A Pediatric Perspective on the Unique Vulnerability and Resilience of the Embryo and the Child to Environmental Toxicants: The Importance of Rigorous Research Concerning Age and Agent

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ABBREVIATIONS. PCB, polychlorinated biphenyl; MPE, maximal permissible exposure; NOAEL, no observable adverse effect level.

There is realistic concern about the impact of environmental influences on the health of human populations. First, exposure to environmental agents continues despite successes in reducing exposures to known toxicants such as lead, polychlorinated biphenyls (PCBs) and tobacco smoke. Second, there has been increasing concern about the cause of autism and other neurodevelopmental problems and hypotheses that environmental influences may play a role in the prevalence of these and other such childhood and adult conditions as asthma and obesity. Third, many other conditions are directly or indirectly related to environmental influences and are preventable, such as injuries, untoward consequences of alcohol, suicide, drug addiction, and gun-related deaths. There have been numerous publications since the 1970s of symposia, proceedings, monographs, and articles dealing with the increased susceptibility of the embryo, infant, and child to environmental toxicants,[1–17] reflecting a greater level of concern about embryonic and childhood exposures. Indeed, great deal of attention has been paid to the vulnerability of the embryo and the fetus to environmental chemicals, drugs, and physical agents. In fact, the publication edited by Miller[1] was primarily devoted to exposures to the embryo and the fetus. Because the embryo and the child are growing and their tissues and organs are differentiating, deleterious effects may occur at lower exposures to some chemicals, drugs, and physical agents and produce more severe effects than those seen in adults. In fact, some effects may not occur in adults. Thus, maximal permissible exposures (MPEs) for some environmental chemicals should be lower for the embryo and the child.

It is important to note that children and adolescents have better recuperative capacities than adults for many toxic agents, and, similarly, appropriate drug dosages may be lower or higher on a mg/kg or surface area basis in children than in adults to attain effective therapeutic blood levels or to avoid toxicity. In addition, effects produced by drugs, chemicals, and physical agents are not always deleterious or always irreversible. This means that for some exposures, the young can recover from some effects more rapidly and completely than adults (Table 1). If the exposure does result in irreversible effects by exceeding the threshold exposure, then the impact on a developing organism can be more severe than in the adult.

Much of the discussion and publications that deal with the vulnerability of the developing embryo, infant, child, and adolescent to environmental agents have focused on particular environmental toxicants or agents, summarizing the spectrum of pathology that results from exposures to these agents. There is nothing wrong with this approach from the toxicologist's point of view, because it is obvious that the developing child and adolescent can be more severely or differently affected by some environmental toxicants.

GOALS

This supplement to *Pediatrics* is being directed toward pediatric clinicians; thus, there are goals that are different from previous conferences, workshops, and publications.

1. To bolster the enthusiasm of practicing pediatricians for diagnosing, treating, and preventing illnesses and subtle but serious long-term negative effects caused by toxic environmental exposures. This supplement contains an article by Dr Robert Miller that provides a historical perspective on the

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TABLE 1. Sensitivity of Infants, Children, Adolescents, and Adults to Environmental Chemicals and Physical Agents*

Environmental Chemicals and Physical Agents	Specific Effects by Age	Ages Most Affected	
Asbestos	Schoolroom exposure has not been shown to result in increased risk of mesothelioma. The risk is related to the magnitude of the exposure, the shape and size of the particles, and the association of smoking in the exposed adult population.	Child?	Adult
Chlordecone (Kepone)	Tremors and neurologic effects were reported in adults who were manufacturing this chlorinated hydrocarbon insecticide, but there are no reports on differences in susceptibility between adults and children.	?	
Curare	Respiratory arrest from exposure. Survival shorter in adult than newborn.†		Adult
Cyanide	Respiratory arrest from injection. Survival shorter in adult than newborn.†		Adult
Dibromochloropropane	Exposure occurred in adults who were manufacturing this soil fumigant to control nematodes. Infertility and sterility as a result of a decrease or absence of sperm in adult male employees. There are no data on the susceptibility of children.		Adult
Endocrine disrupters	This is an issue that has multiple viewpoints that range from minimal concern to serious increased risks for environmental chemicals that have some affinity for sex steroid receptors.	?	
Lead	High exposure can result in convulsions, increased intracranial pressure, hypertension, and anemia for low exposures and decreased intellectual functioning and learning disabilities. The younger the child, the greater the susceptibility to these effects as a result of increased vulnerability from increased exposure, increased absorption, and the sensitivity of the developing brain. Intellectual decrements in children with blood levels above 10 μg/dL have been documented. In recent studies intellectual decrements with blood lead levels below 10 μg/dL have been suggested. Threshold or no-effect level has not been determined, neither has the mechanism of action at low levels.	Infant/child	
Mercury (inorganic)	Acrodynia (irritability, hypertension, flushing, erythema of palms) from hypersensitivity as a result of Hg-containing teething powders. This idiosyncratic reaction occurs most frequently in infants and children.	Infant	
Methyl mercury exposure resulting in central nervous system damage	High exposure of severe effects in the developing embryo and fetus. Threshold and NOAEL in children and adults under investigation.	?	
Mercury (Ethyl)	Low-level exposures in vaccines are unlikely to represent a risk.	?	
Organophosphate insecticide exposures	Data on effects in humans at levels characteristic of environmental exposures are uncertain in contrast to toxic exposures from ingestion or employment. Neurologic symptoms and death if the dose is high enough. High exposures are more toxic in young animal when compared with adults (cholinesterase inhibitors). Neurologic symptoms and death if the dose is high enough.	Infant/child (toxic doses)	
PCBs	Toxic effects of high-level exposure in fetus well demonstrated. Low-level exposure effects in infant and child uncertain. Because of their fat solubility, they are present in breast milk.	Infant/child?	
Radiation (ionizing) induced breast cancer	Adolescents exposed during puberty have the greatest risk from radiation exposure. Infants and children exposed during the preadolescent period are less susceptible to breast cancer induction.		Adolescent
Radiation, ionizing: leukemia risk from high-dose whole-body exposure	Children have a higher risk per unit of exposure for leukemia.	Infant/child	
Radioactive iodine (I) 131 released from Chemobyl resulting in thyroid cancer	Children were the most susceptible to the induction of cancer of the thyroid, although the data are still being analyzed and debated.	Infant/child	
Sarin and other potential terrorism chemical agents	Sarin, chlorine gas, nitrogen mustard. A higher density of gas places a higher concentration of the gas closer to the ground in the breathing zone of children.	Infant/child	
Second-hand tobacco smoke's (ETS) effects on multiple systems	Infants and children are at increased risk for lower pulmonary infections, asthma, otitis media, SIDS, behavior problems, and neurocognitive decrements. Increased risks for lung cancer in adults.	Infant/child	
Strychnine	Respiratory arrest from exposure. Survival shorter in adult than newborn.†		Adult

SIDS indicates sudden infant death syndrome; ETS, environmental tobacco smoke.
* Refer to Tables 6 and 7 on pp 962–964 dealing with the effects of intrauterine (gestational) exposure to environmental toxicants and teratogens.
† Based on animal model data.

discoveries of environmental toxicants by pediatricians and other alert physicians and scientists. It is a thrilling article that honors practicing pediatricians for their accomplishments in discovering environmental toxicants. Dr Miller would like all pediatricians to think of themselves as environmental detectives, and the article is really a charge to every practitioner to become interested in discovering new and unique environmental toxicants. Discoveries of environmental toxicants have been made by alert practitioners who identified a cluster of patients with illnesses associated with an environmental exposure. Such discoveries are a low-probability event in any practitioner's lifetime, given that most clusters of illnesses or diseases that are identified are not found to be causally associated with an environmental toxicant. However, "thinking environmentally" while practicing medicine will make every physician a better practitioner, even if not necessarily a famous one.[18] Please read Dr Miller's article.

2. To provide information about children's environmental health from a clinician's viewpoint rather than that of a toxicologist. Although most previous publications have focused on the effects of particular toxic agents, this supplement presents both the clinical and the toxicologic perspective. Because it is clinicians who evaluate clinical symptoms and clinical disease, we have asked a number of clinicians to discuss the maturation of organ systems during prenatal development, infancy, childhood, and adolescence and their sensitivity to toxicants at different stages of childhood development. There are articles on the heart, lungs, liver, gastrointestinal tract, skin, kidney, central nervous system, hematopoietic system, teeth, and endocrine systems as well as discussions of the present state of our knowledge of the more prominent environmental toxicants. We have asked the authors to present the data and information so that clinicians can use this information when confronted with a clinical problem that may be attributable to an environmental toxicant or drug.[19] In addition, there are articles that describe the role of federal agencies, recent changes in drug monitoring for children, and risk assessment. It is our hope that this supplement will provide pediatricians with a current overview of what is and is not known about the effect of the environment on children's health.

CONTROVERSIES AND CONCLUSIONS

Any discussion of the importance and magnitude of the contribution of environmental agents to human morbidity and mortality tends to provoke spokesmen on both sides of the issue. Segments of the scientific and lay community believe that environmental agents are major contributors to disease and death, whereas other scientists and lay individuals believe that environmental risks have been grossly exaggerated. When it comes to the issue of the vulnerability of children to environmental toxicants, a similar polarization of views exist. Only the facts, impeccable science, and more research will place the field of environmental toxicants and their effects on children into proper perspective. The facts clearly indicate that children are different from adults, which is amply documented in Tables 1 to 5. This necessitates obtaining data on each individual toxicant or potential toxicant to determine children's vulnerability to a particular agent and to determine the magnitude of their increased or decreased sensitivity and vulnerability. Unfortunately, few generalizations about children's vulnerability to environmental exposures apply, given that vulnerability and sensitivity are specific to a child's age and developmental stage and also to the agent.

We have accomplished a great deal in the past 40 years with regard to children's vulnerability to environmental toxicants, and some of the accomplishments have had a very positive effect. The most dramatic example is the reduction in blood lead levels in children in the United States. The topic of lead toxicity is discussed eloquently by David Bellinger in one of the articles in this supplement, but even in the area of lead toxicity, we still have many unanswered questions and much to do to protect children from being exposed. We do not know the no observable adverse effect level (NOAEL) for most environmental toxicants, and, of course, those agents with genotoxic potential are considered to have no threshold.

Some scientists have suggested that because we do not have valid information on most environmental toxicants in adults and children that we should use a factor of 10 in establishing MPEs for children. There is little scientific evidence to validate this suggestion, however. For example, drugs such as morphine and chloramphenicol would still be hazardous even with a 10-fold reduction in the medication dosage. Other drugs and chemicals may be more hazardous to the child than the infant, and in some instances, adults are the most vulnerable. Although as a generalization infants and children are the most sensitive and vulnerable to the effects of environmental toxicants, we should not regulate or practice medicine on the basis of generalizations.

Tables 1 to 5 list numerous differences between developing humans and adults. Most pediatricians and obstetricians are aware of many of these vulnerabilities. For example, we know that the infant's gastrointestinal tract will permit *Clostridium botulinum* to inhabit it and may result in infant botulism.[20] Conversely, we know that the developing embryo, infant, child, or adolescent has better recuperative powers from some insults. The child who has sustained brain damage from an infection, a stroke, or other types of brain injury may regain more function than an adult who sustains the same damage.

It is also important for the clinician to be aware that most environmental toxicants have a toxicologic dose-response curve after various exposures. As the exposure increases into the toxic range, the incidence and the magnitude of the deleterious effects increase. Below certain exposures, the NOAEL, there are no known deleterious effects.[21–24] (Fig 1) The problem for the clinician is that the NOAEL has not been determined or is controversial for many environmental toxicants and may differ by age as a result of

TABLE 2. Sensitivity of Infants, Children, Adolescents, and Adults to Drug Effects

Pharmacologic Drug	Specific Effects by Age	Ages Most Affected	
Acetaminophen overdose	Death from liver toxicity occurs in adults and more rarely in children.		Adult
Alcohol depression	Adults are more readily depressed than newborn; however, children are much more likely to develop profound hypoglycemia and seizures.	Child	Adult
Adrenocorticosteroids	Prolonged administration can reduce stature and skeletal maturation, which can occur only during childhood and adolescence. The younger the child, the greater the impact on growth and maturation	Child/ adolescent	
Alpha interferon	Spastic diplegia in infancy.	Infant	
Aminoglycosides	Infants who are treated with aminoglycosides and have *Clostridium botulinum* in their gastrointestinal tracts may have an increased neuromuscular blockade and prolonged severity of the paralytic phase.	Infant	
Aminoglycosides	Vestibular balance and hearing deficiencies as well as renal disease can occur after use. Rare in children, risk greatest in adults.		Adult
Androgens	May cause masculinization of girls, precocious puberty, exaggeration of masculine features in boys, and growth promotion in infants and children with the potential to reduce the child's mature stature. Exaggerated masculinization can also occur in adults or cause tumors of the liver.		
Aspirin or methyl salicylate overdose	Can lead to alkalosis, acidosis, respiratory distress, and death, occurring more frequently in children.	Child	
Bacitracin, neomycin, and polymyxin B	Nephrotoxicity more readily produced in adults.		Adult
Beta blockers	May cause hypoglycemia in infants and children.	Infant/child	
Chloramphenicol	When administered in the newborn, may cause "gray baby syndrome" with resulting vascular collapse and death. Most severe in the sick newborn. Blood levels may reach levels that are 10 to 20 times the expected therapeutic levels using mg/kg dosage schedule.	Infant	
Diethylene glycol	Was the diluent in an elixir containing sulfanilamide for use in children (1938); 107 children died from this medication, which was never tested for its toxicity.	Child	
Estrogens	Feminization of boys, precocious puberty, exaggeration of feminine features in girls, and growth promotion in infants and children, with the potential to reduce the child's mature stature. Exaggerated feminization can occur in adults.	?	
Fluorine ingestion	Causes tooth mottling and cosmetic damage. Children exposed during enamel formation most susceptible.	Infant/child	
Hexachlorophene	Applied to the skin as an antibacterial agent, there is greater risk of toxicity in premature and newborn infants with extensive skin exposure.	Infant	
Influenza vaccine	Less effective in infants <6 months.	Infant	
Isoniazid (INH)	Therapy with INH complicated by liver disease (ie, hepatitis) more common in adults.		Adult
Menadione (water-soluble vitamin K analogues)	Resulted in hyperbilirubinemia and kernicterus, with greatest sensitivity to effects in premature infants and neonates as a result of increased hemolysis.	Infant	
Meningococcal vaccine	Less effective in infants.	Infant	
Methemoglobinemia	From the administration of bismuth subnitrate, benzocaine and related topical anesthetics, sulfonamide rectal suppositories, phenacitin and long-acting sulfonamides and skin application of bitter almond oil, high levels of nitrates in the water supply or medications, aniline dyes, pesticides, and improperly canned foods. The infant is inordinately susceptible to the induction of methemoglobinemia. Nitrate conversion to nitrites can occur more readily in the neonate and infant's gastrointestinal tract because of bacterial flora.	Infant	
Methotrexate	May cause cirrhosis of the liver; primarily occurs in adults.		Adult
Methylphenidate therapy	May uncover a tic disorder. The majority of ADHD treatment occurs in children, and there are few data on this phenomenon in adults.	Child	
Morphine	A much lower dose of morphine must be administered to newborns because of the sensitivity of the newborn to morphine.	Infant	
Naloxone and other opioid antagonists	Infants who are exposed to morphine and whose respirations are markedly suppressed are treated with 0.01 mg/kg. Adults are treated with 40 times the infant dose for opiate overdose: 0.4 mg/kg	Infant	
Nitrobenzol	Respiratory arrest from injection. Survival shorter in adult than newborn.		Adult
Phenobarbital and diphenhydramine	May result in paradoxic irritability and agitation, which is seen more commonly in children or in the elderly.	Infant/child	
Phthalates	Most of the toxicologic data have been obtained in animal studies at high doses. The human has much lower exposures, and the theoretical risks depend on the phthalate and its source and use.	?	
Progestational drugs	When administered in large doses to pregnant women or children some progestational drugs can result in masculinizing effects to fetus or child. These are rare occurrences because the present-day dosages of progestational drugs are very low. The fetus and children are more susceptible to manifestations, such as clitoral hypertrophy from large exposures.	Infant/child	

TABLE 2. Continued

Pharmacologic Drug	Specific Effects by Age	Ages Most Affected	
Quinolone group of antibiotics	Results in cartilage damage in developing cartilage at very high doses in animal models and some tendon damage. Neither effect has yet been seen in children to any extent, but adults have been reported to have tendon pathology as a complication of therapy.		Adult
Rotavirus vaccine–induced intussusceptions	Occurred in infants and children.	Infant/child	
Seizure activity from strychnine, salicylate, and electroshock	Adult more sensitive to convulsions than newborn.		Adult
Sulfasoxazole	Administration in premature infants and newborns may result in an increase in kernicterus from the redistribution of bilirubin and transport across the blood-brain barrier, as a result of the uncoupling of bilirubin from serum proteins. Other drugs that have this potential are oxytetracycline, sodium salicylate, and sulfadimethoxine, possibly by a different mechanism.	Infant	
Tetracycline	Tooth and bone staining. At low exposures, the teeth and bone staining may have no deleterious effects, but if the exposure is very high, then there may be an effect on growth and tooth structure. The intensity of staining is greatest at the time of greatest enamel production, but children are susceptible as long as bone growth is still taking place. Premature infants treated with very high exposures to tetracycline have had reversible growth retardation.	Infant/child	
Tetracycline	May cause bulging fontanel and increased intracranial pressure in infants.	Infant	
Thiourea toxicity	Adult more sensitive to toxicity than newborn.		Adult
Thyroxine overdosage	More toxic in adults; may lead to atrial fibrillation.		Adult
Trimethoprim	Neurologic idiosyncratic reactions, possibly as a result of lowering of folic acid serum blood level after treatment, has been reported in adults.		Adult
Valproic acid	Therapy for epilepsy and psychiatric illnesses is complicated by hepatic injury (hepatitis) more commonly in adults.		Adult
Varicella vaccine	Less immunogenic in adults.		Adult
Verapamil	Occurrence of asystole in infants and children <2 years when Verapamil is used to treat surpaventricular tachycardia.	Infant/child	
Versed and other bezodiazepines	Adults seem to be more sensitive to these drugs, as in many instances the same total dose is used in children and adults (0.1 mg/kg; total dose in a 20-kg infant: 2 mg). An adult also might be treated with 20 mg.		Adult
Vitamin A /retinoids overdose	In children, can cause increased intracranial pressure, fever, retardation of bone growth, and periosteal bone hypertrophy. Adults can manifest increased intracranial pressure, headache, and bone pain.	Infant/child	Adult
Vitamin D deficiency	Rickets in children, osteomalacia in adults.	Infant	Adult
Vitamin E, alpha-tocopherol, high doses	Increased risk of necrotizing enterocolitis, hepatotoxicity, and thrombocytopenia in premature infants; may be lethal.	Infant	
Vitamin K3 and sulfasoxazole administration	Greatest risk in premature and newborn infants with a risk of clinically significant kernicterus from administration. Sulfadiazine and salicylates could lower the bilirubin serum level and increase the risk of kernicterus by uncoupling the bilirubin and permitting it to cross the blood-brain barrier.	Infant	

INH indicates Isoniazid; ADHD, attention-deficit/hyperactivity disorder

variations in absorption, metabolism, and excretion that themselves change over the course of the child's development. Similarly, when the clinician is confronted with a patient who has been "exposed," he or she may not be able to determine the amount or the length of exposure or even when it occurred. The clinician needs to know which environmental agents can have a greater impact on the developing child and at what exposure.

Animal studies can provide information on the variability of chemical sensitivity.[19] For example, some anesthetics are unable to anesthetize newborn animals at exposures that anesthetize adults, whereas ether alters reflexes at lower concentrations in newborn animals than in adults.[25] Newborn mice and other animal species have demonstrated a tolerance to hypoxic conditions that is not present in adult animals,[26–30] and newborn mice continue to breathe for a longer period when exposed to ether than adult mice.[31] Newborn mice also have a prolonged survival when compared with adults when asphyxiated as a result of exposure to CO, HCN, CO_2, H_2, and CH_3. Longer exposures to strychnine, curare, cyanide injection, strangulation, hypoxia, or nitrobenzol are necessary to produce respiratory arrest in newborn mice as compared with adult mice.[29]

In a summary of much of this animal information, Done[32] was cautious, pointing out the multiplicity and variability of experimental details in these studies. He concluded, "Some tentative generalizations and observations may be worth making. . . . It is apparent that immaturity does not necessarily entail greater sensitivity."

Another example in which infant animals are pro-

TABLE 3. Sensitivity of Infants, Children, Adolescents, and Adults to Infections

Infections	Specific Effects by Age	Ages Most Affected	
Acute hematogenous osteomyelitis	A greater risk in infancy and childhood.	Infant/child	
Chlamydia trachomatis	Pneumonia in young infants only.	Infant	
Clostridium difficile	More severe in adults.		Adult
Coxsackie A-16	Hand, foot, and mouth disease occurs almost always in young children.	Infant/child	
E coli O157:H7	Hemolytic uremic syndrome almost always occurs in young children.	Child	
Group B streptococcalepticemia and meningitis	Highest risk in the neonate.	Infant	
Hepatitis A infection	Clinically more severe in adults.		Adult
Hepatitis B infection	Can cause cirrhosis and hepatic cancer long term.		Adult
Hepatitis C infection			Adult
Herpes zoster	Usually mild in children outside the newborn period but can be devastating in newborns. Disease is more clinically severe and long lasting in older individuals. Post herpetic neuralgia primarily occurs in adults.	Infant	
Human herpes virus-6	Roseola in infants, fever of unknown origin in adults.	Infant	
Human herpes virus-8	No disease in children, Kaposi sarcoma in adults with HIV infection.		Adult
Infantile botulism	Paralysis from *Botulinum* toxin, as a result of ingestion of *Clostridium botulinum* spores, which are not destroyed in the stomach of infants because of the reduced acid secretion in their stomachs. Susceptible during the first several months of life because *C botulinum* spores are able to survive in the infant's gastrointestinal tract but not in a child's, adolescent's, or adult's gastrointestinal tract. Ingestion of toxin by adults results in food-bornebotulism.	Infant	
H influenza type B	Epiglottitis and meningitis in infants and children.	Infant/child	
Meningococcus	More susceptibility in the child and adolescent.	Child/ adolescent	
Influenza virus infection	Clinically more severe in adults with most of the mortality occurring in the aged.		Adult
Legionella pneumophila	Rare in children (a cold), life-threatening pneumonia in adults.		Adult
Listeria	Early/late-onset sepsis in the neonate. Occurs as meningitis in adults who are immunocompromised with AIDS.	Infant	
Mumps	Orchitis seen more often after puberty.		Adolescent/ adult
Parainfluenza virus	Croup in childhood but not in adults.	Infant/child	
Parvovirus B-19	Arthritis rare in childhood. More common in adults, especially women.		Adult
Pneumococcal lobar pneumonia	More severe in adults.		Adult
Poliomyelitis infection	Paralysis and bulbar symptoms are more frequent and severe in adults.		Adult
RSV virus infection	The younger the child, the greater the risk of bronchiolitis, which is especially dangerous in ex-premature infants with bronchopulmonary dysplasia.	Infant	
SARS	Mild disease if contracted in childhood, but nearly 10% mortality rate among adults.		Adult
Staphylococcal septicemia resulting in osteomyelitis	Occurs more commonly in children.	Infant/child	
Toxic epidermal necrolysis	More severe in adults.		Adult
Toxic shock syndrome	More severe in adults.		Adult
Varicella infection	Clinically more severe in a neonate whose mother was not immune, and in adults. Varicella pneumonia occurs primarily in adults and can be fatal. Varicella can be a very serious illness in adults, especially during pregnancy	Infant	Adult

HIV indicates human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome.

tected relative to adults is thiourea, which is 50 to 400 times as toxic in the adult as in infant rats.[33,34] Conversely, animal experiments with chloramphenicol clearly demonstrate that this drug is more toxic in the infant rat than in the adult, providing animal toxicity studies that corroborate the toxicity reported in human infants.[35–37] In Done's review of developmental toxicology,[32] he indicated that the newborn or infant animal was more sensitive to many drugs (chloramphenicol, morphine, some other opiates, picrotoxin, tetracycline, novobiocin, some organophosphate anticholinesterases, atropine, histamine, and sodium salicylate) and less sensitive to others (ethanol, strychnine, Metrazol, codeine, acet-cyclohexi-

TABLE 4. Sensitivity of Infants, Children, Adolescents, and Adults to Other Diseases and Physical Injury

	Specific Effects by Age	Ages Most Affected	
Addiction to alcohol and tobacco	Adolescents who start smoking and drinking in the preteenage and teenage years have a greater risk of permanent or life-long addiction.		Adolescent
Air bag activation injury	Greater risk for children, including death.	Infant/child	
Amblyopia	Blindness from eye disuse as a result of strabismus or discrepancy in visual acuity between the 2 eyes. Restricted to the first few years of life.	Infant	
Apnea of prematurity	Problems primarily related to premature infants and infants.	Infant	
Aseptic necrosis of femoral head	Greater risk in children	Child/ adolescent	
Brain damage from hypoxia	The severity of decrease in brain function is directly related to the length and severity of the hypoxia. Adult has less resistance to permanent brain damage and greater risk for permanent decrease in intellectual level.		Adult
Cardiac arrest	Uncommon in infants and children unless secondary to respiratory failure, or underlying congenital heart defect, but common in adults.		Adult
Colles' fracture	Greater risk for occurrence in adults with a fall.		Adult
Congenital heart block	Caused by maternal passage of anticardiolipin antibody among infants whose mothers have systemic lupus erythematosus. Heart block from localization of this antibody occurs only in newborns as a result of transplacental transfer of antibody. Adults with the antibody rarely have heart block.	Infant	
Convulsions from pyridoxine deficiency	Greater susceptibility in a group of infants who are more likely to convulse because of a need for higher amounts of pyridoxine administration.	Infant	
Epiphyseal disruption	Risk is present only in children.	Child	
Epiphyseal injury	Risk is present only in children with open growth plates.	Child	
Febrile seizures	Greatest risk in children 6 months to 5 years of life.	Infant/child	
Head injuries	Children are at greater risk for severe CNS injury but may have better recoverability if they survive.	Infant/child	
Hypoglycemia resulting in CNS damage	Greatest risk during brain development in neonates, infants, and children.	Infant	
Hypothyroidism resulting in mental retardation	The younger the child at onset, the greater the risk of mental retardation, with the greatest risk occurring in neonates with athyroidic cretinism.	Infant	
Intracranial hemorrhage	From hypoxia and electrolyte imbalance resulting in permanent CNS damage. Susceptibility in the neonate, with the greatest risk in the premature infant <34 wk gestational age.	Infant	
Intussusception	Most common in children <10 years of age; most are idiopathic. Intussusception rare, may be a complication of underlying GI anatomic pathology (eg, tumor).	Infant/child	
Iodine deficiency	Greater risk of decreased CNS functioning as a result of acquired hypothyroidism in infancy and childhood. Goiter in adults.	Infant	
Kernicterus	Resulting in deafness and neurologic problems from elevated bilirubin levels and increased blood-brain barrier permeability in the newborn period. Neonate most susceptible, although kernicterus has been rarely reported in older individuals. Very rare in adults as a result of well-developed blood-brain barrier.	Infant	
Osgood-Schlatter's disease	Occurs more commonly in childhood.	Child	
Osteoporosis	Primarily an adult disease.		Adult
Respiratory distress syndrome or hyaline membrane syndrome	Susceptibility greatest in premature infant.	Infant	
Respiratory failure	Susceptibility to pulmonary function decompensation because of the low ratio of vital capacity to tidal volume in infants. Pulmonary reserve lowest in the premature and newborn.	Infant	
Retinopathy of prematurity	Vascular injury secondary to use of oxygen therapy in the neonatal period, reducing visual acuity or blindness. Most severe in the premature infant.	Infant	
Reye's syndrome	Aspirin (ASA) and some infections (Varicella) are associated with the risk of Reye's syndrome, resulting in liver failure and death. Risk is greatest in children.	Infant/child	
Salter-Harris fracture	Limited to children and adolescents with open epiphyses.	Child/ adolescent	
Scalding from hot water and other heated agents	For each elevation of temperature and time of exposure, the child will sustain more severe damage and possible scarring because of the decrease in the thickness of the epidermis and dermis with decreasing age.	Infant/child	

TABLE 4. Continued

	Specific Effects by Age	Ages Most Affected
Steven Johnson syndrome	Secondary to drug therapy or some infections (diphenylhydantoin, sulfa drugs, varicella). Children and adolescents seem to have the greatest risk for being affected by this autoimmune reaction.	
Sudden infant death syndrome	Exclusively occurs in first year of life.	Infant
Sunburn	Identical physical exposures to the sun can result in more severe effects in the infant and child, which includes, first-, second-, and third-degree burns; hyperthermia, and heatstroke.	Infant/child
Temperature instability, including hypothermia	Greatest in premature infants and sick newborns, but more severe and greater risks in infants because of their decreased ability to maintain body temperature.	Infant
Transient tachypnea of the newborn	Early neonatal period: after cesarean section or birth to a mother with diabetes.	Infant
Volvulus	Susceptibility greatest in infancy and preschool years.	Infant/child

CNS indicates central nervous system; GI, gastrointestinal.

TABLE 5. Examples of Diseases That Primarily Occur in Infancy, Childhood, and/or Adolescence

Adenocarcinoma of the vagina from prenatal diethylstilbestrol exposure primarily in adolescence
Bronchiolitis
Caloric insufficiency as a result of failure to thrive resulting in neurocognitive impairment
Colic
Cow's milk allergy
Craniosynostosis
Croup
Disuse amblyopia
Ewing's sarcoma
Febrile seizures
Group B strep sepsis, pneumonia, and osteomyelitis
Henoch Schönlein purpura
Idiopathic intussusception
Impaired language development as a result of deafness
Increased susceptibility to caries as a result of environmental tobacco smoke
Infant botulism
Kernicterus
Medulloblastoma
Mental retardation as a result of hypothyroidism
Necrotizing enterocolitis
Neuroblastoma
Osteogenic sarcoma
Pyloric stenosis
Respiratory distress syndrome
Retinopathy of prematurity
Salter Harris fracture
Sudden infant death syndrome
Transient tachypnea of the newborn
Wilms' tumor

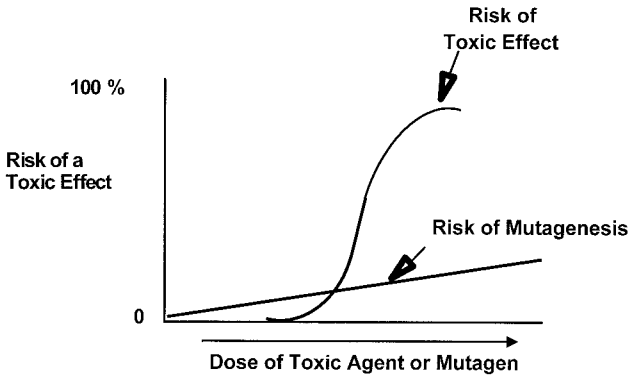

Fig 1. The dose-response curve of environmental toxicants (drugs, chemicals, and physical agents) can have deterministic (threshold) and/or stochastic effects. Mutagenic and carcinogenic events are stochastic phenomena and theoretically do not have a threshold exposure below which no risk exists. At low exposures, the risk still exists but is usually below the spontaneous risk of cancer and mutations. Whether the curve is linear or curvilinear for stochastic phenomena can be debated, but from a theoretical point, it traverses 0. Toxicologic phenomena, such as teratogenesis, that do not involve mutagenic and carcinogenic effects usually follow an S-shaped curve, with a threshold below which no increased risks are expected.

mide, thiourea, and thyroid hormone). Many other drugs have sensitivities that were similar in the neonate and the adult animal.

Tables 1 to 5 list a number of agents that are more toxic in the adult than in the infant and the child. There are many infections that produce more morbidity in adults than in children (eg, hepatitis, varicella, poliomyelitis). Drugs also may be more toxic or result in idiosyncratic effects in adults that occur rarely in children. For example, isoniazid produces hepatitis and methotrexate produces cirrhosis more frequently in adults.

Not only are adults sometimes more vulnerable than children, but also adolescents can be more vulnerable than infants and children. For example, a number of publications have indicated that exposure of adolescents to extensive and repeated radiology examinations increases their risk of developing breast cancer later in life.[38] One might expect that infants would be more susceptible to radiation-induced breast cancer than adolescents; however, the developing and proliferating adolescent breast seems to be more sensitive to radiation-induced oncogenesis than the infant breast.

In the following presentations, you will read about the vulnerability and sensitivity of the infant, child, and adolescent. In many instances, environmental agents will exploit these vulnerabilities and sensitivities. In other instances, there will be no difference between the developing organism and the adult when exposed to toxicants, and in some instances, the developing organism may even withstand the exposures with less insult. The difficulty that we have at this time is that we do not have enough data to arrive at conclusions about the relative sensitivity of the developing organism to many environmental agents. Rather than hypothesize about environmen-

tal agents or exposures for which there are insufficient data, we need to initiate investigative approaches to obtain the necessary data concerning agents and exposures that have not been clarified. It is important that there be an increase in quality research in environmental toxicology.

In human epidemiologic studies, we need to know the exposure sustained by infants, children, adolescents, and adults to environmental agents. In some instances, an apparent increase in sensitivity may actually be because certain child behaviors result in higher exposures. After the intense efforts of individual scientists and regulatory agencies in the United States, the exposures to lead and PCBs are dropping,[39] but that is not so with many other toxicants. The situation in the rest of the world varies considerably. Although some parts of Western Europe also have decreased their population's exposure to lead and PCBs, exposures have not been reduced in many third-world countries. Improving our epidemiologic surveillance is important to quantify more accurately the risks of environmental toxicants and any change in risks after interventional programs. With limited resources, we must invest in research and interventional programs that will have the greatest likelihood of success and the potential for affecting the most individuals.

What can we do to improve our knowledge of the risk of environmental toxicants for children? What information would be helpful to clinicians to assist them in understanding the complexity of the situation? Why are there scientists and clinicians who denigrate and others who exaggerate the impact of environmental toxicants on children as well as all humans?

We propose the following:

1. Rigorous methods must be used to evaluate environmental risks.[40–43] Diverse opinions occur because some scientists reach conclusions without adequate data. Single epidemiologic studies do not refute or demonstrate causality. The most important criteria to permit conclusions from epidemiologic studies are consistent, biologically plausible findings across a number of studies. Causality must be determined by a) epidemiologic studies; b) secular trends or ecological trends; c) mammalian animal toxicologic studies; d) pharmacokinetic and toxicokinetic studies; e) method-of-action studies; and f) biological plausibility: specificity, nature of the effect, receptor affinity, organ selectivity, stage of development, multiple causality, in vitro studies, etc.
2. Information on children's exposure to a wide range of environmental agents and how these exposures are changing over time must be improved.
3. Epidemiologic research dealing with environmental agents and using modern techniques of pharmacokinetics and toxicokinetics must be expanded. It is very difficult to determine toxic exposure levels, NOAEL, or therapeutic levels either in humans or from animal studies without the use of pharmacokinetics and toxicokinetics.
4. A national surveillance system, monitoring changes over time, must be created to determine the prevalence of a wide range of diseases and rapidly identify unusual clusters of conditions in children and in adults.
5. Whenever possible, animal studies at different stages of development should be included in the body of research on which we base public health and clinical policy and practices. It also is essential that we acknowledge the danger of generalizing findings across species.
6. Competent environmental epidemiologists should focus on the special vulnerabilities of developing children.
7. Physicians should be educated about the safe and toxic levels of chemicals and drugs to evaluate individual patients or perform epidemiologic studies.
8. We must counter the individuals who zealously exaggerate or denigrate the risks of environmental toxicants and drugs with data from rigorous scientific studies that treat each environmental agent as a separate entity with regard to its risks and benefits.

It is our hope that this volume will assist pediatricians, other health care workers, toxicologists, epidemiologists, and environmental health experts to understand our current state of knowledge about children's unique vulnerabilities and resistance to environmental agents. We also hope to encourage the investigations and activities of our many colleagues to determine the variable risks of these agents for the purpose of preventing or reducing environmentally produced diseases.

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