhood, and evidence is increasing that adverse environmental exposures may play a substantial role in the initiation and/or progression of these diseases. So, what explanations are plausible for this situation?

We know that children are disproportionally affected by environmental exposures mainly due to their unique exposure pathways and their developing bodies. Research has demonstrated that chemicals and contaminants can cross the placenta and can also be transferred to the child via breast feeding. Children also interact with their environment in a very different manner from adults. They are physically located in a different zone. Although the adult breathing zone is approximately a meter from the floor, the child breathes in a zone much closer to the ground. Children explore their environment and usually put objects in their mouths regardless of whether the object is something to be eaten or not (1). Children do not understand danger especially when they are in the early stages of crawling and walking.

In addition, children are in a state of continuous growth. They breathe faster and take in more air than adults relative to their body mass. They consume more calories and drink more water relative to body mass. Their diet is more restrictive than that of adults, and this potentially exposes them to higher proportions of unwanted substances.

Children around the world today confront environmental hazards that were not known or even suspected a few decades ago. In the past 50 years, more than 84,000 new synthetic chemical compounds have been developed with over 2800 chemicals produced in high volume. Fewer than 20% of these high-volume chemicals have been examined for their potential to cause developmental toxicity to fetuses, infants, and children (2).

Thus, the world is a very different place for a child and an adult. The World Health Organization (WHO) estimates that about a quarter of the global burden of disease is attributable to environmental factors. However, the disease burden for children accounts for approximately one third of this, and with the estimate based on traditional methodology, it almost certainly underestimates the contribution of new and emerging exposures (3).

In the 2006 report (3), which looked at more than 80 diseases and risks, WHO reports that the burden is not equal between the developing and the developed world. Except for some of the non-communicable diseases, the developing world bears the brunt of this burden, and children carry a disproportionally large share. WHO reports that the infant death rate is 12 times higher in the developing world.

How are children exposed?

Local factors like geography, population demographics, and cultural practices all have an influence on how children are likely to be exposed to environmental hazards. They are exposed in the places they spend most of their time, via media like water, air, food, soil, and objects that carry the hazards. They are also exposed as a consequence of their activities (eating, drinking, playing, exploring, learning, etc.) and through specific age appropriate behaviors (crawling, tasting, and "hand-to-mouth" behavior in a toddler; hobbies and drug-taking in adolescents).

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Exposures

Let us look in more detail at the exposures of any given child. This is not a simple process because the child's exposure differs with life stage and with the environmental exposures it encounters. The first exposure environment is in utero during fetal development. Here, the exposures are determined by maternal exposures. However, the outcome is influenced by the timing of the exposure. There is a special concept called "window of susceptibility" that takes into account that the fetus, or later child, is more vulnerable to a given exposure based on the timing of the exposure. Because the different organ systems develop during different periods of fetal life, harm to any one organ system may be very specific to the time of exposure. Some periods are more important for a reaction or response than others.

After the in utero environment, the child becomes exposed to many different environments. The home, school, work, neighbourhood environment, and ambient environment all contribute to the health and well-being of any child. The home environment includes many factors. Indoor air quality, chemical exposure due to cleaning products, nutrition and diet, and housing quality are just a few. Although the family has some control over this environment, they have less control over the neighborhood environment, which may include road safety, drinking water, food safety, drug use, and crime. The home and neighborhood environments all sit within the ambient environment, which includes factors like air quality, waste management, insect-borne diseases, natural hazards, climate, and many others. This last group of factors is less open to change by the family because it is a national or even global issue. To compound this complicated picture, there will also be country-specific environmental hazards. Vector-borne diseases and the types of pollutants common in indoor air may well be country-specific. Low-income countries are more likely to have combustion-related products from biomass or solid fuel use in the indoor air, but higher income countries are likely to have formaldehyde and volatile organic compounds from glues and resins in carpets and particle board furniture.

Although the adult lives in these same environments, the outcome of exposure is often different. The reason for this is that the child is in a state of growth. The child has developing systems that may be more susceptible to insult or injury. Hazards, exposures, dose, and timing of exposure are all key issues for children.

Unique characteristics of children

The world is changing, but in some instances, children are still treated as little adults. Most pharmaceuticals used in children were developed and tested in adults. So, does this matter?

The answer is a categorical yes. There are many ways in which children are different from adults. The differences are what increase the impact of environmental exposures. Children have different and often unique exposure pathways. Their organ systems and ability to metabolize dangerous chemicals are not fully developed early in life, making them more vulnerable than adults. They are in a state of growth, and their early exposure means they may well have a longer life impacted by disease. In addition, they are unable, due to their age, to have any input into the decision-making process that may limit their exposure.

Transplacental

Not all substances in the mother's blood pass through the placenta to the fetus. However, we do know that substances harmful to the fetus, like viruses, alcohol, nicotine, drugs, some types of medicine, as well as lead and organic mercury, all pass freely through the placental barrier (4). Pregnant women who took the sedative hypnotic drug thalidomide gave birth to infants with severe congenital abnormalities. Before this discovery in 1960, thalidomide had been considered a safe alternative to other similar drugs (5). Diethylstilbestrol was given to pregnant women in the late 1940s through to 1971 to prevent multiple pregnancy-related problems. The treatment was stopped after links to vaginal and cervical cancer were identified in exposed daughters. Excessive maternal alcohol intake during pregnancy may result in fetal alcohol syndrome disorder (FASD), with binge drinking thought to pose a particular risk. Maternal smoking has multiple effects on the developing fetus, including decreased birth weight, abnormal lung growth, low lung function at birth, altered control of breathing with blunted response to hypoxia, and increased risk of sudden infant death syndrome (6).

So, what we do know is that many pharmaceuticals cross the placenta as do many pollutants. In addition, physical environmental hazards like radiation and heat can harm a growing fetus. The issue of environmental health of children begins with the parents, and concerns about new exposures begin in utero (7).

Breastfeeding

Breastfeeding is a unique exposure source for small children. It is clear that many environmental contaminants pass into breast milk; however, morbidity from source exposure is unusual. It is known that polychlorinated biphenyls (PCBs) and other persistent organic pollutants are present in the fat of human breast milk, reflecting the levels in the mother's body fat. There are also lower concentrations of toxic metals, like lead and mercury, present in the aqueous fraction. However, this route of human exposure has not been shown to be damaging in the absence of maternal illness. It is important to note that the milk of other mammals is often used as a basis for infant formula, and this is also subject to environmental contamination and may have higher levels of some pollutants. WHO actively promotes breastfeeding as the best source of nourishment for infants and young children (8).

Emerging exposures

The US Environmental Protection Agency has reported that there are some 84,000 chemicals registered for use in the USA alone. Many of these have not been rigorously tested

for adverse effects, especially in children. In addition to the chemicals that have previously been investigated as adversely affecting health, there are now many additions. Although these emerging chemicals are not necessarily new, their use may have changed. An example of this is the chemical bisphenol A (BPA), which was investigated for potential commercial use in the 1930s as a synthetic estrogen. BPA is a known endocrine disruptor and one of the highest volume chemicals produced worldwide. It is often used in food and beverage containers including baby bottles. It is a component of epoxy resins used for some dental materials, CDs, DVDs, electrical and electronic equipment, recycled paper, and often in register receipts. People can ingest, absorb, or inhale BPA. Laboratory experiments document leaching of BPA from baby bottles into the water filled in the bottle, with the migration of BPA rapidly increased when the temperature increases over 80°C (9). BPA has been shown to adversely affect health outcomes in experimental animal studies, particularly following fetal or early life exposure (10).

In humans, increased levels of BPA have been correlated with various diseases. There are various reported adverse effects of BPA, but more investigations are needed to understand the potential adverse health effects and multiple pathways through which it might act. However, the information that is accumulating indicates that developmental exposure to BPA may alter the epigenome (11, 12) and that the prenatal and neonatal periods represent the most vulnerable window of exposure (13, 14). Today's concerns about BPA are primarily driven by lose-dose effects observed in animals, by some epidemiologic observations, and by in vitro studies.

Conclusions regarding the toxicity of BPA are based primarily on animal studies. Braun and Hauser (10) conducted their review of the epidemiologic literature on the association of BPA with adverse health outcomes with special emphasis on childhood health outcomes. However, they were only able to identify six epidemiologic studies that examined infant and childhood health outcomes. They concluded by commentating that the unique susceptibility of the fetus and child to environmental exposures required additional studies to examine the relationship between early-life BPA exposure and childhood health outcomes, including neurodevelopment, somatic growth, and pubertal development. Because BPA has oestrogenic actions, there is particular concern about the prenatal exposure to male fetuses and how such exposure might affect the development of secondary sex characteristics and fertility.

Behavior and size

Children also have pathways of exposure that differ from those of adults due to their size and developmental stage. For example, young children engage in normal exploratory behaviors including hand-to-mouth and object-to-mouth behaviors and non-nutritive ingestion, which may dramatically increase exposure over that in adults.

Xenobiotics, or "chemicals foreign to the biological system", utilize metabolic pathways intended for processing of nutrients and for eliminating metabolites. Some xenobiotics are dangerous when ingested and need to be detoxified by metabolism. Others are not dangerous when ingested but may become dangerous when metabolized. Either way, these processes are likely to be different between children and adults, but, unfortunately, not in predictable ways. Particularly, during fetal growth and in the first 6–12 months of life, important metabolic pathways are significantly reduced in efficiency. Most known toxicants are detoxified in the body, so the immaturity of these systems increases the duration and amount of any given internal dose (15). Low-level exposure to environmental chemicals like lead, methylmercury, or pesticides can result in physical malformations or produce cellular or molecular changes that are expressed as neurobehavioral deficits (16).

The growing child

The child is growing and thus has increased requirements for air, water, and food. Children breathe faster than an adult, so they take in a greater quantity of pollutants from the air than an adult. The child has greater water and calorie requirements than an adult. Thus, if the water is substandard, the child essentially gets a greater dose of any contaminant. Children are usually introduced to food a few at a time and hence have a much more restrictive diet than adults. This smaller range of food can mean that children have the potential to take in greater quantities of unwanted chemicals or toxins.

In addition to this potential to have a higher exposure to pollutants in air, water, and food these exposures may be handled by an immature set of systems different from the way they are dealt with in adults (15). Absorption is different and frequently increased in children because they are anabolic and active. They are geared to absorb nutrients very efficiently. A toddler will absorb between 40% and 70% of a given ingested dose of lead, whereas a non-pregnant adult will absorb from 5% to 20%. Nutritional deficiencies, particularly anemia, which is common in rapidly growing children, will increase lead absorption.

Distribution is different from that in adults and varies with age. For example, the blood-brain barrier is not fully developed for the first 36 months of life; therefore, substances like lead readily cross into the central nervous system. The critical period or "critical window of vulnerability" create unique risks for children exposed to hazards with health consequences often linked to the timing of developmental milestones for organ systems.

Timing of exposure

An exposure occurring early in gestation may have an adverse effect on the structural development of an organ, whereas a similar exposure occurring later in gestation may disrupt the functioning of the organ. The stage of maturity is likely to influence the extent of the exposure. For example, a single pulse exposure to a potent teratogen (a substance that can cause birth defects) on the 10th day of gestation would result in approximately 35% of brain defects, 33% of eye defects, 24% of heart defects, 10% of skeletal defects, and 6% of

urogenital defects, but no palate or airway defects. The percentage of these various congenital malformations would be different if the same exposure occurred 2 to 4 days later (17).

The process of growth and development in children does not stop at birth but continues into adolescence. These maturational processes are susceptible to alteration by physical, biological, and chemical exposures at various points of time, with the effects largely determined by the timing of the exposure. The organ systems most vulnerable to adverse environmental exposures are the immune, respiratory, and central nervous systems. They are potentially vulnerable to both prenatal and postnatal exposures because they are immature at birth but have prolonged periods of postnatal maturation (16).

It is important to recognize that children are essentially powerless to have any impact on changing their environment, and they have to suffer the consequences of many more years to live with toxic damage than an adult exposed to the same hazard in adulthood.

Cognitive and neurobehavioral effects of environmental exposures

The brain is one of the most vulnerable organs to chemical exposures in early life, and there are a number of chemicals that are known to reduce IQ and cause changes in behavior, especially in the ability to pay attention and deal with frustration. The early studies of Needleman et al. (18) reported that children exposed to lead, as determined by an analysis of lead levels in the deciduous teeth, had reduced cognitive function as compared with less exposed children. In any population, there is a range of IQ, with some showing higher and some lower than the average. Children exposed to lead still showed a range of IQ, but the distribution curve was shifted downward by about 5–7 IQ points. Weiss (19) depicts the population effects of a small shift in average IQ (Figure 1). Moreover, there were behavioral differences found in children in relation to the lead level in the teeth. Figure 2, from Needleman et al. (18), shows the various behavioral traits as a function of seven increasing concentrations of lead in the teeth and shows that increased exposure leads to shortened attention span, more disruptive behavior, and poorer overall performance. Exposure to lead is usually greatest at the toddler stage of childhood, when children have a lot of hand-to-mouth behavior. There is evidence that the decrements in cognitive function resulting from exposures at this time of life result in permanent harm (20), even though exposures at any stage of life results in reduced memory function (21, 22). Furthermore, there appears to be no level of lead exposure that is without some intellectual impairment (23).

As more research of cognitive function in relation to exposure to chemicals is done, it has become apparent that many different chemicals do the same things that lead does. While other chemicals have not been as extensively studied as lead, exposure to chemicals, particularly those mentioned in Table 1, generally appears to result to a downward shift of the IQ distribution curve by about 5 to 7 IQ points and be accompanied by the same kind of behavioral changes seen with lead. It is remarkable that chemicals of such different structures as metals, persistent organics, and environmental tobacco smoke appear to have very similar effects on the central nervous system.

Attention deficit hyperactivity disorder (ADHD) is a syndrome that is increasingly being diagnosed in children and is characterized by inattention and hyperactivity. ADHD is usually associated with a somewhat reduced level of cognitive function. The incidence of ADHD globally has been estimated to be 5% of children (33), and symptoms often persist into adulthood (34). It appears that almost every

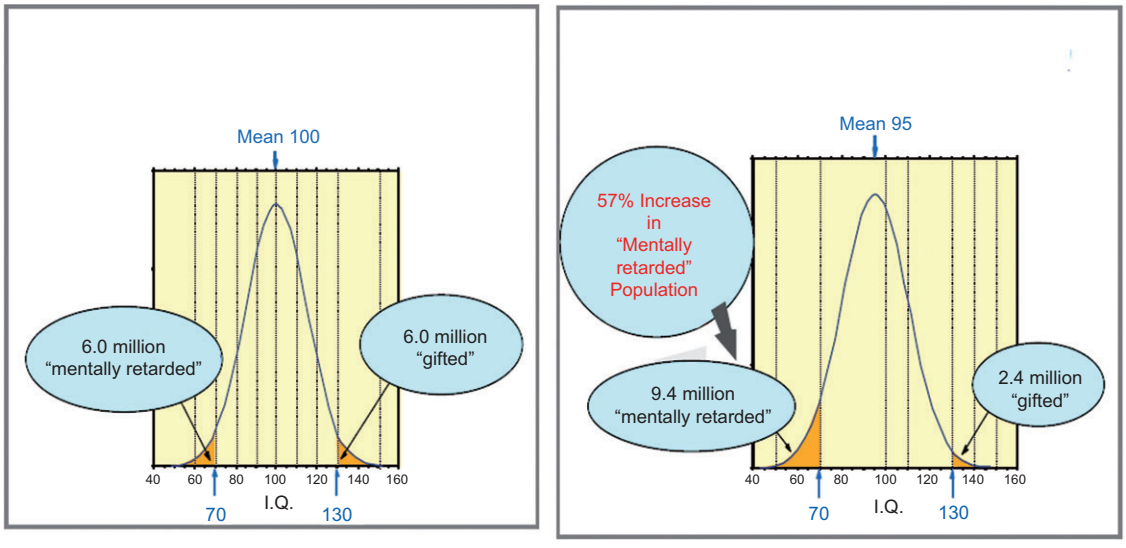

Figure 1 Population effects of a small shift in average IQ. Note the smaller number of gifted and the increased number of mentally retarded individuals resulting from a mere 5 IQ point shift in the population. Modified from Weiss (19), reproduced from www.who.int/ceh.

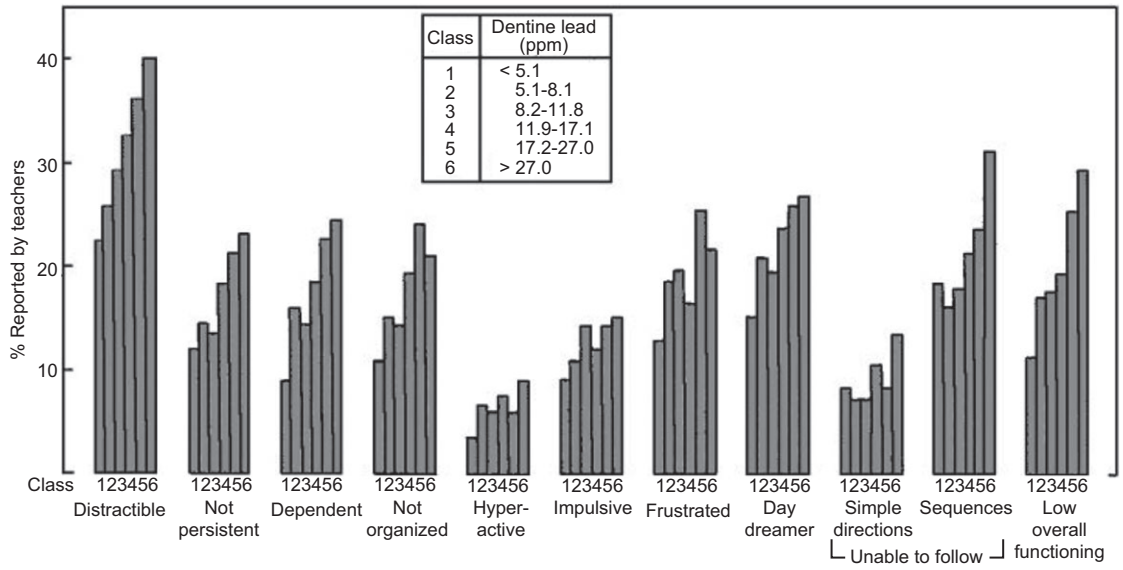

Figure 2 Behavioral traits of children as a function of lead concentration in the teeth. From Needleman et al., p. 691 (18), reproduced with permission.

Table 1 Publications showing associations between chemical exposures and reduced IQ.

Chemical exposures known to result in reduced IQ	Publication
Lead	Needleman et al. (18)
Methylmercury	Axelrad et al. (24)
PCBs	Jacobson and Jacobson (25)
Persistent pesticides	Ribas-Fitó et al. (26)
Organophosphate pesticides	Rauh et al. (27)
Polybrominated diphenyl ethers	Gascon et al. (28)
Environmental tobacco smoke	Yolton et al. (29)
Arsenic	Wasserman et al. (30)
Fluoride	Wang et al. (31)
Manganese	Menezes-Filho et al. (32)

chemical agent that is known to cause a reduction in IQ is also associated with an elevated risk of ADHD, although the level of evidence is greatest for lead (35) and PCBs (36). ADHD has some features in common with FAS, a developmental disease in children that is a consequence of alcohol consumption by the mother during gestation. FASD is associated with some physical deformation of the face as well as the brain, but it is also usually accompanied by immaturity, argumentativeness, inattention, and general disobedience (37). The decrements in cognitive function are often correlated with the severity of the physical defects (38). Autism is yet another developmental disease for which many suspect that environmental exposure plays a causative role (39). However, to date, specific environmental exposures responsible have not been identified.

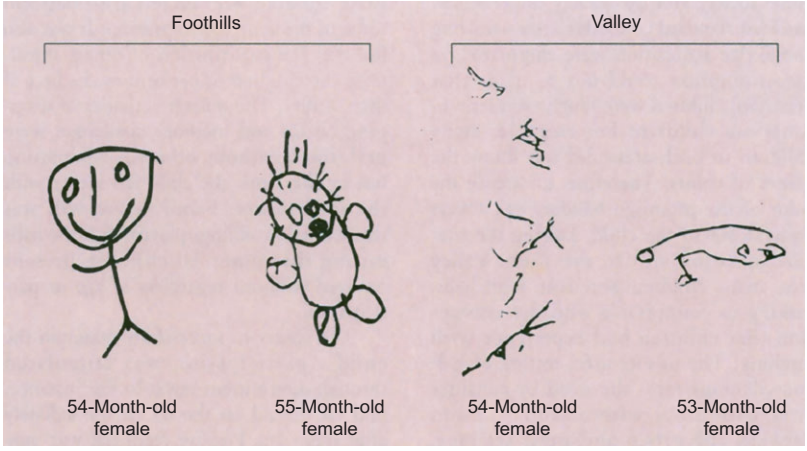

Figure 3 A human figure by 4-year-olds. Children living in the foothills were much less exposed to pesticides, whereas those living in the valley, which was very agricultural, were highly exposed to a variety of pesticides. From Guillette et al. (42), reproduced with permission.

There are many different pesticides, herbicides, and fungicides used both in homes and in agriculture. Chemicals that kills insects and plants are unlikely to be healthy for humans, and children, for all of the reasons mentioned above, are likely to be more exposed than adults in the home (40) and even at school (41). Many pesticides target the brains of insects, and while humans are less sensitive, they can harm children as well. Figure 3, from Guillette et al. (42) shows the results of a study of 4-year-old children, wherein a group exposed to agricultural pesticides by living near the fields was compared with other children from the same ethnic group living away from the field. The exposed children lacked the ability to draw a human figure at the level that would be expected of a child of that age. Clearly, this demonstrates a reduction in cognitive function. There is clear evidence that use of pesticides in the home, the yard, or the garden increases the risk of cancer in children (43).

Conclusion

In terms of hazards and chemicals, the world we know today is different from the world 10 years ago. It is also different from how the world will be 10 years from now, especially if more new chemicals are allowed to be marketed without stringent testing. What will not have changed is the vulnerability of the child. The child will still have unique exposure pathways, a growing body, and no political voice. If the adults of today do not act to protect the interests of the children of today and tomorrow, then the chance of our children and their children being able to enjoy the quality of life of our generation is extremely slim.

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