

## Pediatric Perspectives on Environmental Medicine

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### KEY CONCEPTS

- The prevalence of chronic childhood diseases that are likely caused or exacerbated by toxic environmental exposures has increased since the 1970s. Prominent diseases for which there are concerns about potential environmental origins include asthma, some childhood cancers (including non-Hodgkins lymphoma, acute lymphocytic leukemia, and CNS tumors), obesity, and autism.
- The field of Pediatric Environmental Health seeks both to explain how the impact of children's exposures differs from adults and to prevent such exposures and thus intersects many disciplines including toxicology, exposure analysis, developmental pediatrics, clinical pediatrics, and child development.
- The World Health Organization estimates that globally, 24% of disease burden (life-years lost) is attributable to environmental factors and that a disproportionate burden falls on children.
- Epidemiologic investigation has reinforced many toxicologic studies that indicate that exposures during developmental "windows of susceptibility," when cell proliferation and differentiation are prominent, may have different, more severe, and more permanent consequences than the same exposures in adults.
- Tools for examining the relationship between environmental chemicals and developmental and health outcomes have become more sophisticated, providing the ability to demonstrate synergistic effects created by interactions within the entire web of life (societal, genetic, psycho-social, etc.).



The views expressed by M.D. Miller are his and do not necessarily represent those of the Office of Environmental Health Hazard Assessment, the California Environmental Protection Agency, or the State of California.

In the past century, the United States has seen a steady decline in infant mortality and most infectious diseases. Unfortunately, dramatic increase in chronic childhood illnesses of multi-factorial origin accompanied the decrease in infectious disease and the increase in life expectancy. The prevalence of chronic childhood diseases that are likely caused or exacerbated by toxic environmental exposures has increased since the 1970s. The field of Pediatric Environmental Health seeks both to explain how the impact of children's exposures differs from adults and to prevent such exposures and thus intersects many disciplines including toxicology, exposure analysis, developmental pediatrics, clinical pediatrics, and child development. Prominent diseases for which there are concerns about potential environmental origins include asthma, some childhood cancers (including non-Hodgkins lymphoma, acute lymphocytic leukemia, and CNS tumors), obesity, and autism (Newschaffer, Falb, & Gurney, 2005; Schechter & Grether, 2008; Woodruff et al., 2004). The incidence of type 2 diabetes mellitus, previously rare in children, has been increasing in parallel with the epidemic of obesity (Liese et al., 2006). It has been estimated that in the United States the cost of pediatric diseases of environmental origin exceed 2.8% of the total annual healthcare costs (Landrigan, et al., 2002). During this time period the proportion of disease burden borne by socially disadvantaged children has grown (DiLiberti, 2000). The World Health Organization estimates that globally, 24% of disease burden (life-years lost) is attributable to environmental factors and that a disproportionate burden falls on children (Prüss-Üstün & Corvalán, 2006).

Epidemiologic investigation has reinforced many toxicologic studies that indicate that exposures during developmental "windows of susceptibility," when cell proliferation and differentiation are prominent, may have different, more severe, and more permanent consequences than the same exposures in adults. Originally, Barker examined records in Britain and observed that the geographical areas most associated with fetal or neonatal mortality and low birth weight (i.e., poor nutrition), were not those most associated with known post-natally related risk factors for cardiovascular disease (e.g., high income, increased fat in diet, etc.) (Barker, 2007). Yet, paradoxically, those living in regions with poor fetal nutrition had a higher risk of adult cardiovascular disease. The fetal environment resulted in changes in organ structure, metabolism and function that were permanent. This "programming" during early life associated with lower birth weight, has been linked with increased likelihood of having adult lipid profiles linked to cardiovascular risk and hypertension as well as impaired glucose regulation (Kajantie, Barker, Osmond, Forsen, & Eriksson, 2008). These studies on "the fetal origin of adult disease" have been replicated throughout the world and support observations from animal toxicology showing that early life environmental exposures may demonstrate no readily observable impact until functional deficits are noted later in life.

There are over 80,000 synthetic chemicals in current commerce, most developed since World War Two. Additional thousands are added each year (Landrigan, Kimmel, Correa, & Eskenazi, 2004). During the 1990s, federal agencies began to recognize the

need for additional safeguards for children since the traditional regulatory paradigm for determining safe childhood exposure used information gleaned from studies of adult cohorts and mature animals. Rarely was there toxicologic information in the literature that specifically addressed developing organisms (Miller et al., 2002). In 1996, President Clinton signed an executive order requiring all federal agencies to address the differential impacts of environmental exposures on children (“Protection of Children from Environmental Health Risks and Safety Risks,” 1997). Congress then passed the Food Quality Protection Act (FQPA) of 1996 (“Food Quality Protection Act,” 1996), mandating that pesticide exposures of infants and children be specifically considered in establishing regulatory standards that ensure “reasonable certainty of no harm.” Though implementation is still a work in progress, the FQPA required reassessment of pesticides by the US EPA and resulted in withdrawals and limitations on the use of many of the pesticides most hazardous to children. Pesticides have stricter toxicologic testing requirements than other chemicals. Even so, testing for impacts on neurodevelopment and the endocrine system, endpoints of concern to the developing child, is very limited (Schettler, 2001). For other chemicals, even those produced at a rate of over a million pounds per year, less stringent testing is the norm.

For over 50 years, The American Academy of Pediatrics (AAP) has provided leadership via its committee on environmental health. In 1999, the AAP published the first practical text on Pediatric Environmental Health which is now entering its third edition. (American Academy of Pediatrics Committee on Environmental Health, Etzel, & Balk, 2003).

## **Pediatric Environmental Health and Integrative Medicine**

Integrative medicine strives to take a holistic approach to the person: public health to understand and treat the community and ecologic medicine to address the interplay of the natural and social environment with individual health and societal policy (Schettler, 2006). Tools for examining the relationship between environmental chemicals and developmental and health outcomes have become more sophisticated, providing the ability to demonstrate synergistic effects created by interactions within the entire web of life (societal, genetic, psycho-social, etc.). For example, lead poisoning in children has long been known to cause decreases in cognitive functioning. Recent studies have identified the ability of social/psychological factors to alter the effect of early life lead exposure (Weiss & Bellinger, 2006; Wright, 2008). In rats, social isolation increased the impact of lead exposure and an enriched social environment ameliorated them (Schneider, Lee, Anderson, Zuck, & Lidsky, 2001). The enriched environment after lead exposure altered brain physiology associated with neurotoxicity (i.e., it increased gene expression of hippocampal *N*-methyl-*D*-aspartate receptors, and increased induction of brain-derived neurotrophic factor mRNA) and reversed lead induced learning impairment (Guilarte,

Toscano, McGlothan, & Weaver, 2003). A study performed in the Philippines has found the dose-response of lead exposure on IQ to be much greater than noted previously and related to children's folate levels (Solon et al., 2008). In the Philippines, nutritional, genetic, social factors appear to alter children's response to this environmental contaminant. Perchlorate, a water contaminant, directly reduces production of thyroid hormone by inhibiting the uptake and concentration of iodine in the thyroid gland. Using data from the CDC's human biomonitoring program Steinmaus et al. (2007) identified that perchlorate's impact on T<sub>4</sub> is much more pronounced in women who are low iodine consumers and smoke (Steinmaus, Miller, & Howd, 2007). The true association can only be seen by considering the environmental chemical exposure, the susceptible population (women), diet, and habits (smoking). The field of environmental health is providing evidence that human health needs to be considered within the context of the larger ecosystem, social systems, and other influences. Practitioners embracing an integrative approach are well positioned to translate this to clinical practice and to advocate for holistic health policy that recognizes the interdependence of human health and the larger ecosystem.

## Key Principles of Children's Environmental Health

Children have unique vulnerabilities to environmental chemicals. Though research into children's susceptibilities to environmental exposures has been growing since the mid-1990s, these vulnerabilities are still incompletely understood. The chemicals for which the health effects of early life exposure are well defined represent only the tip of the iceberg as far as the total burden of toxic exposures on child health. For the handful of environmental chemicals in which a large body of research on early life exposures exists (i.e. lead, mercury, secondhand smoke) we have observed a steady decline in the exposure level considered harmful as studies have become more refined.

Due to their higher activity and cellular metabolism, children's minute ventilation per kilogram is higher than that of an adult. This results in greater potential exposure to airborne toxicants. Infants and toddlers frequently play on the floor or carpet where they may be exposed to cleaning products, formaldehyde, contaminants in dust, or pesticide residues. In a case reported by the CDC, a 4-year-old became acutely intoxicated by mercury used in house paint to prevent mold—a product now discontinued ("Mercury exposure from interior latex paint, Michigan," 1990). It is likely that the child's higher exposure resulting from his relatively high ventilatory rate combined with his breathing zone near the floor (mercury vapor is heavier than air) explains why he was affected but not other older family members.

Infants and children tend to have more restricted diets and higher fluid and caloric needs than adults. During the first 6 months of life, a child's diet is exclusively breastmilk or formula. In addition, children consume more than five times as much fluid as

an adult for their weight (Miller et al., 2002). From age 1 to 5 the caloric intake of a child is three to four times that of an adult. During the toddler years, children often consume a much more restricted diet heavy in certain fruits and vegetables, like apples, peas, and carrots. For example, it has been estimated that a non-nursing infant in the United States consumes 16 times as much apple juice as the average adult (National Research Council, 1993). Restrictive dietary preferences can result in larger exposure to any contaminant in the preferred foods. A child's higher surface area to body mass ratio leads to increased potential exposure to dermally absorbed chemicals. Gastrointestinal absorption may vary by age. For example, while an adult will absorb 10% of ingested lead, a toddler may absorb as much as 50%. A child's ability to metabolize and excrete chemicals varies greatly by age and developmental status (Miller et al., 2002; "The Pediatric Environmental Health Toolkit," 2006).

Normal child behavior and play that includes tactile exploration of their environment as well as hand-to-mouth activity may lead to increased exposures to any contaminants in dust and dirt in the home and in outdoor play areas. Though an adult might get up and move away from a noxious stimulus, a pre-ambulatory child is unable to do so. Thus, children may receive quantitatively and qualitatively different exposure than adults to chemicals or contaminants associated with air, foods, water, and certain activities.

### **LONG LATENCY PERIODS**

Some exposures may have effects which are only observed after long term chronic exposure or after the passage of time. For this reason, dangers of certain chemicals may take a long time to recognize which can make epidemiologic studies difficult. Since a child has a potential future life span of 80 years or more, childhood exposure that causes cellular, genetic, or epigenetic damage which predisposes to later life disease such as breast or prostate cancer or Alzheimer's disease has more opportunity to manifest (Dairkee et al., 2008; Prins, 2008; Prins, Birch, Tang, & Ho, 2007; Wu et al., 2008).

### **CRITICAL WINDOWS OF SUSCEPTIBILITY**

During periods of rapid growth, cellular differentiation, and organ development opportunities abound for an environmental toxicant to cause disruption of these vital processes. Critical stages of CNS development occur from embryogenesis, fetal life, and even postnatally through adolescence. The periods of neuronal proliferation, migration, differentiation, and synaptogenesis are especially sensitive to disruption. Damage to the CNS is often irreversible (Horner & Gage, 2000). Since these processes are unidirectional, interference at an early stage may result in disruption throughout the further cascade of events. An example familiar to the pediatrician is ethanol. Fetal alcohol syndrome may result in lifelong mental retardation, behavior and learning difficulties, and permanent structural facial changes. Ethanol affects migration, differentiation, synaptogenesis, and myelination and is capable of causing massive apoptosis during the

period of synaptogenesis/brain growth in the third trimester (Olney, Farber, Wozniak, Jevtovic-Todorovic, & Ikonomidou, 2000). Ethanol exposure during a critical developmental period causes fetal alcohol syndrome when a similar dose in an adult may be trivial or even neuroprotective (Rice & Barone, 2000). Throughout development, there are similar critical windows of susceptibility for different body systems.

## Integrating Environmental Health into Pediatric Practice

Historically, there has been little introduction to environmental health during medical school or pediatric residency. Thus, it is not surprising that most pediatricians in a Georgia study were not comfortable taking an environmental history despite more than half identifying having had a patient seriously affected by an environmental exposure (Kilpatrick et al., 2002).

Since alert clinicians have played important roles in identifying toxicologic hazards such as diethylstilbesterol it is important to maintain a high index of suspicion. Only rarely will a clinician clearly identify an environmental cause for a specific illness, since the symptoms are not usually pathognomonic, diseases are multifactorial, and dose often not well defined. Since low-dose exposures associated with increased risk for illness or disability are common, it is important for clinicians to help families avoid unnecessary, potentially toxic, exposures ubiquitous in our children's environments.

Valuable tools to help the clinician integrate environmental health into anticipatory guidance are available and listed in the resources at the end of the chapter. In particular, the Pediatric Environmental Health Toolkit (endorsed by the AAP and distributed by Physicians for Social Responsibility) provides an overview of environmental hazards and includes visually stimulating age-specific educational materials for use in the office and for distribution to patients. The toolkit is based upon the authoritative information in the AAP published handbook *Pediatric Environmental Health* which includes more detailed information. Below is a short introduction to the environmental history and a brief review of a few selected common environmental hazards, including preventive guidance as an example of a practical approach for clinicians (American Academy of Pediatrics Committee on Environmental Health et al., 2003; "The Pediatric Environmental Health Toolkit," 2006).

### THE ENVIRONMENTAL HISTORY

A thorough environmental history is the foundation for addressing environmental health in clinical practice. Much of the environmental history may be obtained at intake. Forms such as those developed by the National Environmental Education Foundation listed in the resources can make this an easy task. Portions of the history (e.g., hobbies and work exposures for a teenager) can be acquired over time, spreading the time involved over several visits. The history should be adapted to your knowledge

Mnemonic: ACHOO = Activities, Community, Household, Hobbies, Occupational, Oral behaviors

### *Activities*

- School, daycare, after school programs, grandparents
- church, sports

### *Community*

- industrial/agriculture zones
- polluted lakes/streams, dump sites
- water source: bottled, city, well

### *Household*

- type of dwelling: (basement, asbestos, radon, formaldehyde)
- age and condition: lead (esp. if pre-1950)
- heating sources: CO, NO<sub>2</sub>
- environmental tobacco smoke
- pesticides: indoor/outdoor
- household cleaners/chemicals

### *Hobbies*

- arts/crafts, model-building
- increased risk in visually impaired
- lead risks: automotive work; firing ranges
- fishing (mercury and other advisories)

### *Occupational*

- parents' occupation
- known occupational exposures (fumes, dusts, solvents, etc.)
- change or shower at work or home
- potential risks: lead and other heavy metals, asbestos, pesticides
- remember adolescent employment

### *Oral*

- pica/mouthing behaviors

of local hazards, customs, and particulars of your practice. A good environmental history provides a picture of the child's activities and his/her daily environment including neighborhood, daycare or school, church, grandparent's house, and so forth. Some suggested areas to explore in an environmental history have been summarized in the short mnemonic ACHOO below.

## KEY QUESTIONS

1. Do symptoms subside or worsen in a particular location (e.g., home, child care, school, room) on weekdays or weekends, or time of day?
2. Do symptoms worsen during hobby activities, such as working with arts & crafts?
3. Are children your child spends time with experiencing similar symptoms?
4. Do you have concern about any specific exposure?

Adapted from American Academy of Pediatrics Committee on Environmental Health et al., 2003 by the AAP California, Chapter 1.

## OVERVIEW OF SPECIFIC EXPOSURES

### HEAVY METALS

#### *Lead*

Lead is probably the most familiar environmental contaminant to general pediatricians and one of the only for which they routinely screen. Research regarding lead continues to reveal neurodevelopmental effects of exposures at increasingly lower levels. ("Interpreting and managing blood lead levels <10 mcg/dL in children and reducing childhood exposures to lead: recommendations of CDC's Advisory Committee on Childhood Lead Poisoning Prevention," 2007.) In addition, it is a neurotoxicant which affects certain demographics within the US population disproportionately ("Blood lead levels—United States, 1999–2002," 2005).

The combination of routine lead screening, coordinated government intervention to assess children with high lead levels, and the removal of leaded gasoline and paint from the market has resulted in steady decreases in lead levels of American children. While we should celebrate the success of this collaboration between science and policy for the protection of children, it is important to note that the levels we believe are safe for lead exposure have declined equally as precipitously over time and that new novel sources of childhood exposures continue to be reported.

### SOURCES AND ROUTES OF EXPOSURE

Children are exposed to lead in paint on homes built before 1978, through parental occupational exposure (i.e., painters who may be exposed to leaded paint dust when sanding

and then bring home that dust on clothes and shoes) (Roscoe, Gittleman, Deddens, Petersen, & Halperin, 1999), through candies purchased overseas, children's jewelry, and toys manufactured overseas. Additionally, socioeconomic status and race may be associated with risk of lead exposure ("Blood lead levels—United States, 1999–2002," 2005). Younger children more efficiently absorb lead, as do children with poorer nutritional status or iron deficiency. (Wright, Tsaih, Schwartz, Wright, & Hu, 2003) Poor children are more likely to live in older, poorly maintained housing and have increased risk of elevated lead levels (Meyer et al., 2003). In the National Health and Nutrition Examination Survey (NHANES) performed between 1991 and 1994, Medicaid-eligible children accounted for 60% of blood lead levels over 10% and 83% of levels over 20. Despite this, 81% of these children are never screened. ("Recommendations for blood lead screening of young children enrolled in Medicaid: targeting a group at high risk," 2000)

Lead readily crosses the placenta and fetal exposure is associated with the negative neurocognitive effects of lead (Bellinger, 2005). Maternal lifetime body burden is stored in bone and released into the bloodstream at greater rates during times of increased bone resorption such as pregnancy (Tellez-Rojo et al., 2004).

## HEALTH EFFECTS

Lead affects intellect, sensorimotor function, and behavior long after the lead exposure has ceased. Lead is also associated with violent behavior, decreased birthweight, elevation in blood pressure, dental caries, and pubertal delay in girls. The level of concern for childhood blood leads has decreased steadily from 60 mcg/dL in the 1960s to 10 mcg/dL (American Academy of Pediatrics Committee on Environmental Health et al., 2003). Current CDC guidelines say that while 10 is a level requiring intervention, no level of lead is safe in children (Centers for Disease Control and Prevention, 1997).

Some studies have suggested that the rate of neurocognitive decline per mcg/dL of blood lead is greater below 10 mcg/dL (Canfield et al., 2003; Lanphear et al., 2005). The social, educational, and nutritional environment can modulate the effects of lead exposure.

## PREVENTION STRATEGIES

Lead continues to be an important cause of neurodevelopmental toxicity. This is particularly true for African American, Hispanic, and poor children. Childhood exposure to lead may be implicated in adult disease (Basha et al., 2005; Edwards & Myers, 2007; Wu et al., 2008). Prevention of lead poisoning includes careful maintenance of any lead-paint surfaces, including painting or remediation following EPA guidance by trained professionals, control of dust by wet mopping, and avoidance of products with lead in them. Details and patient education materials are available through local, state, and federal public health agencies.

Acute lead poisoning remains an issue today, even as levels have declined. Risks of lower level exposures have been clarified, and guidance for children exposed to lead but with levels below 10 mcg/dL has gained new importance in mitigating the impact of this preventable disease. In response, CDC has issued recommendations for primary care providers including

1. Provide parents of all young children information regarding the sources of lead and assistance in identifying them in their child's environment.
2. Perform blood lead test on all children suspected of having lead exposure and whenever possible utilize laboratories capable of routine performance accuracy to 2 mcg/dL.
3. Establish office procedures that ensure assessment and screening of children required by state or local public health officials and CDC recommendations.
4. Discuss the potential impact of lead on child development and promote strategies that foster optimum child development, including encouraging parents to provide nurturing and enriching experiences for their children.

(“Interpreting and managing blood lead levels <10 mcg/dL in children and reducing childhood exposures to lead: recommendations of CDC’s Advisory Committee on Childhood Lead Poisoning Prevention,” 2007.)

### *Mercury*

#### **SOURCES AND ROUTES OF EXPOSURE**

Mercury is found in the environment in three forms: elemental mercury, organic mercury, and inorganic mercury. Methylmercury (known as organic mercury) is a neurotoxicant with exposure primarily through the consumption of fish. There is great variability in the amount of methylmercury consumed depending on the type of fish eaten as well as where the fish was caught. Methylmercury is readily absorbed, crosses the placenta, and can have significant effects on neurodevelopment.

Elemental mercury is familiar to many in its liquid metal form which is not readily absorbed by the gastrointestinal or dermal routes but poses a risk when vaporized and inhaled. There have been many reports of contamination from children playing with large quantities of elemental mercury taken from old industrial facilities or school science labs. Contamination has also been reported from religious use of elemental mercury, including scattering it about homes. However, mercury’s greatest impact on human health today is as a result of the conversion of elemental mercury to organic mercury in our waterways.

The largest contributing sources of elemental mercury to the environment include coal-fired power plants, cement kilns, medical incinerators, chlor-alkali plants that make caustics, and crematoriums (Goldman & Shannon, 2001). Mercury is emitted

from these sources and then deposited both locally and globally (Evers, Han, Driscoll, Kamman & Goodale, 2007). In regions with a history of gold mining, the waterways were often polluted by mercury used in the extraction process. After elemental mercury settles in the waterways, bacteria metabolize it adding a methyl group and converting it into organic methylmercury. Methylmercury subsequently bioaccumulates and bio-concentrates as it travels up the food chain with the largest and oldest predatory fish routinely demonstrating the highest levels (Orihel, Paterson, Blanchfield, Bodaly, & Hintelmann, 2007).

## HEALTH EFFECTS

Since mercury affects neurodevelopment by interrupting the process of neuronal migration (Choi, 1986; Choi, Lapham, Amin-Zaki, & Saleem, 1978), exposure leads to more permanent and profound effects in fetuses than in mothers. Environmental accidents in both Minamata Bay, Japan, and Iraq led to high mercury levels in pregnant mothers. While the mothers experienced more limited or no neurologic symptoms, babies were born with cerebral palsy, hearing loss, blindness, and seizures (Amin-Zaki et al., 1980; Amin-Zaki et al., 1981; Matsumoto, Koya, & Takeuchi, 1965). Several studies around the world have now demonstrated that at low doses, mercury can affect neurodevelopment in more subtle ways. Mercury has been implicated in difficulties with learning, memory, language, attention, cognition, sensorimotor development, and decreased birthweight (Debes, Budtz-Jorgensen, Weihe, White, & Grandjean, 2006; Gilbert & Grant-Webster, 1995; Grandjean et al., 1997; Harada, 1978; Oken et al., 2005). These difficulties which began with prenatal and early childhood exposure have been shown to persist into adolescence (Debes et al., 2006; Grandjean et al., 1997).

In the 1990s, concern developed regarding mercury found in childhood vaccines and a possible link to autism. At that time, the preservative used in most vaccines was thimerosal which contains ethylmercury. Ethylmercury is also an organic mercury with similarities to methylmercury in that it is a methylated form of the heavy metal. However, it does have toxicological differences in metabolism and half-life. Research into the role of mercury in vaccines has concluded that thimerosal is not causally associated with the rise in autism observed over the past two decades (Hviid, Stellfeld, Wohlfahrt, & Melbye, 2003; Madsen et al., 2003; Parker, Schwartz, Todd, & Pickering, 2004). This conclusion is supported by recent data which shows that rates of autism spectrum disorders have not decreased since the removal of thimerosal from vaccines in 2001 (Hviid et al., 2003; Madsen et al., 2003; Parker et al., 2004; Schechter & Grether, 2008).

## PREVENTION STRATEGIES

Counseling about choosing fish lower in mercury should be a routine part of preventive guidance in pediatrics and prenatal care. Fish are an important source of fatty acids and protein for many people. Despite mercury content, fish consumption has been shown to provide neurodevelopmental benefits. However, for each incremental benefit from

consumption, there is a decrease associated with any mercury content. With this in mind, reasonable advice is to encourage the consumption of fish lower in mercury. Despite current guidelines suggesting limiting fish meals to twice a week or less for pregnant women, to date, evidence suggests that no additional benefit is incurred in cognitive outcome (Oken et al., 2005, 2008). Sport and subsistence fisherpersons should know about and follow public health fish advisories. Though removing fatty tissue and using fat-reducing cooking methods (i.e., grilling) are useful strategies for reducing exposure to fat soluble chemicals (i.e., PCBs, dioxin, and organochlorine pesticides), these precautions are not effective for methylmercury, since it is stored in the muscle tissue of fish. The EPA and FDA have issued very specific guidelines on maternal and child consumption of fish dependent on both the type of fish to be consumed and from which geographic region (US Environmental Protection Agency & Department of Health and Human Services, 2004). These guidelines can be obtained at [www.epa.gov/waterscience/fish/advice/](http://www.epa.gov/waterscience/fish/advice/). Most states publish and post fish advisories for sportfishing.

Elemental mercury spills should be taken seriously; guidelines for cleanup are available from local or state environmental health/public health agencies. Many hospitals and local and state governments have provided mercury thermometer exchanges. Prevention strategies at the federal regulatory level are also critical. The AAP has strongly supported limiting mercury pollution from coal fired power plants under the Clean Air Act (Goldman & Shannon, 2001).

### *Plastics Bisphenol A (Polycarbonate Plastic)*

#### **SOURCES AND ROUTES OF EXPOSURE**

Bisphenol A is used extensively in consumer products and food containers. It is found ubiquitously in human urine, blood, and breastmilk. In children under 6 years old, the NHANES study found it present in 93% of urine samples (Calafat, Ye, Wong, Reidy, & Needham, 2008).

Bisphenol A is used in large quantities in the production of polycarbonate plastics and epoxy resins. It is found in consumer products as diverse as baby bottles, mobile phone housings, and cars. It is also found in plastic food wrappers, canned food linings, and dental sealants. On some consumer products, it can be identified by the recycle symbol 7 and the letters PC. In 2004, the estimated production of Bisphenol A was 2.3 billion pounds (National Toxicology Program, National Institute of Environmental Health Sciences, & National Institutes of Health, 2008).

#### **HEALTH EFFECTS**

Bisphenol A has weak estrogen-like properties, and in animal toxicological studies has been associated with hyperactivity, increased aggression, impaired learning (Ishido, Masuo, Kunimoto, Oka, & Morita, 2004; Kawai et al., 2003; Kiguchi et al., 2008), early puberty, increased mammary tumors, and prostatic hypertrophy (Dairkee et al., 2008;

Prins, 2008). It causes increased adipocytes and increased body weight after prenatal exposure and in adults causes changes in helper T<sub>1</sub> and T<sub>2</sub> cells, thus affecting antibody production (Yan, Takamoto, & Sugane, 2008). Although toxicological information is based on animal studies, these results raise concern about potential effects on human development and carcinogenesis (National Toxicology Program et al., 2008). The dose associated with adverse effects in some animal studies was equivalent to or lower than the doses to which humans are often exposed (Calafat et al., 2008; Vandenberg, Hauser, Marcus, Olea, & Welshons, 2007).

## *Phthalates*

### SOURCES AND ROUTES OF EXPOSURE

Phthalates are chemicals added to plastics for flexibility. They are found in polyvinylchloride (PVC) plastic products, cosmetics, hair, and skin products. Women and children are exposed through diet and dermal application of phthalate-containing products. Infants may be exposed dermally through infant personal hygiene products (Sathyanarayana et al., 2008). Their high surface area to body mass ratio increases the significance of this exposure.

### HEALTH EFFECTS

The mechanism of action of phthalates is anti-androgenic. Animal studies have shown a number of effects on genital development in fetuses; hypospadias, cryptorchidism, testicular dysgenesis, as well as decreased birth weight (Gray et al., 2000; Mahood et al., 2007). In humans, prenatal exposure has led to decreased anogenital distance, implying decreased androgen effects on male target tissues (Swan, 2006). It has also led to increased luteinizing hormone and free testosterone levels in infants (Main et al., 2006). Phthalates have also been associated with rhinitis, eczema, asthma, and wheezing (Bornehag et al., 2004). In adults, it has been associated with abnormal sperm morphology and sperm DNA damage (Duty et al., 2003).

### PREVENTION STRATEGIES TO LIMIT EXPOSURE TO BPA AND PHTHALATES

Familiarize yourself with the recycling labels on plastics. Flexible plastics with a “3,” PVC, contain phthalates. BPA may be found in some type-7 plastics (may have PC on label) and these clear hard plastics should be avoided for baby bottles and food uses. Recycling label 7 also includes other plastics such as those based on corn starch which do not contain BPA. Although Bisphenol A is found in breast milk, breastfeeding remains the best choice for infant nutrition. When using formula, since liquid formula may leach BPA from the can’s lining, powdered formula is a better choice until industry has changed this practice (Environmental Working Group).

Microwaving or heating Bisphenol A and phthalate containing plastics leads to increased leaching into food. Use glass or microwave-safe ceramic for the heating of

food in microwaves. Plastics that are deteriorating or old also leach more and should be discarded. Alternative types of plastics or glass should be used for food, breastmilk, and formula storage. Families should try to buy toys approved by the European Union or toys that are labeled phthalate-free or made from alternative materials. Since there is no labeling requirement for phthalates in US cosmetics, look for brands that market themselves as phthalate-free. Decrease the use of infant personal hygiene products or use phthalate-free alternatives if available. For example, for the treatment of seborrheic dermatitis, olive oil can be used as an alternative to baby oil.

### *Pesticides*

Pesticides are ubiquitous in the modern environment. Most US households use one or more of the over 900 chemicals registered as pesticides (Kiely, Donaldson, & Grube, 2004). Categories of pesticides classified by their use include

**Insecticides**—insecticides include organophosphates, carbamates, pyrethrum and synthetic pyrethroids, organochlorines, and boric acid and borates. In large part as a result of potential health impacts on children, most residential uses of organophosphate pesticides have been eliminated since 2000. In many products, organophosphates have been replaced with pyrethroids. As a result, the incidence of poisonings related to organophosphates has steadily declined from 2000 to 2005, while those related to pyrethrum and pyrethroid pesticides have correspondingly increased (Power & Sudakin, 2007).

**Herbicides**—glyphosate, bipyridyls, chlorophenoxy herbicides (2,4-D). The herbicide 2,4-D is the number-one household pesticide used in the United States, and is commonly found in products used for weed control in lawns and gardens.

**Fungicides**—substituted benzenes, thiocarbamates, ethylene bisdithiocarbamates, copper, elemental sulfur, and various compounds such as captan, benomyl, and vinclozolin.

**Wood preservatives**—pentachlorophenol, chromated copper arsenate (CCA). CCA once was the most commonly used treatment for pressure-treated wood. Most residential and general uses were discontinued in 2004, due to environmental concerns and potential exposure to children when arsenic leached from the wood. Alternative (arsenic-free) chemicals are now used for pressure-treated wood including ACQ, borates, copper azole, and others (US Environmental Protection Agency). These newer treatments have less information available about potential for leaching and environmental impact. Alternative construction materials are also available including composites, high density polyethylene, and rot-resistant woods.

#### **Inert Ingredients**

Along with one or more active ingredients that are designed to kill pests, a pesticide formulation may consist of up to 98% “inert” ingredients that function as dispersants, carriers, solvents, synergists, or otherwise aid in use. Though called inert, these chemicals

may have significant toxicity including CNS depression, dermal irritation, sensitizers, or even may have potential chronic effects such as potential carcinogenicity or reproductive toxicity (Cox & Sorgan, 2006). Symptoms related to a pesticide may result from these inert elements, which may not be listed on the label, rather than the active ingredients. The manufacturers are required to give information on inerts to healthcare providers who call their number on the label.

## SOURCES AND ROUTES OF EXPOSURE

Children may be exposed to pesticides via inhalation, ingestion, or dermal absorption. Home and garden use of pesticides may result in the predominant exposure for those families using household pesticides. In addition to the potential for direct exposure from the areas treated, children may receive significant exposure from residues being tracked into the house by family members and pets (Nishioka et al., 2001). Children may also be exposed to pesticides at schools, through drift of agricultural pesticides after aerial spraying from the intended target field to neighboring homes and schools, residues on fruit and vegetables, and contaminated water. Most streams and many shallow wells have one or more pesticides present during portions of the year, though generally at levels below governmental human health benchmarks triggering action (United States Geologic Survey, 2006).

## HEALTH EFFECTS

The symptoms and treatment of acute health effects of pesticide exposures are well covered in standard toxicology texts as well as in the US EPA publication, *Recognition and Management of Pesticide Poisoning* (Reigart & Roberts, 1999). Chronic low-dose exposure has been linked in animal and epidemiologic studies to a variety of health problems from neurodevelopmental delay to cancer. Maternal body burden of DDE (the metabolite of the organochlorine DDT) has been associated with impaired neurodevelopmental outcomes in infants and toddlers (Fenster et al., 2007). Similarly, prenatal exposure to chlorpyrifos (an organophosphate) has been associated at follow-up at three years of age with Psychomotor Development Index and Mental Development Index delays, attention problems, attention-deficit/hyperactivity disorder problems, and pervasive developmental disorder problems, as identified by the Child Behavioral Checklist (Rauh et al., 2006). Symptoms reported in adult workers exposed to organophosphates include impairment of memory and psychomotor speed, and affective symptoms including anxiety, irritability, and depression (Jamal, 1997). During early life development, some pesticides are known to act as morphogens permanently altering brain structure and function (Ahlbom, Fredriksson & Eriksson, 1994, 1995; Eskenazi et al., 2008). When given during a window of early brain growth, a single relatively modest dose of organophosphate, pyrethroid, or organochlorine pesticide resulted in changes in muscarinic receptor function and behavior in adult rats. Similarly, neonatal

exposure to permethrin (a pyrethroid) results in behavioral changes and altered dopaminergic activity in the striatum of adult rats, lending support to the hypothesis that pesticide exposure in early life may contribute to Parkinson's and other neurologic diseases of aging (Nasuti et al., 2007). Multiple epidemiologic studies have found associations between pesticide exposure and some childhood cancers including leukemia, non-Hodgkins lymphoma, and brain tumors (Buckley et al., 2000; Infante-Rivard & Weichenthal, 2007).

## PREVENTION STRATEGIES

There is now evidence that diet is a large and perhaps predominant source of childhood exposure to organophosphate pesticides in US children (Lu, Barr, Pearson, & Waller, 2008). While the health consequences of this level of exposure are still debated, a precautionary approach would be to emphasize a varied diet rich in fresh fruits and vegetables, but advise peeling or washing before eating to reduce residues. When available and affordable, changing from conventional to organic fruits and vegetables has been shown to significantly reduce exposure (Lu et al., 2008). Pesticide residues on imported fruits and vegetables are more frequent and sometimes dramatically higher than on US produce, suggesting more limited consumption of these is prudent (US Environmental Protection Agency, 2006). The environmental advocacy organization Environmental Working Group publishes an annual ranking of fruits and vegetables by the amount and toxicity of pesticide residues based on testing conducted by the US Department of Agriculture and Food and Drug Administration (Environmental Working Group). If expense is an issue, consumers may choose to purchase organic produce for those items listed as the most frequently contaminated.

Integrated Pest Management (IPM) refers to an approach to pest control for home and agriculture that emphasizes using non-chemical methods primarily, and then the least toxic pesticides only if needed. It also emphasizes managing pests as they emerge rather than treating for pests on a schedule. Methods used with IPM include physical barriers (i.e., caulking), mechanical (i.e., picking tomato hornworm off plant), cultural (choosing plants most suited to conditions), and educational (i.e., cleaning food from kitchen). Always avoid "preventive" applications or regularly scheduled home or lawn programs. When pesticides are used, IPM methods emphasize forms that present the least likelihood of exposure such as using baits, traps, and gels instead of sprays or dusts. When pesticides are used on lawns be sure to water in before children walk or play on them and remove shoes before coming indoors.

Though it is no longer sold for general use, CCA pressure-treated wood is still present in decks, play equipment, picnic tables, etc. Since it continues to leach arsenic to the surface for many years, it is prudent to replace if possible, or coat annually with paint or sealant if not, and to wash children's hands after using. CCA-treated wood should never be burned.

## AMBIENT AIR POLLUTION

The fetus, infant, and young child are considered among the most susceptible to pollutants in the air. In children, ambient (outdoor) air pollution has been associated with respiratory illness, asthma exacerbations and hospitalizations, development of asthma, preterm birth, infant mortality, and deficits in lung growth (Kim, 2004). Ambient air pollution is a worldwide problem with levels in large cities in developing nations often greatly exceeding World Health Organizations (WHO) guidelines. One percent of global childhood deaths from acute respiratory disease annually is attributed to ambient air pollution (Cohen et al., 2005). Contaminants of concern include “criteria” pollutants such as ozone, particulate matter, and carbon dioxide as well as “hazardous air pollutants” which are carcinogens or developmental toxicants like benzene and polycyclic aromatic hydrocarbons from fuel combustion or solvents from industrial emissions. Roads with heavy traffic create locally high levels of pollution and have been associated with respiratory complications in children (including chronic cough, wheezing, and asthma hospitalizations) and various childhood cancers (Kim et al., 2004).

## PREVENTION

The air quality index (AQI) reported daily on television and newspapers in most metropolitan areas, provides information to the public on air quality and potential health concerns associated with forecast levels. Forecast levels are divided into six categories of risk ranging from good to very hazardous. Pediatric providers can play an important role in educating children and families, particularly those with asthma and respiratory diseases, about the effect of air pollution and the use of the AQI to adjust activities. For example, since ozone levels are highest during the afternoon (as it is formed by the action of sunlight on smog), on high-ozone days, scheduling any outdoor strenuous activities for the morning will reduce exposure.

Since roads with heavy traffic create locally high levels of pollution the AAP recommends that when determining sites for school and childcare facilities authorities consider proximity to roads with heavy traffic and other sources of localized pollution. (Kim, 2004) There is some evidence to suggest that antioxidant supplementation may reduce the impact of ozone exposure in children with asthma (Gilliland et al., 2003; Romieu et al., 2002). Healthcare providers can advocate for (and provide an example of) energy-saving and pollution-reducing lifestyles, including choices in automobiles and office design. Ultimately, ambient air quality improvements will largely depend on regulatory and legislative actions.

## *Herbals, Alternative and Traditionally Based Remedies, and Chelation Therapy*

There have been many reports in the literature of contamination of herbal preparations, ayurvedic and other alternative therapeutics, and folk remedies. In an evaluation of 260 samples of Asian patent medicines collected from herbal retail stores in California, the

California Department of Health Services found 32% contained undeclared pharmaceuticals or heavy metals and many had more than one adulterant. Contaminants included arsenic, mercury, and lead, as well as ephedrine, chlorpheniramine, methyltestosterone, and phenacetin (Ko, 1998). In a similar small survey of ayurvedic medicine sold in Boston, 20% contained potentially harmful levels of mercury, lead, and or arsenic (Saper et al., 2004). One study of adult lead poisoning found a group of adults exposed from ayurvedic medicine had significantly higher blood lead levels compared to those with occupational lead poisoning (Kales, Christophi, & Saper, 2007). The experiences noted above underscore the need for practitioners to be alert to potential symptoms that may result from heavy metals or pharmaceuticals and to utilize herbal preparations from companies known to be able to guarantee them free from adulteration or contamination (Hohmann & Koffler, 2002).

As is the case for medicine in general, a well-conducted environmental history as well as a physical examination is essential in evaluating potential environmental causes of disease. The approach to laboratory investigation of potential exposure may be confusing to those not trained in environmental medicine. For many chemicals, biologic testing may only provide information about very recent exposure (e.g., those water-soluble compounds with a short half-life) or be subject to other serious limitations (Hussain, Woolf, Sandel, & Shannon, 2007). At times, environmental testing supervised by a certified industrial hygienist is the best approach to confirming exposure suggested by the history and physical. There are many chemicals for which population “normal” values do not exist, making it difficult or impossible to interpret results for an individual. The CDC conducts a biennial “National Report on Human Exposure to Environmental Chemicals,” which publishes biomonitoring data for an increasing number of compounds allowing at least a comparison with the distribution seen in the general US population aged six years and up (Department of Health and Human Services & Centers for Disease Control and Prevention, 2005). If biologic testing is deemed necessary and possible, it is essential that the appropriate specimen be obtained and that a laboratory capable of reliable and accurate results for that test be chosen. Unconventional testing methods may provide misleading and inaccurate results. Results from six laboratories performing hair mineral analysis differed by more than 10-fold in a study performed by California Department of Health Services (Seidel, Kreutzer, Smith, McNeel, & Gilliss, 2001). Proficiency testing does not exist for trace-metal hair analysis (Steindel & Howanitz, 2001). Except for mercury, and possibly arsenic, data are lacking to be able to reliably indicate the source of exposure, internal dose, or relationship to health effects for a particular substance in hair (Harkins & Susten, 2003). An expert panel review conducted by the US Agency for Toxic Substances Disease Registry concluded, “before hair analysis can be considered a valid tool for assessing exposure and health impact of a particular substance, research is needed to establish standardized reference ranges, gain a better understanding of biologic variations of hair growth

with age, gender, race and ethnicity, and pharmacokinetics, and further explore possible dose–response relationships” (Harkins & Susten, 2003).

Mercury and other environmental exposures have been increasingly suspected by parents and some clinicians as underlying individual children’s neurodevelopmental diagnosis including autism. To date, mercury exposure has not been clearly identified as a cause of autism spectrum disorder (ASD). The window of exposure noted as the critical time period for causing an increased risk of ASD for five environmental factors associated in some studies with ASD (rubella, thalidomide, valproate, misoprostol, and ethanol) is during embryogenesis (first eight weeks of gestation) (Arndt, Stodgell, & Rodier, 2005). Neuro-anatomical studies also suggest a prenatal origin of the disorder. If an assumption is made that an environmental chemical’s exposure is needed during early gestation to be related to ASD risk, it is unclear what relationship a level in a biological sample at the time of diagnosis (usually 2 years of age or more) would have with risk. Mercury’s half-life of approximately 2 months in adults (Goldman & Shannon, 2001) would mean that essentially none of the prenatal body burden would be present by 2 years of age.

Chelation for presumed heavy metal poisoning has been a treatment modality utilized for some children with ASD. Chelation agents used most commonly are parenteral calcium disodium ethylenediaminetetraacetic acid (CaNa<sub>2</sub>EDTA) and meso-2,3-dimercaptosuccinic acid (succimer, DMSA) an oral medication (Hussain et al., 2007).

### Principles in consideration and use of chelation therapy

Laboratory and clinical evidence must support a metal intoxication. Laboratory evaluation must be performed using conventional assays for which there are quantitative results that can be monitored during chelation and for which there are normative values to guide interpretation.

The goals of chelation are clear and quantifiable and established at the outset of therapy.

The chelator, in the form administered, is proven to chelate the toxicant in question. Chelating agents differ greatly in their properties and in their ability to bind metals.

The benefits exceed any risks. All chelating agents, like all drugs, have adverse effects associated with their use. The adverse effects include allergic reaction, hepatotoxicity, renal injury, and depletion of essential nutrients.

The risks and nature of the evidence supporting treatment is explained in understandable language to the patient and/or family as appropriate. Experimental use of medications should follow established human research protocols to ensure patient safety and ethical treatment.

*(Adapted from Hussain et al., 2007)*

Both have the potential for significant complications, such as cardiac arrhythmias, neuropathies, renal dysfunction, and excretion of essential minerals. A pilot study of 15 autistic and four normally developing children, testing the hypothesis that a chelatable heavy metal body burden was related to the symptoms of autism, performed a DMSA provoked challenge excretion test (Soden, Lowry, Garrison, & Wasserman, 2007). There was no evidence of chelatable excess body burden of arsenic, cadmium, mercury, or lead among the children with autism. Currently, there are no published double-blinded, placebo-controlled studies examining potential benefits of chelation for autism. Even in the relatively well-studied field of lead poisoning, chelation treatment with DMSA for moderate levels of poisoning (20–44 micrograms/dL) has not been shown to improve overall outcome though some evidence exists that measures of neuromotor activity may be improved (Bhattacharya, Shukla, Auyang, Dietrich & Bornschein, 2007; Dietrich et al., 2004).

## The Future

Many of the statutes under which the US environmental regulations act were enacted three or more decades ago. The European Union has now taken the lead in changing the operating paradigm for assuring chemical safety. Under their new REACH regulations, manufacturers will be required to provide the data necessary to determine whether a chemical is safe, including for children and other vulnerable groups (“Regulation (EC) No 1907/2006,” 2006). Legislation following this example has now been introduced in the United States. Every day the US produces or imports 42 billion pounds of chemicals, 90% created from oil (Wilson, Chia, & Ehlers, 2006). New initiatives are underway worldwide to develop “green chemistry” approaches designed to reduce or eliminate chemicals that are hazardous to health and to consider the environmental impact of products from “cradle to cradle.” Three scientists working in the area of green chemistry were awarded the Nobel prize in 2003 (“The Nobel Prize in Chemistry, The Royal Swedish Academy of Science press release October 5, 2003,” 2003). With the coming of age of these approaches, we will hopefully see hazardous chemicals replaced over time with ones that are less toxic to humans and wildlife, as well as easily recycled.

Since there will always be environmental hazards for children, and parents will continue to be concerned as new hazards enter the news, healthcare workers should be informed about current and newly arising environmental health hazards, maintain an index of suspicion so that new threats are identified, and provide preventive guidance for their patients. The Pediatric Environmental Health Units are a network of regional clinical centers that combine broad expertise in pediatrics, toxicology, occupational and environmental medicine, and other related areas. These centers are funded by the US Agency for Toxic Disease Registry and the US Environmental Protection Agency

and are available to provide clinical consultation and education for healthcare providers faced with environmental health problems. Affiliated centers have been developed in Canada, Argentina, Spain and at other international sites. Contact information is below, along with additional resources.

## RESOURCES

**Pediatric Environmental Health Specialty Units (PEHSU)**—This federally funded network of clinics provides consultation services for clinicians and governmental agencies on children's environmental health. They also train healthcare professionals and others in environmental health. They can be contacted through the Association of Occupational and Environmental Clinics, (888) 347-AOEC (2632) or <http://www.aoec.org/PEHSU.htm>.

**Organophosphates and Children's Health** —This 1.5-hour online CME course developed by the Northwest PEHSU for healthcare providers presents the current scientific evidence regarding health risks for children exposed to organophosphate pesticides. <http://depts.washington.edu/opchild/>

**American Academy of Pediatrics Committee on Environmental Health (COEH)**—The COEH publishes policy statements and technical reports on pediatric environmental health issues (available free to the public). They also publish *Pediatric Environmental Health*, an authoritative and practical text for the clinician. <http://aap.org/>

**Pediatric Environmental Health Toolkit**—The Toolkit is a combination of easy-to-use reference guides for health providers and user-friendly health education materials on preventing exposures to toxic chemicals and other substances that affect infant and child health. Developed by Physicians for Social Responsibility and the UCSF PEHSU, the materials are visually appealing, practical and easy to use. The Toolkit is endorsed by the American Academy of Pediatrics. The materials are available for free download or online ordering at <http://www.psr.org/>

**National Environmental Education Foundation (NEEF)**—This foundation's "health and the environment" program has developed many materials to advance environmental education and training for health professionals. Materials available without charge via their website include pediatric environmental history forms, environmental management of asthma guidelines, and materials supporting inclusion of environmental health in the training of health professionals. <http://www.neefusa.org/health/index.htm>

**Agency for Toxic Substances Disease Registry (ATSDR)**—ATSDR, a federal agency, publishes the *Case Studies in Environmental Medicine* (CSEM), a series of self-instructional publications (available online) to aid in the evaluation of potentially exposed patients. Continuing medical education (CME) for physicians, nurses, and for other professionals (CEU), is offered. Topics include specific chemicals, such as asbestos and trichloroethylene as well as taking an environmental history and an introduction to pediatric environmental health. <http://www.atsdr.cdc.gov/csem/csem.html>

Federal agencies involved in environment health all try to support clinicians including the Environmental Protection Agency (Office of Children's Health Protection), ATSDR and the CDC Center for Environmental Health, and the National Institute of Environmental Health Sciences. Each has web-based materials on a variety of topics.

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