

Training Manual on Pediatric Environmental Health: Putting It Into Practice



Children's Environmental Health Network
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A Developmental Approach to Pediatric Environmental Health

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This module provides a framework for the study of children's environmental health by examining how children's exposure and susceptibility to environmental toxicants varies with their developmental stage. It explores common sources of exposure to toxicants, routes of absorption, metabolism, sensitive target tissues, and health effects at the following points in development: preconception, fetus, newborn, infant/toddler, preschool and school age, and adolescence. This approach allows clinicians to look at specific aspects of children's environmental health longitudinally throughout childhood. Environmental tobacco smoke (ETS) and other environmental exposures are used as examples of how a child's susceptibility to a toxicant varies at each developmental stage.

Learning Objectives

After completion of this module, faculty will be able to teach students and residents to:

- Understand the following principles of toxicology at each stage of child development:
 - Micro- and macro-environmental sources of exposure to toxicants
 - Routes of absorption
 - Metabolism of toxicants
 - Sensitive target tissues
 - Health effects
- Understand the toxicology of environmental tobacco smoke and how it affects children at different stages of their development.

Developmental Stages

Introduction

Much like canaries in coal mines, children may unwittingly serve as environmental health sentinels for our society, as they are becoming the first to manifest adverse responses to environmental exposures. This is true for two reasons: one, adults and children living in the same space may experience very different environments within that space; and two, a given environment may be more hazardous to a child than to an adult.

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Children are more susceptible to environmental toxicants in part because they are in a continual and rapid state of growth. This development process, in turn, causes variance in a child's vulnerability and susceptibility to environmental hazards. This module will examine how a child's exposure and susceptibility to environmental hazards varies with each developmental stage: preconception, fetus, newborn, infant/toddler, preschool and school age, and adolescence. Environmental tobacco smoke (ETS) and other environmental exposures are presented as examples of how a child's susceptibility to a toxicant is affected at each developmental point.

Environmental Tobacco Smoke

Environmental tobacco smoke (ETS) poses a significant risk to children's health. ETS is the smoke coming from the end of a burning cigarette and from the smoker's exhalation, and is a complex mixture of chemicals. It includes carbon monoxide, nitric oxide, nitrogen oxides, benzene, formaldehyde, acetaldehyde, acrolein, particulate matter, and nicotine. The relative contribution of each chemical to the mixture will differ with each cigarette; knowing the exposure to each component is currently impossible. (Nicotine's metabolite, cotinine — with a half-life of days in serum — has become the biologic marker of choice for measuring ETS exposure.) ETS differs from mainstream smoke (MS), the smoke inhaled by the smoker, in several different ways. First, ETS contains more incomplete by-products of combustion. For example, the extremely carcinogenic N-nitrosamines is 6 to 100 times more concentrated in ETS than in MS. Second, studies in mice have found ETS to be more tumorigenic than MS.

The components of ETS are metabolized by different pathways and can be both activated and detoxified by a single system. For example, benzo(a)pyrene, the highly carcinogenic component of ETS, which is metabolized by the P450 cytochrome system. First, benzo(a)pyrene is activated by a chemical reaction called epoxidation. It can then either be conjugated to glutathione and excreted, or it can be reduced and metabolized into the carcinogen. The balance between the conjugation and the reduction steps determines the carcinogenicity of benzo(a)pyrene.

Developmental Stage: Preconception

The potential for environmental damage to a fetus begins long before conception: fetal harm can result from prior parental exposure to toxicants that can have a major impact on the outcome of pregnancy. These exposures threaten the health of the fetus in two ways: one, they can directly affect the maternal or paternal reproductive organs, or two, they can be stored in the body and later mobilized during pregnancy to affect the developing fetus.

Exposure Routes and Toxic Effects

Generational Exposures

Because cells are most susceptible to toxicants when they are in an active phase, the period of potential susceptibility to harmful preconception exposures is quite long. For example, the most active phase of the ovum occurs during maternal fetal life; injury to a fetus can therefore result from an exposure that occurred while the fetus' future mother was, herself, developing in the grandmother's womb. Indeed, the effect of smoking by grandmothers on the incidence of Down's syndrome is currently under investigation.

Maternal Exposures

The fetus's health can also be threatened by preconception exposures to the mother that have accumulated in her body and are subsequently mobilized during pregnancy. The following are two examples of fetal damage due to preconception maternal exposures:

- **Lead:** Congenital lead poisoning has been diagnosed in infants born to women who were, themselves, lead-poisoned as children. The mother's body-burden of lead — probably stored in bone — was mobilized during pregnancy when 30% of the maternal skeleton becomes available to the fetus to supply calcium needs.
- **PCBs:** Polychlorinated biphenyls (PCBs), a ubiquitous environmental pollutant, are stored in fat and have a long half-life. They consequently accumulate in the food chain and in the adipose tissue. Studies have shown that female monkeys fed PCBs 12 to 14 months prior to conception give birth to infants with the stigmata of congenital PCB exposure. These results suggest that a woman with no overt exposure to PCBs during pregnancy may have an affected fetus if she was exposed to this toxicant prior to pregnancy.

Paternal Exposures

The mechanisms by which paternal exposure to toxicants might cause effects in offspring are poorly understood, while the effect of paternal preconception exposures on the fetus is the subject of intense debate.

It is known that the short life-span of sperm limits the period of their vulnerability to toxicants, while the rapid differentiation of sperm increases their susceptibility to harm from exposures. Several epidemiologic studies link paternal environmental exposures with poor pregnancy outcomes. Recently, the Institute of Medicine listed paternal Agent Orange exposure as a possible cause for spina bifida in offspring. Sperm abnormalities are associated with male cigarette-smoking, which may induce mutagenesis and, hence, an increased cancer risk in the man's offspring. One study showed an increased risk of brain cancer in the children of fathers who smoked.

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Developmental Stage: The Fetus

Rapid cell growth makes fetal tissue particularly susceptible to damage from environmental toxicants. The more cell divisions that occur, the more opportunity for toxic-

cants to cause cells to make inaccurate copies of DNA, which can lead to mutations and cancers.

Exposure Routes

As an interface between mother and fetus, the placenta presents idiosyncracies, in some cases acting as a barrier and in other cases allowing toxicants to pass through to the fetus. The placenta does not block the following compounds from reaching the fetus:

- compounds of **small molecular weight**, such as carbon monoxide
- **lipophilic** compounds, such as polycyclic aromatic hydrocarbons or ethanol
- compounds using **active transport mechanisms**. (Lead, for example, is thought to displace calcium, iron, or other nutrient metals, and thus be transported across the placenta.)

Many toxicants reach the fetus independently of the placenta, including ionizing (penetrating radiation), electromagnetic fields, heat, and noise.

Toxic Effects

There are several notable examples of toxicants crossing the placenta and causing harm to the fetus.

DES: One example of transplacental carcinogenesis is the well-known association of maternal use of diethylstilbestrol (DES) and the eventual development of vaginal adenocarcinoma in offspring exposed in utero.

Mercury: Congenital Minamata disease is another example of the fetoplacental unit's particular vulnerability to maternal environmental exposures. Starting in 1956 and continuing until 1967, residents of Minamata, Japan consumed fish contaminated with methyl mercury discharged from a local chemical factory. An increase in incidence of cerebral palsy was initially noted in offspring of exposed mothers. Other characteristics of the disease were mental retardation, a diffuse brain atrophy as seen by CT scan, and visual field deficits. Peripheral neuropathy was notably not a cardinal sign of congenital disease, in contrast to adult disease. Mothers were usually significantly less affected than their children. Umbilical cord sampling revealed elevated levels of mercury in affected children (of note is the availability of umbilical cords for analysis as Japanese families traditionally preserve this part of the conceptus).

ETS: Maternal smoking or exposure to ETS affect the fetal stage of life because the fetus is exposed to "passive smoking" through the placenta. Cotinine levels of cord blood measured at the time of delivery have been found to be elevated in both mothers who smoke and those who are passively exposed to ETS.

Epidemiological studies of pregnancies complicated by both active and passive maternal smoking have shown the following outcomes:

- increased rate of spontaneous abortion
- intrauterine growth retardation
- increased neonatal morbidity and mortality
- low Apgar scores
- increased incidence of cleft lip and palate
- increased risk of sudden infant death syndrome
- increased risk of cancer
- impaired pulmonary functions
- impaired postnatal growth
- poorer cognitive and behavioral development

The mechanisms by which these toxic effects occur have not been established. It is known, however, that carbon monoxide readily crosses the placenta, and that fetal hemoglobin has a greater propensity to bind with carbon monoxide than does adult hemoglobin. This formation of carboxyhemoglobin is thought to lead to general fetal hypoxia with resultant intrauterine growth retardation (a global fetal effect).

PCBs and Dioxin: There is an ongoing debate about the possible effects of pre-natal exposure to low levels of PCBs and dioxin. Two studies in Michigan and North Carolina have shown statistically significant decrements in neurobehavioral and neurocognitive development in children born to mothers exposed to background levels of PCBs and other dioxin-like compounds. A collateral controversy is whether it is in utero or breast milk exposure that contributes most to developmental effects in children. The Yusho, Japan and Yucheng, Taiwan poisoning incidents demonstrated several adverse outcomes in offspring of women exposed to high levels of polychlorinated dibenzofurans (PCDF), a heat degradation product of PCBs that has significant dioxin-like properties. In these episodes, exposure occurred by ingestion of rice oil that was contaminated during processing with PCBs and PCDFs. (For further queries in this area, see references, including ongoing studies in the Netherlands.)

Developmental Stage: The Newborn

In the newborn, interactions with critical macromolecules take place in those organs and tissues which continue to undergo rapid growth or have rapid turnover, including the nervous system, lung, blood, somatic cells, and epithelium. The most spectacular rate of multiplicative growth, that is, growth from cellular division, occurs before birth. Although cell division continues after birth, most of the growth is accretionary, resulting from the accumulation of extracellular matrix, and the accumulation within differentiated cells of fat, muscle proteins, and hormones.

In the nervous system, for example, neuronal cell division is thought to be complete by six months gestational age. However, the nervous system continues to undergo migration, differentiation, and myelination until adolescence. The lung also continues to undergo alveolar development postnatally, including cell division and cell dif-

ferentiation. Somatic growth will continue to be rapid over the first year. Other tissues which will continue to have rapid cellular division throughout life include the hematopoietic system and epithelium.

The metabolism and excretion of various compounds is also rapidly changing during the newborn stage of development. The metabolic reactions labeled here are functions of the Phase II enzymes, whereas the excretory functions are primarily renal functions. Clinically familiar examples of these changes are:

- the development of physiologic jaundice in the newborn due to low glucuronidation activity, and
- the slow metabolism of many drugs during the first month of life, which necessitates adjustments in drug dosing schedules.

Exposure Routes

The neonate stage is characterized by highly permeable gastrointestinal tract and skin. Main sources of toxicants are ingested substances, such as breast milk or packaged formula, and dermal contact. Parental occupational exposures — transported to the home environment on clothes, shoes, and body — can also affect the newborn, as demonstrated by documented case reports of lead poisoning resulting from exposure to dust carried home on the father's clothing. The multitude of exposure routes underscores the need for a thorough history-taking that includes occupational and recreational habits in the family.

Gastrointestinal Exposures and Toxic Effects

The gastrointestinal tract is particularly permeable during the newborn period (gastric pH, an important factor in oral drug absorption, is initially high in neonates, and does not drop to adult levels until three years of age). Immunoglobulins from colostrum cross the gut epithelium by means of a specific transport mechanism, while studies have shown that PCBs and other dioxin-like compounds have a greater propensity for absorption through the newborn gut than through a more developed gastrointestinal system.

Breast milk contains several environmental pollutants, including smoking by-products, PCBs, and lead. Even low-dose lead is of some concern in the neonate because of the sensitivity of the brain at this stage to the metal. Cognitive function has been shown to be impaired in newborns who are exposed to PCBs or lead in breast milk. Despite the fact that breast-fed babies are at the pinnacle of the food chain and biomagnification process, and are therefore subject to the highest concentration of lipid-soluble substances such as PCBs, the American Academy of Pediatrics strongly endorses breast-feeding and does not recommend any routine biomonitoring of breast milk contaminants.

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Dermal Exposures and Toxic Effects

Particular thought should be given to substances that come into contact with the baby's skin, because skin is highly permeable during the newborn period. An epidemic of methemoglobinemia occurred following the exposure of to diapers that

had the name of a laundry service stamped on the fabric in an aniline dye. The dye had been absorbed through the skin in quantities sufficient to turn the babies blue. A more recent example of percutaneous poisoning is that of hexachlorophene-induced neurotoxicity in babies. Other well-known examples are dermal exposure to lindane and DEET and their associated neurotoxic effects.

Respiratory Exposures and Toxic Effects

At birth, the respiratory tract also becomes a potential route for the absorption of toxicants. It is known that fetal lung fluid is rapidly cleared by the newborn's pulmonary lymphatic system, demonstrating the integrity of this clearance pathway. This lymphatic route then becomes the primary route for absorption of airborne pollutants, including ETS.

Babies exposed to ETS have been shown to have smaller lung volumes, general developmental delay, and reductions in somatic growth. Cognitive function has been shown to be impaired in newborns who are exposed to lead in dust.

Developmental Stage: The Infant and Toddler

Compared to adults, children in all postnatal developmental stages have higher rates of respiration and calorie consumption per kg body weight. These physiologic factors, combined with the infant and toddler's expanded ability to interact with the environment, make children in this developmental stage more vulnerable to oral and inhaled environmental exposures.

Oral Exposures

Infants are also at risk for exposure to toxicants from their normal oral exploratory behavior. Lead poisoning, for example, frequently occurs by this mechanism. Other sources of toxicants include the yard around the house, which may be contaminated with pesticides or herbicides.

Diet can also become a source of exposure. Legal levels of food additives are calculated based on a lifetime exposure for an adult. The infant's higher rate of calorie consumption per kilogram body weight means that any food additive will constitute a higher dose for an infant. Acceptable levels of food additives may therefore be grossly in error for an infant. Furthermore, by virtue of their processing, infant foods tend to have higher concentrations of additives and residues such as pesticides. There is also a qualitative difference in the infant and toddler's diet. It is higher in fruit, vegetables, and milk products, and tends to be less varied than the average adult diet. These facts affect the relative ingestion of toxicants in the infant. Two examples are a case of diazoxon poisoning in an infant whose family utilized an unlicensed pesticide applicator, and the recall of bananas due to high levels of aldicarb. The former example illustrates the susceptibility of children to levels of toxins that do not affect adults – the infant was the only symptomatic individual in the family. The latter example demonstrates a child's heightened vulnerability to exposure to toxicants based on dietary habits.

Inhaled Exposures

Infants have a high rate of respiration and inhale more air per kilogram than adults, due to their higher metabolic rate and need for oxygen. As in the case with diet, these physiological differences mean that infants and toddlers receive proportionately higher doses of toxicants with each breath. Given the same concentration of pollutants from ETS, for example, an infant will absorb more toxicants per kilogram than an adult. Acute effects in infants exposed to ETS include: bronchitis, pneumonia, tracheitis, laryngitis, increased morbidity with RSV infection, and chronic middle ear effusions. The chronic effects of ETS are unclear, although there are reports of increased incidence of adult-onset cancers with lifelong exposure to tobacco smoke.

Exposures on the Floor

The floor of the home is an important micro-environment for infants and toddlers, who typically spend a good deal of time in a playpen or lying, and crawling or walking on the floor. Both the floor surface and the layer of air near the floor are major sources of toxicants.

Some of the surface contaminants that have been described in the literature include pesticide residues and formaldehyde from new synthetic carpeting. Contaminants that tend to be found in higher concentrations near the floor include mercury vapor, from old formulations of latex paint, and radon, which is found in highest concentrations in the lowest elevations of the house. The heavier particles in ETS also tend to settle near the floor. Consider also the accumulation of allergens on household surfaces and their propensity to exacerbate atopy in sensitized toddlers.

Recent studies demonstrate significantly greater accumulation of pesticide residues in dust samples taken from the homes of pesticide applicators and persons who reside near agricultural activity as compared to control homes. The same studies suggest that infants and toddlers who live in these homes have higher levels of pesticide metabolites in their urine than control children, with a statistically significant inverse correlation with the age of the child (i.e., the younger the child, the higher the level of pesticide residue in the urine).

Immune Effects

Research is ongoing regarding the significance of toxic exposures in young children and a phenomenon called "immune deviation." The hypothesis is that early exposure to certain potential environmental triggers can manipulate the immune system to have a propensity towards atopic disease. In susceptible individuals, immune deviation would have a long term impact on health.

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Protective Effects of Child Physiology

In certain circumstances, the physiology of children may actually provide some protection from exposures. Two examples of note are acetaminophen toxicity

and organophosphate-induced delayed neuropathy (OPIDN). In the case of acetaminophen, the hepatic detoxifying process is more active in children and thus they are less prone to liver injury. OPIDN, similar to the “Ginger-Jake’s paralysis” noted during the Prohibition Era, is the result of inhibition of neuro-pathic target esterase (NTE) by organophosphates. Case series and animal models have shown that older age groups are more prone to NTE inhibition than are younger age groups.

Developmental Stage: The Preschool and School-Aged Child

Sources of Exposure

In this stage, the child ventures beyond the immediate confines of the home and parental environment, and explores the neighborhood. New environments, and new sources of exposure at this stage may include the following:

School

The school is a particular source of concern for parents, due, in part, to well-publicized instances of friable asbestos in many buildings. Schools are often situated near the right-of-way for a power line, which may be a source of harmful electromagnetic radiation, or near old industrial sites with unknown emissions and waste. Parents may also express concern about the quality of the school drinking water. In rural areas, for example, schools often use small private wells that may be contaminated with lead. School exposures may include higher allergen burdens, infectious organisms and ETS. Children may also use toxic arts and crafts products, while “non-toxic” art products could cause health problems if ingested or used improperly.

Day care

Some preschool and school-aged children spend a significant period of time in day care. All school exposures could also be present in the day care setting and should be considered.

Playground

Play areas may also contain environmental toxicants. Wooden playground equipment is often treated with preservatives containing substances such as arsenic, pentachlorophenol, or chromium which are toxic if ingested. Playground sand is sometimes contaminated with asbestos. Prior uses of the area on which school facilities and playgrounds are built may also present hazards to children’s health. Previous tenants such as petroleum refineries and chemical manufacturers may have left residues which could be absorbed by children who interact with such environments. A German study, for example, demonstrated exposure to dioxin occurring in playgrounds previously occupied by copper smelters.

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Routes of Absorption and Metabolism in Preschool/School-Aged Children

The metabolism of xenobiotics continues to undergo change in the preschool and school age developmental stage. One common example is the metabolism of theo-

phylline, which peaks during this developmental stage. The pattern of urinary metabolites of theophylline produced by school-aged children differs from that of newborns or toddlers: the metabolic enzymes in older children are more active, while the relative quantities of enzymes also range with age. In the case of the ETS component benzo(a)pyrene, the ratio of glutathione conjugation to epoxidation may increase or decrease with age. Another consideration for the pre-school/school-aged stage of development (as well as in others) is the pertinence of past exposures with delayed effects. Signs and symptoms may be the result of a past exposure: thorough exposure assessment when obtaining the patient's medical history is of utmost importance.

Toxic Effects

The chronic effect of low-dose lead on cognitive development at this stage is of intense public concern. In addition, chronic effects of exposure to ETS in the pre-school/school-aged child include:

- asthma
- increased IgE levels
- decreased FEV1
- chronic cough
- increased phlegm production
- snoring
- chronic middle ear effusions
- decreased height attainment
- increased incidence of lung cancer in later life

Developmental Stage: The Adolescent

Sources of Exposure

Adolescents may venture into two new environments that entail exposure to toxicants.

Substance use

Adolescents may actively choose to expose themselves to environmental toxicants, i.e., they may decide to start smoking. More dire habits - including drug abuse such as "huffing" of solvents - may also be acquired during the adolescent period. The health care provider needs to be savvy in establishing permissive lines of communication and to employ sensitive clinical observational skills to discern such possible exposures.

Occupational exposures

Adolescents may have jobs that expose them to occupational hazards. Employment can expose them to dangerous equipment, such as farm machinery. Child labor laws are often modified to adapt to social needs, such as those of a family farm. In other circumstances, laws are outright violated or disregarded in hiring teenagers.

Routes of Absorption and Metabolism in the Adolescent

Routes of absorption in the adolescent are much the same as in the adult: The xenobiotic metabolic pathways, however, continue to undergo change. The rate of metabolism of xenobiotics decreases in adolescents in the case of the cytochrome P450. Again, a common clinical scenario is that of theophylline. As the rate of theophylline metabolism decreases, the blood level of the drug will rise. This can result in toxicity if the patient is not carefully monitored. It appears that the metabolic rate is reduced in response to growth hormone, which is secreted in greater amounts during the pubertal growth spurt. The change in metabolic rate may also be linked to changes in steroid metabolism during puberty, as steroid metabolism is also dependent on the P450 cytochrome system. Again, the effects of the changes in the activity of these pathways are unknown and require further study.

Target tissues may differ in adolescents due to the changes brought on by puberty. Growing, dividing, differentiating tissues are those that are most sensitive to environmental influences. During puberty, rapid accretionary, and hypertrophic growth

Role of the Health Care Provider in Preventing Exposure to ETS

Prevention of exposure to toxicants such as cigarette smoke is the cornerstone of pediatric environmental health. Prevention and anticipatory guidance are also specific to each developmental stage. Prospective parents need to be educated about the preconceptual and prenatal risks that MS and ETS pose to the fetus. To reduce the exposure of children to all ages to ETS, parents and those in close proximity to children should be encouraged to stop smoking, or at least not to smoke near children, in rooms in which children spend a significant period of time, or in the car. School-aged children can be taught that smoking is a harmful and addictive behavior so that they can both avoid ETS and refrain from smoking themselves. Parents and physicians can promote nonsmoking by educating adolescents about smoking's physiologic and social consequences, and by helping them develop the social skills to enable them to say "no" to cigarettes.

In addition to counseling patients and parents, pediatricians need to serve as advocates for their patients. Tobacco advertisements have been effectively designed to attract the teenage population. Even many 6-year old children are as likely to recognize the Joe Camel logo as the Walt Disney logo. Smoking is associated with glamour in both movies and magazines. Magazines that carry tobacco ads do not address the health hazards of smoking. The average age of new smokers is 17 years, making this a pediatric care provider's problem. The health care provider can make a difference in these areas of public policy by speaking out and taking action. (Some health care offices, for example, cut the cigarette ads out of the magazines kept in their waiting rooms.) The "Advocacy" module in this training manual can provide suggestions for taking action.

occurs in the viscera, skeleton, and muscles. There is also development and differentiation of the reproductive system. Some researchers have suggested that this may be one reason why school-aged/adolescent chimney sweeps were prone to the development of scrotal cancer from their exposure to soot.

Toxic Effects of ETS

Acute effects of ETS exposure in the adolescent include cough, acute asthmatic attacks, and eye irritation. Chronic effects include abnormal pulmonary functions, altered lipid profiles, increased risk of cancer during later life, and nicotine addiction.

Key Points for the Clinician

Be alert to the unique physiology and behaviors of children and how they interface with the environment. Take into consideration such potential risks as take-home exposures from parents, day care circumstances, and acquisition of new life habits. Incorporate the awareness of these factors into the general pediatric knowledge-base. In particular, ask: how do children's physiology and behaviors increase their susceptibility to environmental exposures and in what ways do they broaden the differential diagnosis in clinical situations?

Learning Methods

This material is suitable for lecture presentation.

Questions For Discussion

- 1) List examples of characteristics that would predispose a child to environmental exposures at each of the following developmental stages:
 - Preconception
 - Fetal
 - Newborn
 - Infant/Toddler
 - Pre/School-age
 - Adolescent

Answers should address sources of exposure, routes of absorption, metabolism, and toxic effects.

- 2) For each developmental stage, identify an environmental health hazard to which the children in your community could be exposed.

Evaluation

The above questions for discussion can be used to evaluate residents' understanding of the material and to assess whether learning objectives have been met.

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