

Chapter 11

Environmental Toxicology: Children at Risk

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Glossary

Adult	The time of life usually starting at 18 years (some systems such as skeleton and brain may continue to develop).
Adverse effect	A treatment-related alteration from baseline that diminishes an organism's ability to survive, reproduce, or adapt to the environment.
Carcinogen	Any substance that can cause cancer.
Critical period	A specific phase during which a developing system is particularly susceptible.
Developmental disorders/effects	Adverse effects such as altered growth, structural abnormality, functional deficiency, or death observed in a developing organism.
Dose (exposure)–response relationship	Characterization of the relationship between administered dose or exposure and the biological change in organisms.
Embryonic period	The period from fertilization to the end of major organogenesis.

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Environmental exposures and environmental hazards	For this entry, these terms refer to specific environmental chemicals and environmental pollutants.
Exposure	Contact with a chemical by swallowing, by breathing, or by direct contact (such as through the skin or eyes). Exposure may be short term (acute) or long term (chronic).
Fetus	The period from 8 weeks of pregnancy to birth.
Gestation	Length of time between conception and birth.
Infant	The period from 28 days of age to 1 year.
Lowest observed adverse effect level (LOAEL)	The lowest concentration of a chemical in a study, or group of studies, that produces statistically or biologically significant increase in the frequency or severity of adverse effects between the exposed population and an appropriate control.
Mechanism of action	The detailed molecular knowledge of the key events leading to an adverse effect in an organism.
Neonate	The period from birth to 28 days of age.
Perinatal stage	The period of 29 weeks of pregnancy to 7 days after birth.
Pregnancy	The condition of having an implanted embryo or fetus in the body, after fusion of an ovum and spermatozoon.
Preterm birth	A birth occurring at 24–37 weeks of pregnancy.
Risk assessment	An empirically based paradigm that estimates the risk of adverse effect(s) from exposure of an individual or population to a chemical, physical, or biological agent. It includes the components of hazard identification, assessment of dose–response relationships, exposure assessment, and risk characterization.
Route of exposure	Exposure route refers to the different ways a substance may enter the body. The route may be dermal, ingestion, or inhalation.
Sexual maturation	Achievement of full development of the reproductive system and sexual function.
Susceptibility	An individual's intrinsic or acquired traits that modify the risk of illness (e.g., high susceptibility to cancer).
Toxicokinetics	The process of the uptake of potentially toxic substances by the body, the biotransformation they undergo, the distribution of the substances and their metabolites in the tissues, and the elimination of the substances and their metabolites from the body. Both the amounts and the concentrations of the substances and their metabolites are studied. (Pharmacokinetics is the term used to study pharmaceutical substances.)

Vulnerability A matrix of physical, chemical, biological, social, and cultural factors that result in certain communities and subpopulations being more susceptible to environmental factors because of greater exposure to such factors or a compromised ability to cope with and/or recover from such exposure.

Definition of the Subject

Children today live in a world that is vastly different from a few generations ago. While industrialization has maximized (for many) children's opportunities to survive, develop and enjoy high levels of health, education, recreation, and fulfillment, it has also added significant challenges to their development.

In the countries in the Organization for Economic Co-operation and Development (OECD), an infant born today has about 20 years longer life expectancy than one born at the beginning of the twentieth century [1]. Infant mortality has gone down by over 90%. Despite AIDS, SARS, West Nile virus, and the constant threat of other emerging infections, the ancient epidemics of smallpox, yellow fever, cholera, bubonic plague, polio, and measles are no longer the dominant causes of disease and death. However, an increase in the incidence (new cases) of many chronic diseases in children has been observed. These include asthma, cancer (which is the second leading cause of death in children after injuries), birth defects, developmental disabilities, and autism. For some of these conditions, an environmental origin has been established, and for others it is hypothesized.

Environmental threats to children's health range from asthma-inducing air pollution and lead-based paint in older homes, to treatment-resistant microbes in drinking water and persistent industrial chemicals that may cause cancer or result in reproductive or developmental changes.

Patterns of illness among children in the industrially developed nations have changed substantially. Infant mortality has declined. Life expectancy has increased. However, an increase in the incidence (new cases) of some diseases, such as asthma, birth defects, neurodevelopmental disorders and certain types of childhood and adolescence cancers, and obesity has been observed. Evidence is accumulating that toxic chemicals are responsible for at least some of these changing patterns of disease.

Children are uniquely susceptible to chemicals. This great vulnerability reflects the juxtaposition of two phenomena early in life: first, that infants and children have disproportionately greater exposures than adults to environmental chemicals, and second, that children are exquisitely sensitive to these exposures, because they are poorly equipped to metabolize many toxic compounds and because they are progressing through the complex, delicate, and easily disrupted stages of early development. The protection of children from environmental

health hazards requires the consideration of their exposure patterns and susceptibility factors when conducting risk assessments, development of child protective legislation, and wider application of the Precautionary Principle in the face of early warning of danger.

Introduction: Brief History of the Issue of Children's Vulnerability to Environmental Hazards

Children's risks from environmental health threats have received considerable political attention during the last two decades. In 1989, the United Nations Convention on the Rights of the Child laid down basic standards for the protection of children and proclaimed that they are entitled to special care and assistance. A year later, the World Summit for Children (WSC) adopted a Declaration on the Survival, Protection and Development for Children, in which the signatories agreed to join efforts on taking measures to protect the environment, so that all children can enjoy a safer and healthier future.

Agenda 21, adopted in 1992 at the United Nations Conference on Environment and Development ("the Earth Summit") gives attention to the protection of children from the effects of a deteriorating environment in several chapters. Chapter 6 of Agenda 21 "Protecting and Promoting Human Health" emphasizes the need to pay special attention to protecting vulnerable groups, particularly infants, young people, women, indigenous people, and the poor. Agenda 21 urges governments to develop programs to protect children from the effects of environmental and occupational toxic compounds.

In the USA, the National Research Council report [2] "Pesticides in the Diet of Infants and Children" was critical in raising awareness about the importance in risk assessment of children's environmental health. This report elevated concern on a broad national level about children's special vulnerabilities to environmental agents. It made clear that protection of the health of vulnerable populations would require a new approach to risk assessment. The NRC report recommended an approach to risk assessment that moved beyond consideration of average exposures based primarily on adult characteristics to one that accounted for the heterogeneity of exposures and for potential differential sensitivities of various life stages, particularly during prenatal development, infancy, and childhood.

Responding to recommendations in the NRC report [2], the US Government took decisive steps to attend to the growing concern on children susceptibility to environmental toxicants. In 1995, the EPA issued a National Policy to consistently and explicitly take into account health risks to children and infants from environmental hazards when conducting assessments of environmental risks. In 1997, the Clinton Administration issued an Executive Order, Executive Order 13045: Protection of Children from Environmental Health Risks and Safety Risks. The Executive Order requires all federal agencies to address health and safety risks to children, to

coordinate research priorities on children's health, and to ensure that their standards take into account special risks to children. To implement the order, the US EPA established the Office of Children's Health Protection (OCHP) (renamed the Office of Children's Health Protection and Environmental Education – OCHPEE – in 2005), whose job is to work with Program and Regional Offices within the US EPA to promote a safe and healthy environment for children by ensuring that all regulations, standards, policies, and risk assessments take into account risks to children. Legislation, such as the Food Quality Protection Act and the Safe Drinking Water Act amendments, has made coverage of children's health issues more explicit, and research on children's health issues is continually expanding. As a result of the emphasis on children's risk, the US EPA Office of Research and Development (ORD) developed a strategy for research on environmental risks to children. The goal of this research agenda is to discover the environmental causes of disease in children and then to convert these research findings into blueprints for disease prevention and health promotion.

The 1997 Declaration of the Environmental Leaders of the Eight on Children's Environmental Health intensified their commitment to protecting children's health from environmental hazards. The Environment Ministers of the G8 countries acknowledged the special vulnerabilities of children and committed their countries to taking action on several specific environmental health issues such as lead, microbiologically safe drinking water, endocrine disrupting chemicals, environmental tobacco smoke (ETS), and air quality. They called on financial institutions, the World Health Organization (WHO), the United Nations Environment Program (UNEP), and other international bodies to continue ongoing activities and to pay further attention to children's environmental health, in particular the economic and social dimensions of children's health. In addition, they committed their countries to fulfilling and to promoting the Organization for Economic Co-operation and Development (OECD) Declaration on Risk Reduction for Lead. The underlying rationale for each of these actions is that disease of environmental origin in children can be prevented by controlling harmful exposures in the environment.

International organizations such as the World Health Organization (WHO), the United Nations Environment Program (UNEP), and the European Union (EU) responded to this call and also developed initiatives on Children, Environment and Health. Children's Health and Environment has been the central focus of Europe wide Ministerial Conferences organized by WHO, and other EU initiatives, such as SCALE (Science, Children, Awareness, Legal Instrument, Evaluation). Thus, the protection of children from environmental hazards has been a subject of intense political and scientific attention and effort during the last two decades. Since the initial reports on this issue, research has intensified, and scientific literature abounds with new findings on children's differential vulnerability to environmental health threats that have provided the basis to maintaining the political attention on children's health.

Toxicological Basis of Children's Vulnerability to Environmental Hazards: Susceptibility and Exposure Factors Affecting Children's Vulnerability

Over the past 2 decades, a number of scientific reports have integrated the knowledge available on the susceptibility of children to environmental toxicants, have highlighted knowledge gaps, and have pointed to future directions of research to fill these gaps. This has expanded and deepened the knowledge of the differential susceptibility of children to environmental toxicants, and at the same time has allowed the firm establishment of certain fundamentals concerning children's susceptibility to environmental toxicants.

The International Life Science Institute (ILSI) and the EPA, recognizing the need for examining the scientific evidence on the broad question of the differential susceptibility of children to environmental hazards, organized in 1990 a conference titled: "Similarities and Differences Between Children and Adults: Implications for Risk Assessment." The results from this conference were summarized in the publication "Similarities and Differences Between Children and Adults" [3] and was incorporated into ongoing work of the National Research Committee on Pesticides in the Diets of Infants and Children. The National Academy of Science (NAS) published the NRC report "Pesticides in the Diets of Infants and Children" [2], which was critical in raising awareness of the importance of considering the vulnerable life stages of children when conducting risk assessment of exposures to children. In 2001, the International Life Sciences Institute convened a number of scientific experts to develop a conceptual framework for conducting health risk assessments of children exposures, which takes into consideration their unique characteristics and special vulnerabilities [4].

The ILSI report highlighted the fact that "children are not little adults," but a unique subpopulation that needs to be considered in risk assessment due to differential exposure patterns, immaturity in physiological development, or differential toxicant metabolism.

In 2006, the WHO published the Principles for Evaluating the Health Risks in Children Associated with Exposure to Chemicals in the Environmental Health Criteria 237 [5]. This publication constitutes the most recent monographic work of the subject of children susceptibility to environmental toxicants, and provides comprehensive information on children's developmental stages and the critical windows of susceptibility that appear through the course of their development.

In summary, it is clear from these three major scientific reports – NAS, ILSI, and WHO – that there is broad scientific consensus that risks to children from environmental health threats differ qualitatively or quantitatively from those of adults for a variety of reasons:

- Differential exposure patterns: Compared to adults, children have heavier exposures in relation to body weight because they drink more water, eat more food, and have higher breathing rates per unit of body weight than adults

do. As a consequence, children have substantially heavier exposures than adults to any toxicants that are present in water, food, or air.

- Children's ability to metabolize, detoxify, and excrete chemicals is different from that of adults. During the first months after birth, their metabolic pathways are immature. In some cases, children may actually have a higher metabolic capacity for some toxicants than adults. Commonly, however, they are less able to deal with toxic chemicals and thus are more vulnerable to them.
- Children undergo rapid growth and development, and their development phases are perfectly scheduled to achieve complete functional development. If a development phase is disturbed at a given time, its time to take place may be lost definitively. Thus, interferences with certain phases of development may have irreversible effects. If cells in a child's developing brain are destroyed by chemicals such as lead, mercury, or solvents, or if false signals are sent to the developing reproductive organs by endocrine disruptors, there is a high risk that the resulting dysfunction will be permanent and irreversible.
- Children's exposures are affected qualitatively and quantitatively by their behavior and the unique microenvironment in which they spend their time. Their hand-to-mouth behavior brings contaminated items or soil to their mouth, and living and playing closer to the ground also exposes them to pollutants in a different pattern than adults, both in quantitative and qualitative terms.
- Because children generally have more years of life ahead than adults, they have more time to develop chronic diseases triggered by early exposures. Many diseases, such as cancer and neurodegenerative diseases, are thought to arise through a series of stages that require years or even decades from initiation to actual manifestation of disease. Carcinogenic and toxic exposures, sustained early in life, including prenatal exposures, would then be more likely to lead to disease than similar exposures encountered later.

The purpose of this chapter has been to select, integrate, and summarize the most relevant and illustrative information that explains and highlights the potential susceptibility of children to environmental exposures. The goal of the chapter is to promote understanding of the issue of differential susceptibility and exposures of children to environmental threats among scientists from adjacent fields, and to encourage scientists to consider the issue of children's differential susceptibility and exposures in their research. Recognition of children's exquisite vulnerability to toxic exposures in the environment is critical to child-protective risk assessment and to disease prevention.

For a more in-depth study of any of the particular health issues or particular toxicants, extensive and rigorous reviews that are cited through this document can be consulted. The following sections will elaborate on the general toxicological aspects of children's susceptibility.

Exposure

There are several factors that influence the differential exposures of children to environmental toxicants. These are: (1) their higher ingestion, drinking, and breathing rates per unit of body weight, (2) their unique behaviors, (3) where they spend their time, and (4) their unique microenvironments.

Ingestion, Breathing, and Drinking Rates

In toxicology, exposure is defined as the contact that occurs between a receptor (a living organism) and an environmental agent. The most commonly considered exposure pathways are inhalation, ingestion, and dermal absorption. For infants in the womb, transplacental transfer of toxic chemicals is another unique route of exposure, and for nursing infants, the proportion of the toxicant that enters the body through each of these pathways will depend on both external, environmental factors, and on biological factors that will determine the rate of uptake of the chemical by the organism. Exposure can also be referred to as the concentration that a target organ receives, once the chemical has been absorbed.

The environmental concentration and duration of exposure will determine the extent of exposure. In addition, other environmental factors such as for example, temperature, humidity, and pH, may alter pollutant concentrations. For example, the concentration of some volatile chemicals may vary under different temperature conditions. Sometimes, chemical reactions between pollutants in the environment may change qualitatively the nature of exposure, such as in the case of ozone formation in the air from nitrogen oxides (NO_x), carbon monoxide (CO), and volatile organic compounds (VOCs) in the presence of sunlight.

The patterns of exposure to ingested and inhaled toxicants are different between children and adults. Young children drink more water on a body weight basis than adults do (seven times as much water per kilogram of body weight). For the first 6 months, for example, children consume on average 88 mL/kg/day of tap water directly or indirectly (water added in the preparation of formula or fruit juice) compared to adults who drink 17 mL/kg/day [6]. As a result of this greater consumption of water, children may be disproportionately exposed to chemicals found in drinking water, including the water used to make infant formula [2].

Infants and young children have a higher resting metabolic rate and rate of oxygen consumption per unit body weight than adults. The oxygen consumption of a resting infant aged between 1 week and 1 year is 7 mL/kg body weight per minute, compared to that of an adult in the same condition, which is 3–5 L/kg/min [5]. Thus, on a body weight basis, the volume of air passing through the lungs of a resting infant is twice that of an adult, and therefore twice as much of any chemical in the atmosphere would pass through the lungs of an infant. An additional consideration is the smaller lung surface area per kilogram in the early stages of development. Thus, the higher amount of inspired air will affect a relatively smaller area of lung

tissue. In addition, children have narrower airways than those of adults. Thus, irritation caused by air pollution that would produce only a slight response in an adult, can result in potentially significant obstruction in the airways of a young child [6]. Furthermore, the fact that children spend more time engaged in vigorous activities than adults exacerbates the differential effects. Children also ingest more food per unit of body weight than do adults. A 1–5 year old child eats three to four times more food per kilogram than the average adult, resulting in larger amounts of chemicals and infectious agents per unit of body mass [2, 7]. A child's diet is very different from an adult's. The diet of children contains more milk products and more fruits and vegetables per unit of body weight than adults. During the first year of life, human milk or cow milk-based products constitute most of their energy and nutrient source. The NRC report [2] reported that over the first year, cow milk products comprise 36% and 58% of the diets of nursing and non-nursing infants, respectively, compared to adults, where milk and milk products constitute only about 29% of their diet. Environmental pollutants, such as PCBs and dioxins, accumulate in fat and have been found in breast milk, although it is broadly accepted that the benefits of breast-feeding still outweigh the risks of exposure [5].

After the first few months of life, fruits and fruit juices constitute a large proportion of infants' diet. For example, the average consumption of apples for children between birth and 5 months of age is almost ten times that of an adult older than 20 years old [6]. Fruits can be contaminated with pesticides and other toxicants, causing children to be exposed to these chemicals.

Behavioral Patterns Influencing Exposure in Children

Two characteristic behaviors of children have been considered and studied in relation to children's exposure to chemicals: mouthing behavior and pica behavior. Infants and toddlers pass through a developmental phase, characterized by intense oral exploratory behavior, when they indiscriminately bring their hands and objects to their mouths. Mouthing behavior can result in oral exposures to chemicals that may be part of the surfaces of objects, or adhered to them in dust particles.

Pica is a behavior of some children that has been defined as the craving or ingestion of nonfood items. The cravings found in patients with pica have been associated with a nutritional deficiency state, such as iron-deficient anemia; with pregnancy or with mental illness. Pica tends to disappear as children grow older, except for mentally retarded children [8]. Pica behavior can give rise to the ingestion of soil, paint, and other possibly contaminated substances. About 95% of children ingest 0.2 g of soil per day or less, but studies have shown that children with pica behavior ingest up to 60 g of soil per day [8]. Children living in neighborhoods built on soil contaminated with heavy metals (such as lead), aromatic hydrocarbons, and other compounds were found to be at increased risk for elevated blood levels [8].

Children may also have higher exposures because of their higher levels of physical activity, at least during certain stages of their development. When they

are outdoors, they are more prone to run, jump, or play vigorously than adults do. Their breathing rates may reach exercise levels more frequently during a day than in adults. When near water, for example, children tend to spend more time in the water than adults. This can lead to higher exposures of air pollutants, such as ozone, or to toxicants in water due to the inhalation of volatilized chemicals, ingestion of pool water, and dermal exposures.

Other behaviors characteristic of children such as overexposure to sunlight for sun tanning among adolescents, or drug and alcohol ingestion, can also lead to disproportionately higher risks. However, in this chapter, the central focus is on those risks that are completely involuntary, and that would be difficult to change without altering the normal behavior of a child.

The Unique Microenvironment of Children

The children's microenvironment is different from that of adults from the very beginning of conception. The womb, where the fetus is exposed to environmental chemicals and other agents from previous exposures of the mother is a unique environment to this developmental stage. In fact, humans are among the living mammals that have the longest gestational period, resulting in a long in-utero exposure. Many pollutants are known to cross the placenta and enter the fetal circulation, resulting in fetal exposure to toxicants present in the mother. Once the baby is born, breast-feeding can also result in exposures to chemicals accumulated in breast milk.

Children spend a large proportion of their time indoors, and because of their smaller stature and because they crawl and play on the floor, they are more highly exposed to ground-level contaminants. In indoor environments, for example, formaldehyde exposure from carpeting would be higher at ground level than about 4 or 6 ft above, the breathing zone of adults. House dust or particles to which pollutants adhere accumulate near the floor both in the indoor and outdoor air. Further, outdoors where there is traffic, their breathing zone is close to the height at which car exhaust systems expel their fumes.

Indoor air pollutants can originate indoors, such as formaldehyde from carpeting, fumes from home cooking, and solvents from freshly painted rooms, or can enter the inside of homes through windows or open airways. Sometimes, pollutants may be carried inside by persons entering the indoor environment. For example, children whose parents work on farms where pesticides are applied can be exposed to pesticides carried inside in the clothes and skin of adults who walk into the house. Studies have found higher levels of pesticides in farmworker households in agricultural areas compared with those in non-farmworker households in the same area [9]. In addition, some studies have demonstrated that degradation of pesticides is slower in the indoor environment, so pesticide exposure persists longer [9].

Toxicokinetics

Once exposed, the amount of toxicant being absorbed, its metabolism, and excretion from children's bodies may be very different from that of adults. Rates of absorption through the oral, dermal, and respiratory pathways vary between children and adults. For example, children have a larger lung surface area per kilogram of body weight than adults and, under normal breathing, breathe 50% more air per kilogram of body weight than adults [6]. Therefore infants potentially receive a greater internal exposure to airborne compounds on a body weight basis.

Children's absorption of chemicals through the gastrointestinal route is also different from that of adults. For example, the absorption of lead from the intestine was found to be 40 times higher for children than for adults [3]. Gastric pH is higher in newborns than in adults, thus causing differences in ionization and absorption of certain chemicals. The alkaline gastric pH in newborns and infants may enhance the absorption of certain compounds.

The skin surface area of children relative to body weight is greater for children than for adults, resulting in a higher potential dose absorbed through the skin of about three times greater for infants than for adults [10]. In addition, hydration of the skin in neonates is greater than in older children, which potentially could result in them having a greater absorption of some hydrophilic chemicals. The permeability of the epidermal is incomplete in the preterm infant, resulting in greater percutaneous absorption of chemical agents [5].

Once absorbed, the different body composition of children will result in a different distribution and accumulation of chemicals compared to adults. For example, the relatively larger extracellular fluid volume of the infant means somewhat greater dilution of water-soluble chemicals. However, the lipid-soluble substances would be distributed in a smaller volume of fat in infants relative to adults. The body composition in terms of water, fat, and protein changes from birth to adulthood resulting in corresponding changes in the bioaccumulation, metabolism, and excretion of contaminants from the body throughout development. Water content, for example, decreases rapidly during the first 6 months of life and then remains fairly constant. Body fat, on the contrary, increases rapidly up to 6 months and then decreases, accounting for similar percentages of body weight at ages 4 and 12 months [5]. This can result in changes in the concentration of chemicals in different tissues and organs that can override the child's ability to metabolize and excrete the chemical.

Metabolism and elimination rates are generally lower in neonates than in adults. Many metabolic pathways are not fully developed in the infant. Renal clearance is lower in neonates than in older children and adults for all classes of chemicals. These factors will lead to differences in the bioaccumulation and persistence of environmental agents in children's and adult's bodies and the concentration of the agents in specific organs. The maturation of these metabolic and elimination rates can result in the mobilization of chemicals, and higher exposures of the target organs or systems to the products of metabolism. In terms of excretion, certain life stages such as

pregnancy, lactation, and also menopause, will result in the mobilization of chemicals from fat or bone stores, and the exposure of other organs or the developing fetus and lactating child to the toxicants that were accumulated in the mother.

Developmental Aspects of Children's Susceptibility: Critical Periods of Development

Effects During Gestation

From conception to birth, the human organism advances rapidly through a complex set of developmental processes that culminate in the newborn. These development processes include cell division, organ formation, and growth as well as functional development. During development, some biological processes occur only during certain stages of development and not in others, or they occur at a different rate in different developmental stages. For example, cell division in most organs takes place rapidly during early development and much more slowly at later stages. Other processes such as apoptosis, or programmed cell death, occur more widely during development and are less prominent during adulthood.

These biological processes need to be effectively coordinated and require the cellular and intercellular signaling systems to work correctly. Because of the complexity and speed at which these processes take place and the intricate relation between them, interference at the sequence of any of these processes can have damaging and irreversible effects. Exposure to environmental toxicants can have a completely different effect depending on whether it occurs at one developmental stage or another. In addition, damage due to environmental exposures may occur and manifest itself immediately, or may not appear until subsequent stages of development, after development is complete, including late adulthood.

Identifying and understanding these "critical" periods of unique susceptibility is essential to developing strategies to protect children from adverse health effects associated with environmental exposures. The following sections describe the current state of knowledge about the windows of susceptibility during childhood development.

Effects on Germ Cells

Germ cells (sperm and egg cells) carry the genetic information from each parent that will provide the unique genetic blueprint for each child. In the male fetus, primordial germ cells develop in utero. From puberty to adulthood, these cells undergo cell division, mitosis, and meiosis, to produce mature sperm and continue to be produced from stem cells through adulthood. In females, primordial germ cells undergo mitosis and the first phase of meiosis during fetal life, and in women, mature oocytes are produced every month from follicular cells.

Environmental toxicants that harm germ cells can affect an adult's own fertility as well as the health of the offspring. In animal models, preconceptional carcinogenesis has been demonstrated for a variety of types of radiation and chemicals, with demonstrated sensitivity for all stages from fetal gonocytes to postmeiotic germ cells [11]. Although this link in humans is not demonstrated, it is theoretically possible that environmental toxicants that harm germ cells can affect an adult's own fertility as well as the health of the offspring.

Results of environmental damage to germ cells may include reduced fertility later in life or offspring with congenital health problems [12, 13]. For example, men exposed to diethylstilbestrol (DES) in utero had lowered sperm count and increased frequency of abnormal sperm [14]. Women exposed to cigarette smoke during their mother's pregnancy had reduced fertility [13]. There is a substantial body of evidence demonstrating that exposures to environmental agents and medical radiation can injure germ cells in such a way as to cause increased incidence of cancer, particularly leukemia, among offspring of the exposed individuals. For example, paternal exposures to benzene have been linked to leukemia and lymphoma in children [15]. Animal studies support these findings [11].

Embryonic and Fetal Development During Pregnancy

Several stages of embryonic and fetal development are susceptible to environmental harm. During development, gene expression is very active because a large number of genes are being "switched on" or "switched off" to control cellular activities. This high level of metabolic activity provides for a wide range of opportunities for environmental agents to interfere with cell development and growth.

Environmental toxicants may interact directly with DNA (e.g., alkylating agents) and disturb gene expression or may interact with the products of gene expression, such as enzymes and control molecules. A toxicant that interferes with gene expression may prevent the synthesis of enzymes necessary for toxicant metabolism, resulting in the accumulation of the toxicant in the body. DNA activation by a chemical may result in excessive synthesis of enzymes that catalyze the bioactivation of a toxicant (production of a toxicant metabolite more toxic than the compound originally present).

Chemicals can interfere with the activation or inactivation of genes that occur during early fetal life and that may be essential for the protection of the organism to external or internal harmful processes. For example, interference with genes involved in DNA repair, such as p53, a tumor suppressor gene important for DNA repair, may result in enhanced vulnerability to specific toxicants during development. Studies with transgenic mice that are missing this gene have shown an increased sensitivity of mice fetuses to benzo[a]pyrene exposure and an increased death rate when exposed to the chemical during gestation [16]. Damage to p53 in humans could likewise increase sensitivity to agents that damage genetic material.

If a toxicant interferes with cell differentiation, cells may not reach their specific form and function necessary for their final role in the body, and organ function may

be compromised. Also, undifferentiated cells may be more vulnerable than differentiated cells to toxic effects. Some chemicals such as ethanol [17] and TCDD [18] have been demonstrated to affect specific types of undifferentiated cells.

Apoptosis or programmed cell death is a critical biological process for healthy development. Apoptosis involves the removal of certain cell types when they are no longer necessary. In some instances, one type of cell is succeeded by another during a specific developmental period. Apoptosis is involved, for example, in the elimination of cells in the immune system that, if they survived, could cause autoimmune disease [19]. Apoptosis is also critical in the development of the nervous system, where phases of cell proliferation alternate with phases of apoptosis on the basis of the progression of neuronal development [20] and remains active through the postnatal period because of ongoing nervous system development.

Normal patterns of apoptosis may be altered through altered gene expression or failure of signaling mechanisms resulting from environmental exposures. Certain autoimmune lympho-proliferative diseases and certain cancers have been related to the disruption of normal patterns of apoptosis. For example, Wilms' tumor, a relatively common childhood cancer, may arise from the transformation by postnatal exposures of renal stem cells that fail to disappear 4–6 weeks prior to birth [21].

Neuronal migration is an important process in nervous system development and its alteration may result in irreversible damage. For example, schizophrenia is thought to result, in part, from abnormal neuronal migration [22], but the role of prenatal exposures to environmental agents in causing this disease is not clear. Exposures to ionizing radiation and methylmercury, for example, have been shown to affect the migration of neurons during development [20, 23].

During the period of organ development, which occurs (varying according to organ system) between the 3rd and 16th week, disruption of development can disrupt the large-scale structure of organs, often resulting in physical malformations (congenital anomalies). The best known example of such gestational damage is exposure to diethylstilbestrol (DES). DES caused genital anomalies among male children born of women who took the medication before the 11th week of gestation twice as often as among those who were exposed later in gestation [14].

Other effects such as low birth weight, pregnancy complications, or late fetal death have been shown to be a result of environmental exposures during later stages of prenatal development [24]. Disinfection by-products have been linked to the risk of spontaneous abortion for some time. There is now fairly consistent evidence for associations between early and late fetal deaths and indices of transplacental exposure to disinfection by-products [25–27]. Maternal smoking during pregnancy increases the risk of pregnancy loss, stillbirth, and infant mortality [28].

Development During Childhood

Several organs and systems continue to grow and develop during childhood and in some cases almost until adulthood. For example, neuron migration, cell

proliferation, and synapse formation are very active until 3 years of age, and myelination continues until adolescence [29] and possibly well into adulthood [20].

The immune response is also immature at birth and develops during infancy and childhood until about 1 year of age, while establishment of immunologic memory is not fully established until 18 years of age [30]. Exposure to environmental agents during early childhood may affect immune system development and may contribute to the development of certain diseases such as asthma and cancer later in life.

Physical growth and maturation of organ systems continues through adolescence. The process of sexual maturation is accompanied by complex interactions between the central nervous system and hormone-secreting organs, which can be affected by environmental exposures. For example, the risk of breast cancer has been found to be greater among women who were exposed to radiation before 20 years of age [31].

Cellular Metabolism and Biotransformation

Many important metabolic and biotransformation processes are poorly developed in the fetus, and full metabolic activity is not fully developed until after childbirth. Metabolism can increase or decrease the toxicity of a chemical, depending on the metabolic products of the chemical and pathway involved. Metabolism may also make elimination from the body easier or harder, although the most common metabolic pathways usually render chemicals more hydrophilic and thus, more easily excreted. In some cases, the adult biotransformation of a certain chemical may consist of a bioactivation pathway that makes the compound more hazardous than the one originally present. The absence of a metabolic pathway may result in the bioaccumulation of the chemical in the body and a later bioavailability and disposition to exert its toxic effects. Immaturity could be an advantage if the activation pathway is not present in the fetus or child and there is an alternate pathway for the toxicant to be metabolized. However, according to [32], given the primary evolutionary function of detoxifying and eliminating potentially toxic chemicals, immature or underdeveloped metabolic pathways are likely to render infants and children more sensitive to common environmental contaminants.

Major Groups of Pollutants to Which Children are Exposed

Heavy Metals

Heavy metals are natural elements that have been extracted from the earth and used in human industry and products for centuries. As a consequence of human activity, concentrations of heavy metals in air, water, and surface soil today are hundreds of times higher than in the preindustrial era. Some metals are naturally found in the

body and are essential to the functioning of critical enzyme systems. Iron, for example, prevents anemia, and zinc is a cofactor in over 100 enzyme reactions. Magnesium and copper are other familiar metals that, in minute amounts, are necessary for proper metabolism to occur. The body has need for approximately 70 trace elements, but there are others, such as lead, mercury, aluminum, arsenic, cadmium, and nickel, that have no roles in human physiology and can be toxic at even trace levels of exposure. Nutritionally, heavy metals can compete with nutrient elements, such as the case of lead, which is stored in the bones in the place of calcium.

Metals are notable for their wide environmental dispersion, their tendency to accumulate in select tissues, and their overall potential to be toxic at even relatively minor levels of exposure. In general, heavy metals are systemic toxins with specific *neurotoxic*, *nephrotoxic*, *fetotoxic*, and *teratogenic* effects. Heavy metals can directly influence behavior by impairing mental and neurological function, influencing neurotransmitter production and utilization, and altering numerous metabolic body processes.

Exposure to heavy metals can occur through drinking water, air, or ingestion of heavy metal-contaminated soil. The amount that is actually absorbed from the digestive tract can vary widely, depending on the chemical form of the metal and the age and nutritional status of the individual. Once a metal is absorbed, it distributes in tissues and organs. Excretion of metals typically occurs through the kidneys and digestive tract, but they tend to persist in some storage sites, like the liver, bones, and kidneys, for years or decades.

Lead is one of the best known heavy metals in terms of its toxicity. Exposure to lead can occur in the prenatal stage through the placenta, and in infants through the mother's milk and the water used in milk formula [3]. During pregnancy, body stores of lead may be mobilized and transferred from the mother to the fetus [33]. Behavioral characteristics of children later on, such as the hand-to-mouth behavioral pattern of 1–3 year olds, can result in high exposure and internal levels of lead. Lead paint is a major source of environmental exposure for children who ingest flaking paint, paint chips, and weathered powdered paint (mostly from deteriorated housing units in urban areas). Lead can leach into drinking water from lead-based solder used in water pipes. Lead also leaches into foods or liquids stored in ceramic containers made with lead glazing, which is still used in some countries.

The absorption of lead from ingestion of lead-contaminated water is higher for children than for adults, so that for a given level of exposure, the resultant internal dose is higher in children than in adults [3]. Children are also more sensitive than adults to the toxicological effects of lead at a given internal exposure level. The lowest observed adverse effect levels (LOAELs) for several health endpoints occur at lower blood lead levels in children than in adults. The most sensitive targets for lead toxicity are the developing nervous system, the hematological and cardiovascular systems, and the kidney. There appear to be no safe exposure "thresholds" for lead or for other metals in early development.

Mercury is a ubiquitous heavy metal of both natural and anthropogenic sources. Mercury occurs in both inorganic and organic forms, and it is most hazardous in its organic form of methylmercury. The nervous system is very sensitive to all forms of mercury. Methylmercury and metallic mercury vapors are more harmful than other forms, because methylmercury can cross the blood brain barrier. Methylmercury in the marine and freshwater environment is absorbed by fish and shellfish and bioaccumulates in the food chain. Increased risk is of particular concern in children and in populations that have an increased dietary exposure to fish.

Arsenic occurs naturally in the environment and in some areas of the world is a natural contaminant of underground water that is used as drinking water. It is also an anthropogenic contaminant. Once absorbed into the body, arsenic undergoes some accumulation in soft tissue organs such as the liver, spleen, kidneys, and lungs, but the major long-term storage site for arsenic is keratin-rich tissues, such as skin, hair, and nails.

Cadmium is another chemical that is toxic to adults, although it has not been extensively studied in children. The US Department of Health and Human Services has determined that cadmium and cadmium compounds are known human carcinogens. Cadmium has been linked to diminished kidney function lung disease, chronic bronchitis, and lung, kidney, and prostate cancers. In the USA, smoking is the primary source of cadmium exposure, although high levels of cadmium can also be found in organ meats, shellfish, and vegetables.

Pesticides

Pesticides are substances that are used to prevent, repel, or destroy pests – organisms that compete for food supply, adversely affect comfort, or endanger human health (FIFRA 1996). More than 20,000 pesticide products with nearly 900 active ingredients are registered for use as insecticides, miticides, fumigants, wood preservatives, and plant growth regulators. It cannot be denied that pesticides have beneficial economic and also public health impacts. Pesticide usage helps improve human nutrition through greater availability, longer storage life, and lower costs of food. It also reduces human labor requirements and attendant risks of injury. Pesticides also assist in the control of food-borne and vector-borne diseases, such as malaria, which kill millions of persons in the world. Pesticides also pose human health concerns because they are toxic substances and widely spread in the environment. Although the toxic mechanisms on targeted pest species are well characterized, the potential for adverse health effects in humans is not fully known.

Pesticides are composed of several classes of chemicals with different mechanisms of action. Most insecticides work by interfering with nervous system function. Organophosphates, which account for approximately one-half of the insecticides used in the USA, and carbamates, which are widely used in homes and gardens, inhibit the activity of acetyl cholinesterase at nerve endings, resulting in an excess of

acetylcholine in the synapsis and a depolarizing blockage of neural transmission. The effects of carbamates are readily reversible and of shorter duration. Organochlorines, such as dichlorodiphenyltrichloroethane (DDT) and lindane, interfere with nerve cell membrane cation transport, resulting in neural irritability and excitation of the central nervous system. Herbicides, including the chlorophenoxy compounds 2,4 D and 2,4,5 T are primarily irritative to the skin and respiratory tract during acute exposures and work by different mechanisms. Some substances, such as paraquat, are highly corrosive and can cause multisystem injury and progressive pulmonary failure [34].

Arsenical pesticides, such as copper chromium arsenate, have been used, until recently, as wood preservatives to prolong the useful life of exterior wooden structures. These compounds cause central nervous system depression at sufficient doses.

Pesticides are ubiquitous in the environment. They are found in food, water, homes, schools, workplaces, lawns, and gardens. They are present in soils that have been spread with pesticides or where pesticides from adjacent agricultural areas have drifted, and may reach water supplies from agricultural runoff. In the USA alone, more than 0.45 billion kilograms of pesticides are applied each year, in agriculture, in homes and gardens, and in schools and hospitals. In developing countries, many highly toxic and biologically persistent pesticides such as parathion, DDT, and paraquat, which are no longer permitted in many developed countries, are still in wide use and result in chronic exposures and acute, too often fatal poisonings of thousands of young children each year.

Most children in the world are exposed to some degree to pesticides. Children in rural and agricultural areas and especially children whose parents are farmworkers or pesticide applicators are at highest risk of having increased exposures to pesticides. Pesticides may reach their homes due to the drifting of pesticides that are applied to the ground through aerial spraying. Children may work or play near their parents in the fields where pesticides have been used. Parents who work with pesticides may bring pesticides to their homes, impregnated in their clothes and bodies. In countries where residential housing with gardens and lawn predominate, homes and garden pesticide use may result in significant levels of exposure [34].

Exposure of children to pesticides may occur through inhalation, ingestion, and dermal absorption. Ingestion of pesticides occurs either through accidental exposure due to pesticides stored in food containers (i.e., soft drink bottles), or through ingestion of pesticide-treated foods, particularly fruits and vegetables. Foods grown in pesticide-contaminated soils and fish from pesticide-contaminated water can also carry significant amounts of pesticides. Children may also ingest pesticides adhered to the surface of toys or other objects through their hand-to-mouth behavior. The potential of dermal exposure of children to pesticides is higher than that of adults because of their relatively large body surface area and extensive contact with lawns, gardens, and floors by crawling and playing on the ground.

Prenatal and early childhood exposures are of special concern because of the susceptibility of the developing organ systems to pesticides (the central nervous system in particular) as well as behavioral, physiological, and dietary characteristics of children. Breast-feeding infants may ingest pesticides or

pesticide metabolites present in the breast milk. The quantity of pesticide that is passed to the infant via breast milk is influenced by many variables such as maternal age and parity, maternal body burden of the chemical, and breast-feeding patterns. As infants are weaned and progress to solid foods, they consume, per unit of body weight, proportionally more fruit and more fruit juice than adults. The NAS in 1993 reported that children's dietary exposures to pesticides differed from adults both quantitatively and qualitatively and questioned the protection provided to infants and children from pesticide tolerances in effect at the time. The report estimated that 50% of lifetime pesticide exposure occurs during the first 5 years of life [2].

Environmental Tobacco Smoke

Environmental tobacco smoke (ETS), also known as second-hand smoke, is exhaled smoke and sidestream smoke emitted from the burning of the tip of the cigarette. The inhalation of ETS is known as "involuntary smoking" or "passive smoking." ETS contains more than 4,000 different chemical compounds, many of which are toxic. In 1992, the US Environmental Protection Agency (EPA) declared ETS as a Group A carcinogen.

The effects of passive smoking begin in utero, where constituents of tobacco smoke, such as PAHs, nicotine, and carbon monoxide, cross the placenta and are concentrated in the fetal circulation [35]. Children are also exposed during childhood if any of the parents smoke.

Persistent Organic Compounds: PCBs, Dioxins, and Related Organohalogens

Polychlorinated biphenyls are synthetic compounds with two linked phenyl rings and variable degrees of chlorination. They have been used for many years because of their thermal and chemical stability. They are nonvolatile, hydrophobic oils that are not easily biotransformed in the environment or metabolized by the human organism, so they are very persistent in the environment, and bioaccumulate in the food chain and in the fat compartment of the human body. Although they have been banned in the USA for more than 30 years, they are still widely present in the environment. They have been found in wildlife, human tissue, and human milk. Polychlorinated dibenzofurans (PCDFs) are partially oxidized PCBs that appear as contaminants of PCBs. Polychlorinated dibenzodioxins (PCDDs), commonly referred as dioxins, are formed during paper bleaching and waste incineration. One dioxin congener, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), is considered to be the most toxic synthetic chemical known.

The most significant source of exposure is contaminated food, particularly fish at the top of their trophic chain. Of greatest concern are the populations that consume high amounts of fish. Because PCBs and PCDFs are not metabolized or excreted, they can accumulate in the fat tissue of the body, as well as in human milk, resulting in high exposures of the developing fetus and the newborn.

Disinfection By-products (DBPs)

Disinfection by-products (DBPs) form when disinfectants are added to drinking water and react with naturally occurring organic matter. Chlorine, the most widely used primary disinfectant, reacts with naturally occurring organic matter to form a range of unwanted by-products such as the trihalomethanes (THMs) which include chloroform, bromodichloromethane (BDCM), chlorodibromomethane (DBCM), and the haloacetic acids (HAAs), such as monochloroacetate, dichloroacetate, and trichloroacetate.

Exposure to DBPs occurs through ingestion of water or through inhalation and absorption during showering, bathing, and swimming. While there is some concern that these chemicals may pose a health risk, the potential risks arising from not treating drinking water are considerably greater, and the disinfection of water should never be compromised as a result.

Environmental Threats to Children on Specific Organ Systems

Nervous System

The developing nervous system is more susceptible than the adult brain to the disrupting effect of toxic chemicals [5]. The lengthy period of brain development and the extensive number of processes needed to take place contribute to the susceptibility of the developing nervous system. In the 9 months of pregnancy, the human brain and spinal cord must develop from a thin strip of cells along the back of the embryo into a complex organ comprised of billions of precisely located, highly interconnected, and specialized cells. Brain development requires that neurons move along precise pathways from their points of origin to their assigned location, that they establish connections with other cells near and distant, and that they learn to intercommunicate. Each connection between and among neurons must be precisely established at a particular point in development, and redundant connections need to be pruned away through programmed cell death, apoptosis. All these processes must take place within a tightly controlled time frame, in which each developmental state must be reached on schedule and in the correct sequence.

Critical windows of vulnerability, which exist only in the 9 months of pregnancy and to a lesser extent in early childhood, are unique to early brain development. They have no counterpart in adult life. Exposure to toxic chemicals during these windows of vulnerability can cause devastating damage to the brain and nervous system.

Any toxic or other environmental exposure that interferes with the tightly orchestrated sequence of events involved in brain formation is likely to have profound effects on intellect, behavior, and other functions. If a developmental process in the brain is halted or inhibited, if cells fail to migrate the proper sequence to their assigned locations, if synapses fail to form, or if pathways are not established, there is only limited potential for late repair, and the consequences can be permanent [36].

Environmental toxicants can affect both the structural and functional development of the nervous system. Depending on the developmental stage at which exposure occurs, sensory development, intelligence, or behavior will be affected differentially. While early-developing neural systems have been considered the most vulnerable to chemical insult, scientists have called attention to the importance of chemical exposure that occurs late in childhood, as it has been recently suggested that behavioral and physiological foundations of cognition continue to develop during childhood and adolescence [5, 37].

Exposure to environmental toxicants such as lead, methylmercury, and certain pesticides and PCBs even at very low levels have been shown to produce neurobehavioral (functional) deficits, and increased susceptibility to neurodegenerative diseases much later in life [38]. Of critical concern is the possibility that developmental exposure to neurotoxicants may result in an acceleration of age-related decline in function that could lead to Parkinson Disease, Alzheimer Disease, and other forms of brain degeneration. This concern is compounded by the fact that developmental neurotoxicity that results in small effects on the individual at a particular stage can have a profound societal impact when considered in the whole population or across the life span of the individual [36]. For example, a five-point decline in average population intelligence (IQ score) can result in reduction by more than 50% in the number of children with superior IQ (>130) and concomitant doubling in the number of children with IQ scores in the retarded range (<70). Behavior is also disrupted, sometimes permanently, by such exposures.

The following sections will give a short overview of some neurotoxicological effects of the best known chemicals for their effect on the developing nervous system. Some toxicants such as ethanol have been excluded, as the focus of this chapter is on exposures to toxicants to which the majority of children are exposed.

Lead

Lead is one of the best studied toxicants and one of the few pollutants for which susceptibility of children has been clearly established. The best known health

effects on children are its neuropsychological effects although other effects have also been studied and are partially documented.

The neurotoxic effects of lead in children have been extensively studied. One distinctive characteristic of the research findings on lead neurotoxicity over the past 2–3 decades is that it has led to a progressive decline in the LOELs (lowest observed adverse effect levels). The early finding in the 1970s by Landrigan et al. [39] and Needleman [40] that low-dose exposure to lead is associated with a significant decrease in intelligence quotient (IQ) has been confirmed in many studies. The recommended action level of blood lead levels established by the Centers for Disease Control is 10 $\mu\text{g}/\text{dL}$ of blood. However, epidemiological studies during the last decade have found strong evidence for cognitive deficits among school-aged children at blood lead levels below the current CDC action level [41, 42]. Further, in a pooled analysis of seven prospective longitudinal studies, the average IQ deficit associated with an increase in concurrent blood lead concentration from <1 to 10 $\mu\text{g}/\text{dL}$ was about threefold that for an increase from 10 to 20 $\mu\text{g}/\text{dL}$ [42]. Birth cohort studies have shown inverse dose-response relationships between transplacental lead exposure indices and central auditory processing indices among infants and children at maternal blood lead levels below 10 $\mu\text{g}/\text{dL}$ [43].

Research has also demonstrated a link between developmental lead exposure and behavioral outcome. In a prospective study, the behavior of lead-exposed children at 8 years of age was significantly related to tooth dentine levels [44], suggesting that social and emotional difficulties correlate with lead exposure. In another prospective, longitudinal study, both prenatal and postnatal lead exposure was related to antisocial and delinquent behavior in adolescents [45]. It is generally accepted in the scientific and medical community that the adverse neurobehavioral consequences of lead are not reversible and remain in place across the life span [41]. Further, the possibility that a threshold level for the effects of lead does not exist has been suggested [42].

Mercury

Methylmercury is a well-established neurotoxicant that can cause serious adverse effects on the development and functioning of the human central nervous system, especially when exposure occurs prenatally. The well-known episodes of community-wide poisoning in Japan and Iraq revealed the particular sensitivity of the fetus to the toxic effects from mercury exposure. In these communities, pregnant women exposed to methylmercury and who themselves had no or minimal symptoms, had babies with devastating neurological handicaps, including delayed attainment of developmental milestones, blindness, deafness, and cerebral palsy.

At levels of exposure lower than those encountered in the Minamata Bay, there is limited epidemiological evidence of neuropsychological effects. A birth cohort of 1,000 children was established at the Faroe Islands in 1986–1987, and the methylmercury exposure was determined from the mercury concentration in the cord blood [46]. More than 90% of these children were then examined at age 7 years.

Neuropsychological effects in the areas of language, attention, and memory and to a lesser extent in visuospatial and motor functions were observed [46]. In Brazil, cross-sectional studies of Amazonian children aged 7–12 years show mercury-associated effects in agreement with the Faroe findings [47]. However, a large cohort study conducted in the Seychelles did not reveal consistent associations between perinatal methylmercury exposure indices and developmental milestones or neuropsychologic test scores up to age 5 years old [48].

Some studies have found an association between central auditory processing deficits and current childhood hair mercury levels as low as 5 $\mu\text{g/g}$ [49]. These findings are supported by animal studies, showing that transplacental or postnatal methylmercury exposure affects auditory systems at the cortical level [50].

The important question is to which degree these findings relate to fish-consuming populations in general. Although this question cannot be answered with any confidence at this time, it looks like the recommended one to two fish meals per week during pregnancy would be very unlikely to cause any risk to the fetus, unless the seafood is severely contaminated. The National Academy of Sciences recommended that a limit of about 0.1 $\mu\text{g/kg}$ of body weight per day should not be exceeded by pregnant women [51].

PCBs, Dioxins, and Related Organohalogenes

Polychlorinated biphenyls are known to interfere with thyroid hormones, some of which are critical for normal brain development, and this effect of PCBs on the thyroid function of the newborn has been postulated as the mechanism of action of neuropsychological effects [52].

The earliest evidence of PCB-related neurotoxicity comes from the poisoning episodes in Japan (Yusho) and Taiwan (Yucheng) where people became ill after ingesting rice oil that was highly contaminated with PCBs. Infants born to mothers who consumed PCB-contaminated rice oil during pregnancy were at increased risk for low birth weight, abnormal brown pigmentation of the skin, and clinical abnormalities of the gingival, skin, nails, teeth, and lungs [53]. In addition, children of both cohorts had various neurobehavioral deficits such as delayed attainment of developmental milestones, lower scores on intelligence tests, and higher activity levels [54]. Children were followed and examined 6 years later and showed persistent behavioral abnormalities and ectodermal defects [55].

Many studies after the Taiwan event provide evidence of neuropsychological effects of PCBs [56]. The evidence indicates that PCBs cause neurobehavioral deficits in children who are exposed prenatally, while the evidence of effects of exposure to background levels commonly found in the general population is not conclusive. Studies support the association between low-level transplacental PCB exposure and childhood deficits in cognitive, psychomotor, memory, language, and attention functions [56, 57]. None of the studies up to date has been able to document an adverse effect of PCBs exposure from breast-feeding. It has been postulated that the larger fat compartment of the nursing infant than the fetus may

make it possible to dilute somewhat the lipid-soluble contaminants absorbed through human milk. Thus, despite the occurrence of these contaminants in human milk, the advantages of breast-feeding for 4–6 months apparently override any limited neurotoxin damage due to the contaminants. Still, of particular concern would be the populations who frequently eat contaminated fish or who reside in contaminated areas and may still be exposed at levels that have been associated with adverse effect.

Pesticides

Current knowledge about the neurotoxicological effects of pesticides is limited, despite the extensive knowledge available of the mechanisms of pesticide toxicity in animals. One observational study in children from a region in Mexico with intensive pesticide use found a variety of developmental delays compared with otherwise similar children living in a region where the population had not adopted a pesticide-based agriculture. The children were similar in growth and physical development, but significant delays were noted among the exposed children in physical stamina, gross and fine hand-eye coordination, short-term memory, and ability to draw a human figure [58]. However, these conclusions have been questioned, as pesticide levels were not reported for the individual children who received neuropsychological testing.

Fetal and neonatal animals are often more sensitive than adults to the neurotoxic effects of some organophosphates [2], and levels presumed to be nontoxic in adults may not be adequately protective of the developing organisms. For example, the young rat is deficient in the actions of two enzymes that detoxify chlorpyrifos, and young rats have increased sensitivity to chlorpyrifos toxicity [59]. In rats, chlorpyrifos appear to affect cholinergic function [60]. Infants may be particularly vulnerable to reductions in brain cholinesterase given that acetyl choline plays an important role in normal brain development and plasma and erythrocyte (and therefore probably brain) cholinesterase do not reach adult values until 6–12 months of age [61].

Animal studies suggest that exposure to pesticides such as DDT and its metabolites DDE and dichlorodiphenyldichloroethane at the levels found in the environment affect the developing brain. Ten-day old mice treated once with DDT showed behavioral changes compared with controls when tested at 4 months of age. These effects occur only after DDT dosing at 10 days of age and not after similar dosing at 3 or 19 days of age [62].

In spite of the absence of direct conclusive evidence of the neuropsychological effects of pesticides, the known subclinical effects observed in adults through neuropsychological testing, and what is known on the mechanism of action of pesticides and susceptibility of the developing brain, has led many investigators to infer that chronic low-dose exposure to certain pesticides might pose a potential hazard to the health and development of infants and children. Other investigations have concluded such inferences can be neither supported nor refuted at the present time.

Endocrine System

The endocrine system is one of the body's main communication networks and is responsible for controlling and coordinating numerous body functions. Hormones are first produced by the endocrine tissues, such as the ovaries, testes, pituitary, thyroid, and pancreas, and then secreted into the blood to act as the body's chemical messengers. They direct communication and coordination among other tissues throughout the body, and they exert a powerful influence over growth and development of every organ system in the body.

The endocrine system regulates metabolic, nutritional, reproductive, and behavioral processes, as well as growth, responses to stress, and the function of the digestive, cardiovascular, renal, and immune system. Programming of endocrine set points is a unique aspect of endocrine system development that takes place during fetal/neonatal development, and exposure to toxicants during this critical period of programming can result in permanent abnormalities in endocrine function [5]. Disruption of endocrine function can have severe health consequences in adults, and exposures that interfere with the development of the endocrine system during early life stages can have even more far-ranging consequences [63].

Endocrine disruptors are natural compounds or man-made chemicals that may alter the production or activity of hormones of the endocrine system leading to adverse health effects. Although there is limited scientific information on the potential adverse human health effects, concern arises because endocrine disrupting chemicals, while present in the environment at very low levels, have been shown to have adverse effects in wildlife species, as well as in laboratory animals at these low levels. Many of these chemicals have been linked with developmental, reproductive, neural, immune, and other problems in wildlife and laboratory animals. The potential adverse effects of EDCs include neurodevelopmental and neurobehavioral abnormalities, reproductive disorders such as declined fertility, immune impairment, and certain hormone-related cancers [1].

An example of a phthalate is di(2-ethylhexyl) phthalate (DEHP). DEHP is a high-production-volume chemical used in the manufacture of a wide variety of consumer food packaging, some children's products, and some polyvinyl chloride medical devices. Recently, an independent panel of experts assembled by the National Toxicology Program (NTP) found that DEHP may pose a risk to human development, especially critically ill male infants.

In 2000, an independent panel of experts convened by the NIEHS and the National Toxicology Program (NTP) found that there was "credible evidence" that hormone-like chemicals can affect test animals' bodily functions at very low levels – well below the "no effect" levels determined by traditional testing. Although there is little evidence to prove that low-dose exposures are causing adverse human health effects, there is a large body of evidence in experimental animals and wildlife suggesting that endocrine disruptors may cause [1]:

- Reductions in male fertility and declines in the numbers of males born
- Abnormalities in male reproductive organs

- Female reproductive diseases including fertility problems, early puberty, and early reproductive senescence
- Increases in mammary, ovarian, and prostate cancers

Endocrine disruptors may interfere with the endocrine system through several mechanisms. Some mimic or partially mimic occurring hormones in the body like estrogens and androgens and thyroid hormones, potentially producing overstimulation. Another group of natural and synthetic substances interferes with the hormones at receptors. Substances that compete with a hormone at the receptor, and imitate its effect are called agonists, those that block the receptor are antagonists. Other chemicals interfere, or block the way natural hormones or their receptors are made or controlled, for example, by blocking their metabolism in the liver. Environmental chemicals with estrogenic activity are probably the most well studied; however chemicals with antiestrogen, androgen, antiandrogen, progesterone, or thyroid-like activity have also been identified.

A wide range of substances are thought to cause endocrine disruption. Chemicals that are known endocrine disruptors include diethylstilbestrol (DES), dioxin and dioxin-like compounds, PCBs, DDT, and some other pesticides. Some chemicals, particularly pesticides and plasticizers, such as Bisphenol A are suspected endocrine disruptors based on animal studies.

Phthalates, a class of chemicals that soften and increase the flexibility of polyvinyl chloride plastics, are considered to be endocrine disruptors on the basis of extensive animal research plus emerging studies in humans. An example of a phthalate is di(2-ethylhexyl) phthalate (DEHP). DEHP is a high-production-volume chemical used in the manufacture of a wide variety of consumer food packaging, some children's products, and some polyvinyl chloride medical devices. Recently, an independent panel of experts assembled by the National Toxicology Program (NTP) found that DEHP may pose a risk to human development, especially critically ill male infants.

Research shows that endocrine disruptors may pose the greatest risk during prenatal and early postnatal development when organ and neural systems are developing. In animals, adverse consequences, such as subfertility, premature reproductive senescence, and cancer, are linked to early exposure, but they may not be apparent until much later in life.

There is some evidence that endocrine disruptors may not only impact the individual directly exposed but also future generations. It has been found that animals exposed to low doses of the natural human estrogen estradiol, or the environmental estrogen bisphenol A (BPA) (a chemical used in great quantities in the production of polycarbonates and epoxy resins), during fetal developmental and estradiol as adults were more likely to develop a precursor of prostate cancer than those who were not exposed [64]. This suggests that exposure to environmental and natural estrogens during fetal development could affect the way prostate genes behave, and may lead to higher rates of prostate disease during aging. It has also been shown that the adverse effects of diethylstilbestrol in mice can be passed to subsequent generations even though they were not directly exposed [64].

The increased susceptibility for tumors was seen in both granddaughters and grandsons of mice who were developmentally exposed to DES [65]. One study found that endocrine disruptors caused fertility defects in male rats that were passed down to nearly every male in subsequent generations [66]. These intergenerational effects may be the consequence of epigenetic changes caused by endocrine disruptors.

There is concern that alterations in thyroid hormone signaling by endocrine disruptors during fetal and neonatal development could disrupt central nervous system development. There have been several epidemiological studies of the neurobehavioral effects of in utero exposure to PCBs that have been mentioned in the section on nervous system effects. Thus far, few studies have directly linked neurobehavioral effects of exposure to polyhalogenated hydrocarbons to disruption of thyroid hormone signaling. One example is a study that showed that low-frequency hearing loss caused by developmental exposure in rats to PCBs could be partially reversed by replacement of T4 [67]. In animals, many polyhalogenated aromatic hydrocarbons such as dioxins and PCBs alter thyroxin levels via an increased metabolism and excretion of these hormones [52].

Perchlorates are another class of environmental chemicals that affect thyroid function via inhibition of iodine uptake by the thyroid gland, reducing T4 and T3 synthesis. There has been a concern that contamination of drinking water with perchlorates from industrial sites would suppress fetal thyroid hormone synthesis, disrupting central nervous system development. Increased rates of congenital hypothyroidism have been found in communities with detectable perchlorate levels in the drinking water [68], although others have not detected such elevated rates [69].

Evidence from epidemiological studies demonstrates that exposures during early life can result in greater susceptibility to diabetes and obesity later in life [70]. In the course of development of the pancreas and pancreatic function, for example, several windows of susceptibility have been identified [71]. Studies about the Dutch Famine Winter have shown that poor maternal nutrition, especially during the last trimester of pregnancy had an impact on glucose tolerance and insulin resistance, and that in terms of obesity, those individuals born to mothers who were exposed to the famine around the first half of pregnancy were more obese than those of mothers exposed during the last trimester [72]. A number of subsequent studies have documented the role of the intrauterine environment, and low birth weight in the development of diabetes [71, 73] and other metabolic disorders.

Reproductive System

The development of the reproductive system is a long process that takes place from the beginning of gestation, when organ development starts to take place, to maturation of the reproductive system during puberty. This long developmental

period provides for several windows of susceptibility. Adverse effects of reproductive toxicants can become manifest at birth (e.g., hypospadias and cryptorchidism in humans), in puberty (as delay or precocity), or in adulthood (e.g., infertility, alterations in accessory sex organs, disturbances in pregnancy maintenance, endometriosis, or premature reproductive senescence) [74].

The developmental susceptibility of the reproductive system was clearly demonstrated through the diethylstilbestrol (DES) exposure. In utero exposure of men to DES has been linked to increased incidence of meatal stenosis, epididymal cysts, testicular hypoplasia, cryptorchidism, microphallus, and sperm abnormalities. In females, DES exposure resulted in adenosis, clear cell adenocarcinoma, and structural defects of the cervix, vagina, uterus, and fallopian tubes [75].

Environmental tobacco smoke has been associated with decreased fecundity and earlier menopause in women smokers [76]. Women whose mothers smoked while pregnant also had reduced fecundity compared with women whose mothers did not smoke [13]. In men whose mothers smoked tobacco during pregnancy, reduced semen quality, smaller testis size, and reduced fecundability odds ratios have been observed [77].

Phthalates such as diethylhexyl phthalate (DEHP) are developmental toxicants in experimental animals. The organ system most sensitive to phthalates is the reproductive tract of immature males [78]. In utero exposure of male rats to some phthalate esters results in changes in the reproductive tract, such as decreased anogenital distance, hypospadias, cryptorchidism, disturbed development of prostate, epididymis, vas deferens, and seminal vesicles, retained nipples and decreased sperm production [79–82]. In humans, similar dysgenetic changes in the histology of the testis have been found in patients with testicular cancer, subfertility, or cryptorchidism [83, 84]. It has been hypothesized that all these human disorders (testicular germ cell cancer, cryptorchidism, hypospadias, and low sperm counts) have common origins in fetal life and that they all represent different symptoms testicular dysgenesis syndrome [87].

Neonatal Mortality, Growth Restriction, and Birth Defects

Birth defects are normally defined as structural problems in the newborn, attributable to faulty development or deformation, but defects in function, metabolism, or body chemistry that lead to physical or mental problems or to death may also be considered birth defects. The broader term “developmental disorders” is generally used when considering all effects observed on the conceptus from fertilization to sexual maturity. Developmental disorders include both structural birth defects and functional defects, such as blindness, deafness, or neurobehavioral disabilities.

The majority of birth defects are considered the result of multiple environmental and/or genetic causes acting together. Environmental toxicants studied for their relation with birth defects include maternal smoking and alcohol use, pesticides,

disinfection by-products, plastics and plastic components, solvents, metals and numerous air pollutants [88]. Other environmental causes such as maternal diseases (e.g., rubella), and use of pharmaceuticals (e.g., valproic acid, an anticonvulsant, and mood stabilizers), have served to document the potential environmental role in developmental birth defects.

Many epidemiological studies have attempted to evaluate whether some chemical exposures are linked to increased rates of spontaneous abortions. For example, occupational exposure of the mother to organic solvents has been associated with spontaneous abortion in several studies [89, 90]. A review of six occupational studies found suggestive evidence for an association between toluene exposure and spontaneous abortion, although most workers were simultaneously exposed to multiple chemicals, which may have confounded the interpretation of results. According to this review, spontaneous abortion has generally not been observed as a major problem among highly exposed women who abuse toluene during pregnancy.

Many studies have investigated the effects of *disinfection by-products* (DBPs) on the developing fetus and children. Review of epidemiologic studies reveal that there is fairly consistent evidence for associations between early and late fetal deaths and indices of transplacental DBP exposure [25, 26, 89]. Associations between late fetal deaths and drinking water chloroform, bromodichloromethane, and total THM concentration at levels below the Canadian drinking water guideline of 100 $\mu\text{g/L}$ have been found in Canada [90]. In England, increased risks of late fetal deaths among women living in regions with THM concentrations above 30 $\mu\text{g/dL}$ [91]. These findings are supported by animal studies, where high prenatal maternal exposure to chloroform, bromodichloromethane (BDCM), haloacetonitriles, or haloacetic acids produced fetal resorption and reduced fetal survival [26].

Evidence on the effects of maternal *DBP* exposure and SGA (small-for-gestational-age) effects is mixed. Recent reviews have found limited evidence for association with this effect [25, 26], but a cohort study in Massachusetts demonstrated associations between SGA and drinking water trihalomethanes and mutagenic activity levels during the third trimester in the town of maternal residence [92]. In experimental animals, high prenatal maternal exposure to chloroform, BDCM, haloacetonitriles, or haloacetic acids reduced fetal weight [26, 27].

The evidence of the effects of chlorination disinfection by-products in drinking water and birth defects is inconclusive. Some studies have shown an association between neural tube defects and prenatal maternal DBP [25, 26]. The evidence of effects of water disinfection from five previous studies with a cross-sectional study of all Taiwanese births in years 2001–2003 was reviewed [93] and evidence of an effect of exposure to chlorination by-products on the risk of neural tube defects, urinary system defects, and ventricular septal defects was concluded. However, a recent review of a small number of recent studies reported inconsistent results for an association between drinking water chlorination by-products and risk of all congenital anomalies combined and of specific groups of anomalies, and there was little evidence of an exposure–response relationship [94].

Maternal *smoking* during pregnancy increases the risk of pregnancy loss, still-birth, and infant mortality [28]. There is some strong evidence that exposure to ETS increases the probability of preterm birth [95]. A large birth cohort study in California found borderline statistical association between maternal serum cotinine concentrations during early pregnancy and late fetal deaths (borderline statistical significance), preterm birth, and a significant association with reduced birth weight (significant) [24].

The association between sudden infant death syndrome (SIDS) and maternal smoking has been firmly established. As reported by Wigle et al. [98], a meta-analysis of 39 epidemiological studies and an expert panel review concluded that there is sufficient evidence of a causal association between sudden infant death syndrome and postnatal ETS exposure, independent of prenatal maternal active smoking [95]. Sudden infant death syndrome was also associated with paternal smoking, even when the mothers did not smoke.

Active *smoking* by mothers has been shown to significantly reduce the rate of fetal growth, and the effect was shown to be dose-dependent. DiFranza and Lew [97] using data from 23 studies, calculated an odds ratio of 1.82 for the association between maternal smoking and low birth weight (<2,500 g). The risk of intrauterine growth retardation caused by maternal smoking appears to increase with maternal age, from twofold for mothers aged 17 years to fivefold for mothers aged 35 years [98]. Although smoking throughout pregnancy is known to affect birth weight, there is some evidence that the final trimester may be particularly important [99]. In some studies, babies of smoking mothers have been reported to be shorter and to have smaller head circumferences at birth than babies of non-smoking mothers [98].

Studies *on pesticide* exposures and birth defects have found evidence of associations between paternal pesticide exposure and cryptorchidism [99], although other studies have failed to find a similar association. Cryptorchidism was associated also with maternal serum DDT/DDE and hexachlorobenzene levels [100] and with adipose tissue or maternal serum DDE concentrations [101]. In animal studies, trans-placental exposure to the pesticides DDT/DDE vinclozolin, procymidone, or linuron, produce hypospadias, cryptorchidism, and other abnormalities [102]. The epidemiological evidence of the link between pesticide exposure and hypospadias is not conclusive enough to affirm a link between pesticide exposure and this type of birth defect.

Respiratory System

Lung development is a continuous process from embryonic life to adolescence. At birth, about 85% of the human alveoli are present. Alveolar number and lung surface area increase through childhood and begin to level off between 2 and 4 years of age, whereas lung expansion continues up to 8 years of age [5]. Immature (neonatal)

differentiating cells of the respiratory tract are more sensitive to injury following exposure to respiratory toxicants than mature cells, and at dose levels that cause no effects in adult cells. Children are usually physically active, and have greater exposure to air pollutants. Because of their higher metabolic rates, they breathe more rapidly and inhale more pollutants per kilogram of body weight than adults. Their narrower airway passages compared to adults can be more easily obstructed in a greater proportion than in adults. Thus, because of the immaturity of the lungs during childhood and the greater exposures relative to body weight in children than in adults, it is inferred that children may be more susceptible to the effects of respiratory toxicants than adults, whose lung growth is complete.

Air pollution has been extensively studied in relation to respiratory health and in general it has been easier to demonstrate the effects of air pollution on exacerbation of certain conditions than on the causing of disease in previously normal individuals. Both outdoor and indoor air pollution have been identified as potential risk factors for both the initiation/induction and the exacerbation of respiratory diseases, especially asthma. Evidence of the effect of air contaminants such as ozone and ETS on lung function has been demonstrated in both animal and human studies. Air pollution is now linked to SIDS [103].

Indoor Air Pollution

Indoor air pollution is the most important source of respiratory exposure to toxicants in children, given the fact that children spend up to 90% of their time indoors and the large range of pulmonary irritants that can be found in the home. Exposure to pollutants in the home environment in developed countries has increased with improved insulation and reduced ventilation and the use of chemical detergents and building or furnishing constituents that contain noxious pulmonary irritants [5]. Infants and young children in particular have little control over their exposure to pollutants in the home environment and are vulnerable to the activities of the adults (particularly ETS). Common indoor air pollutants include nitrogen dioxide, formaldehyde and other volatile organic compounds (VOCs), and ETS.

Environmental Tobacco Smoke

Environmental tobacco smoke has been extensively studied in relation to children's respiratory health. The developing fetus can be involuntarily exposed to tobacco during pregnancy through a smoking mother or by the pregnant mother's exposure to environmental tobacco smoke. Exposure may continue throughout childhood if any of the parents smoke. The early exposures may have persistent adverse effects throughout life.

There is evidence of ETS effects on the increased risk of lower respiratory illness rates, especially in the first year of life, increased rates of chronic middle ear effusion in children, impairment of lung function and exacerbation of certain

conditions such as asthma. Exposure to environmental tobacco smoke is a risk factor for sudden infant death syndrome. Children exposed to ETS are more likely to suffer from respiratory illness (bronchitis, pneumonia) and to be hospitalized because of the illness than unexposed children [103]. EPA estimates that between 150,000 and 300,000 of bronchitis and pneumonia cases annually in infants and young children up to 18 months of age are attributable to exposure to ETS. Of these, between 7,500 and 15,000 will result in hospitalization. Furthermore, there is evidence that exposure to ETS leads to increased infant mortality from respiratory illness as well as increased morbidity [104].

Exposure to pollutants during critical periods of lung development may have effects that would not be seen if exposure occurred during adulthood [105]. Maternal smoking during pregnancy was related to impaired lung function in newborn infants [106]. Permanent effects of parental smoking on lung function were found in adults of 30–59 years of age [107], indicating that the impairment of lung function persists through life.

The exacerbating effect of ETS on asthma has been known for some time, and many studies evidence this effect. ETS exposure increases the frequency of episodes and severity of symptoms and the rates of hospitalization in asthmatic children. In addition, ETS exposure is a risk factor for new cases of asthma in children who have not previously displayed symptoms (EPA <http://www.epa.gov/smokefree/healtheffects.html>) [69].

Another group of environmental agents that have been studied in relation to respiratory health are the bioaerosols. Bioaerosols include inhaled allergens (house dust mites and other insects, molds, pets, pollens) and bacterial (lipopolysaccharide) and fungal (glucans) products. Sensitization to one or more common inhalant allergens is consistently associated with childhood asthma especially in developed countries [107]. An expert panel concluded that house-dust mite allergens produce incident (new onset) asthma and that cat, cockroach, and house-dust mite allergens induce episodes in sensitized asthmatics [96]. However, the relationship between exposure to inhaled allergens in early life and the development of asthma or wheeze in childhood is controversial [107]. Contrarily, it has been hypothesized that early exposure to some allergens may be protective of later development of asthma [109], although this hypothesis was discarded in later studies [110].

Outdoor Air Pollution

Air pollution, from both vehicular and stationary sources, is associated with an increase in respiratory symptoms, a decrease in lung function, and the exacerbation of asthma symptoms among asthmatic children. Recent studies have evidenced the relationship between traffic air pollution and incident development of asthma. Most of these effects occur at levels within the ambient air quality standards of most countries that have the potential to affect a large population of children. Air pollution effects contribute significantly to children's respiratory morbidity and

have a significant economic impact in terms of health expenses. Most studies attribute respiratory symptoms to particulate matter, although the close correlation of particulate matter levels with nitrogen dioxide and sulfur dioxide levels makes the contribution of individual pollutants difficult to determine [5].

There is a consistent body of evidence that outdoor air pollution is associated with increased respiratory symptoms, such as cough, bronchitis, respiratory infections, and upper respiratory tract illness in children [111]. Several studies have demonstrated an increase in respiratory symptoms such as cough and bronchitis associated with increases in PM₁₀. A recent study in Eastern Germany evaluated the association between respiratory symptoms and air pollution levels before and after political reunification. A reduction in air pollution since reunification is associated with reductions in the rates of chronic cough and bronchitis symptoms in a new cohort of children, suggesting a potentially reversible effect of air pollution [112]. A similar dramatic effect was observed with children who moved out of an area to other areas of higher and lower PM₁₀ concentrations. Those children who moved to areas of lower PM₁₀ concentrations showed higher rates of growth in lung function, whereas the opposite effect was observed in children who moved to areas of higher PM₁₀ concentrations than before [113].

The role of air pollution in the exacerbation of asthma is well established, and there is mounting evidence that air pollution, particularly from traffic, is implicated in the pathogenesis of asthma [114]. Because children with asthma have increased airway reactivity, the effects of air pollution on the respiratory system can be more serious for them. Children with asthma have been shown to experience more respiratory symptoms, use extra medication, produce chronic phlegm, and have more bronchitis following exposure to high levels of particulate pollution [115, 116]. Air pollution is also associated with increased school absenteeism due to respiratory illness [117], and increased admissions to hospital emergency department [118].

The role of the different components of air pollution in the development and exacerbation of asthma is difficult to elucidate. Oxidant gases such as nitrogen oxide and ozone have been associated with asthma prevalence [119]. Other studies suggest that traffic pollution, but probably not NO₂ from traffic, is associated with atopy and wheezing [120]. The authors suggested that diesel particles or some component of those particles, such as polycyclic aromatic hydrocarbons, may be the most important etiologic component. A recent review of the short-term effects of PM₁₀ and NO₂ on respiratory health among children with asthma or *asthma*-like symptoms concluded there were clear effects of PM₁₀ on the occurrence of asthma symptom episodes, and to a lesser extent on cough and PEF (pulmonary expiratory function). Results with respect to NO₂ were inconclusive [121].

Of great relevance have been recent studies that have related proximity to heavily trafficked roads with asthma and reduced lung functions as well as other respiratory symptoms such as wheeze and dry cough. Lin et al. [122] found significant odds ratios for living within 200 m of a street with the highest tertile of traffic density and asthma prevalence, and the children with asthma were more likely to have truck traffic on their street. Although some studies showed no

increased risk [123], the weight of evidence suggests that traffic pollution is associated with the risk of developing asthma [114].

Lung function is also affected by air pollution. Acute exposure to ozone, nitrogen dioxide, sulfur dioxide, and particulate matter is known to cause transient reversible decreases in lung function [124, 125]. Some recent studies indicate that long-term exposure to ozone and related co-pollutants (individually and synergistically) is associated with impairment of lung function capacity in children and adolescents [126], although other studies are not consistent. Further, it has been hypothesized that a fraction of the increases in the prevalence of chronic obstructive lung disease in adults who live in more polluted areas could be the result of exposures that occurred during childhood [127].

Cancer

Childhood cancers are relatively rare diseases during the first 2 decades of life, but are the leading cause of death of children in many countries. The most common types of childhood cancer are lymphoid neoplasms (leukemia, lymphoma) and cancers of the central nervous system. Other kinds of childhood tumors include embryonal tumors of the retina, sympathetic nervous system, kidney, and liver; tumors of bone and soft connective tissues; and certain gonadal neoplasms. Carcinomas in epithelial tissues, the most frequent type of cancer in adults, are rare in children. Neoplasms in adults resulting from known or iatrogenic exposure typically have latency periods of 20 years or more. Thus, cancers in children are qualitatively distinct from those in adults.

Although childhood cancer is a rare disease, the occurrence of new cancer cases among children has continued to rise during the last 2 decades. While medical advances have led to a sharp reduction in mortality from childhood cancer, it is still a group of diseases with potentially devastating outcomes, which can be at least partially prevented; so the study of the environmental causes of cancer is essential. A recent report from the European Automated Childhood Cancer Information System (EACCIS) provides evidence of a 1% increase per year in childhood cancers and 1.5% increase per year in adolescent cancer in Europe for the period 1970–1999. All of the common types of neoplasms showed significant increases, including leukemias, lymphomas, central nervous system tumors, neuroblastomas, soft tissue sarcomas, retinoblastoma, and germ cell, renal, hepatic, and bone tumors in children and carcinomas, lymphomas, soft-tissue sarcomas, and germ cell and CNS tumors in adolescents. There were in addition significant differences between Eastern and Western Europe with regard to leukemias, lymphomas, carcinomas, and central nervous system tumors in children, and carcinomas, lymphomas, leukemias, and soft-tissue tumors in adolescents. Earlier reports of European populations also noted increases in several of these types of childhood cancers. Similarly, in the USA, there was an overall increase of about 25% in childhood

cancers between 1975 and 2000. While the reported increases in the 1980s may have reflected improvements in diagnosis and reporting, it is unlikely that the most recently reported trends reflect the same bias. Evidence from both epidemiological and mutagenicity/carcinogenicity studies suggest that environmental toxicants may be involved at least in the causation of some forms of cancers such as acute lymphoblastic leukemia (ALL), which is most common in industrialized countries.

Most cancers result from the interaction between genetic factors and the environment [128]. In this context, environment is defined broadly and includes diet, alcohol, drugs, tobacco, and all other nongenetic factors as well as classic environmental toxins. It has been estimated that about 80–90% of all cancers are attributable to environmental factors acting in conjunction with both genetic and acquired susceptibility. For cancer in adults, different opportunities for environmental exposure have commonly been considered a major (albeit not exclusive) reason for the geographical distribution of cancer. Geographical differences in incidence of most cancers (except lymphomas) are less marked for childhood than for adult cancer, thus suggesting that the fraction of childhood cancers due to environmental factors is probably lower than for adults [128].

The potentially higher susceptibility of the developing fetus and children to the effect of environmental carcinogens is based on several aspects. Chemical carcinogenesis is a multistep process involving genetic and epigenetic changes in susceptible cells that gain a selective growth advantage and undergo clonal expansion as the result of activation of protooncogenes and/or inactivation of tumor-suppressor genes. The occurrence of these events is modulated by several factors that themselves change in the course of development. Thus, DNA damage may be repaired by the action of DNA repair enzymes, whose presence and activity may change with age. Similarly, changes in metabolism will determine whether carcinogenic metabolites are formed, thus allowing for the initiation of the cancer process.

DNA repair mechanisms play an important role in cancer protection. DNA repair enzymes have been found to be well expressed in embryos and fetuses. In fact, there are a number of DNA repair genes/activities that have higher expression in fetuses or embryos than in adults. Interference with the synthesis of DNA repair enzymes during development may result in increased susceptibility to cancer during childhood or later in life. An example of the important role of DNA repair mechanisms is the p53 gene, which encodes a protein that modulates DNA repair and cell division. Mutations of the p53 genes are involved in at least 50% of all cancers [129]. p53 mutations have been linked with tobacco smoking [130], and it is possible that p53 mutations occur in the offspring of smoking mothers.

The higher rates of cell proliferation during development can contribute to increased likelihood of carcinogenesis. For example, PAHs and aflatoxin B1 (AFB1) produce liver tumors when administered to newborn rodents but not when administered to older animals, presumably because the liver proliferates rapidly in the developing system but more slowly in older animals [131]. Women who were in their teens at the time of atomic bombings had the greatest risk of radiation-induced breast cancer [132]. Some organs, such as the brain, are fully developed in early childhood, whereas others such as the skeletal system do not achieve maturity until adolescence

[131]. This may be the reason why osteosarcoma, the most common bone cancer, peaks in late adolescence, a period of rapid bone growth.

The immune system of the newborn is not fully developed until about 6 months of age. Chemicals that affect the immune system, such as halogenated aromatic hydrocarbons that bind to the Ah receptor [133], may modify the host defense mechanism against infection and cancer [134].

The susceptibility of children to cancer may be influenced by the presence/absence of metabolizing enzymes. The role of these enzymes is potentially complex, especially for those that carry out the phase I (usually detoxifying) reactions. Usually, chemical metabolism protects the adult and fetus from carcinogenicity, but the activity of enzymes can also result in bioactivation, such as in the case of bioactivation of benzo[a]pyrene to its carcinogenic form, which has been demonstrated by the observation of the formation of DNA adducts in mice and monkey fetuses, which probably originated in maternal liver [135].

The first step in metabolism is usually oxidation, carried out by cytochrome P450 enzymes. This group of enzymes are named as CYP enzymes and grouped in families according to their genotype and activity. Several groups of these enzymes are involved in the metabolism of exogenous carcinogens, such as the CYP families 1–3, which are thought to be the most relevant to effects of exogenous carcinogens. Other examples are the CYP4B1, which activates aromatic amines, and CYP2E1, which metabolizes nitrosamines and organic solvents that have been implicated in causation of childhood cancers.

Phase II detoxification enzymes have received less attention than CYPs in the perinatal context, though they are also likely to be important. For example, among the glutathione S-transferases (GSTs), the I (P) form is apparently expressed at the highest levels and in many tissues in human fetuses from early in gestation, and levels of total GST activity in all fetal tissues studied was comparable to that in the corresponding adult organ [135]. An increasing body of evidence implicates GST polymorphisms in risk of childhood leukemias. Glucuronidation, a type of Phase II reaction, catalyzed by uridine diphosphate-glucuronosyltransferase (UDG), is a key detoxification step for solubilization of high molecular weight carcinogens such as polycyclic aromatic hydrocarbons, heterocyclic amines, and tobacco-specific nitrosamines. Low expression of UDG in the fetus and neonate, and as a result of polymorphisms in children, could well increase sensitivity to carcinogenesis by some chemicals. Sulfotransferases (SULT) have been proposed to constitute a major enzymatic detoxification system in the fetus [136, 137]. However, these enzymes also catalyze activation of several types of chemical carcinogens to DNA-damaging forms, including aromatic amines, polycyclic aromatic hydrocarbons, heterocyclic amines, 3-nitrobenzanthrone, and benzylic alcohols. This illustrates how alteration of enzymatic metabolism can greatly influence susceptibility to perinatal carcinogenesis.

While mutagenicity/carcinogenicity studies, as well as the study of enzymatic systems and DNA repair enzymes, provide mounting evidence that the interplay between chemical agents and these biological factors are significant in the development of cancer, epidemiological studies have only been of limited usefulness to

confirm this hypothesis. The increasing trends over the last 20–30 years and the geographical distribution of childhood cancers, clearly point to environmental causes. However, few studies have been able to firmly establish the environmental origin of childhood cancers. Cumulative epidemiological evidence pertaining to childhood cancers, including international variation, time trends, and risk factor studies was reviewed and analyzed by Bunin [138]. This review concluded that ionizing radiation and a variety of genetic conditions are thought to explain 5–10% of childhood cancers. There are clear associations between Epstein-Barr virus infection and Burkitt's lymphoma in Africa, and between human immunodeficiency virus and Kaposi's sarcoma [138].

Other risk factors have not been conclusively identified. Among the nongenetic causes, the pattern of international variation and associations with surrogates of infection suggested an infectious etiology for acute lymphoblastic leukemia, although no agent has been identified. For brain tumors, cured meats, polyomaviruses, and farm exposures were pointed out as potential causes. Changes in the incidence and characteristics of children with hepatoblastoma as well as risk factor studies suggest a role for an exposure of very low birth weight babies. High birth weight, tea or coffee consumption, and certain paternal occupations have shown some consistency in their association with Wilms' tumor. For most of the other cancers, very few epidemiologic studies have been conducted, so it is not surprising that nongenetic risk factors have not been detected. The most important difference between the cancers for which there are good etiologic clues and those for which there are not may be the number of relevant studies.

This section summarizes the evidence found in the recent literature of the associations between environmental factors and childhood cancer. Attention is given only for those agents for which there is at least limited evidence of an association between environmental agent and disease.

Ionizing Radiation

Evidence of the potential of ionizing radiation to induce childhood cancer comes from events such as Hiroshima and Nagasaki, populations affected by accidents at nuclear plants, as well as investigations on the longer effects of indoor radon and on the consequences of exposure to x-ray for diagnostic or therapeutic reasons.

Japanese children exposed to the atomic bombings of Hiroshima and Nagasaki had increased risks of adult cancers, including leukemia and solid tumors. The highest risk was that of children who were exposed in utero. Radiation-related leukemia started to occur 2–3 years after the bombing, reached its peak within 6–8 years, and has declined steadily since then. For people exposed as adults, the excess risk was lower than that of people exposed as children, but the excess risk appears to have persisted throughout the follow-up period [5].

Thyroid adult carcinomas were also increased in survivors who were children at the time of the bombings at Hiroshima and Nagasaki. The greatest risk for thyroid cancer occurred in individuals who received a radiation dose to the thyroid greater than 1 Sv before age of 10 years. Similarly, breast cancer risk among women survivors to the atomic bombings was highest for the women who were less than 10 years of age or between 10 and 20 years of age, lower for women who were between 20 and 40, and even lower for women exposed after 40 years of age [132].

Prenatal diagnostic X-irradiation has also been linked to increased risk of leukemia in offspring, as has therapeutic, high-dose, ionizing radiation in childhood for other cancers and for various non-neoplastic conditions [139].

The Chernobyl nuclear reactor accident in 1996 caused a significant increase in the incidence of thyroid cancer in children since 1990. Most of the tumors have been observed among individuals who were very young at the time of the accident [31]. In Belarus, over half of the tumors occurred in people who were less than 6 years old at the time of the accident. In a series of 472 children with thyroid cancer diagnosed up to 1995 in Belarus, only 2% had been conceived after the accident, 9% had been exposed in utero, and 88% were under 15 years of age at the time of diagnosis [140]. The very early age at which the thyroid cancers have begun to be diagnosed is one of the most striking examples of the special sensitivity to a carcinogen other than an infectious agent occurring exclusively during preadult life.

UV Light

Sun exposure is known to be a risk factor for the development of skin cancer later in life. The occurrence of sunburn is an indicator of risk [141]. Numerous studies have assessed the carcinogenic effect of sunburn at different ages and concluded exposure to solar radiation before 10 years of age was a primary contributor to risk of melanoma. The IARC concluded that childhood is an especially vulnerable life stage [142] to the carcinogenic effect of UV radiation. While the use of sunscreen reduces the risk of sunburn, an expert working group convened by the International Agency for Research warned against the risk of relying solely on sunscreens for protection from ultraviolet radiation [143], as the use of sunscreens may lead to an extension of the duration of intentional sun exposure, which can increase the risk of melanoma.

Environmental Tobacco Smoke

Environmental tobacco smoke is an established human carcinogen by the International Agency for Research on Cancer [144]. Over 50 epidemiological studies have reported risk ratios of lung cancer for secondhand smoking in adults. A recent meta-

analysis of epidemiological studies of lung cancer and adult exposure to environmental tobacco smoke resulted in risk ratios of 1.22 in women and 1.36 in men from workplace exposure. Other meta-analyses have produced similar results. The evidence of a causal relationship between ETS exposure and cancers in organs other than the lung is inconclusive.

Tobacco smoke contains many carcinogens, such as PAHs and 4-aminobiphenyl, that can cross the placenta and be transferred to the fetus. The genotoxicity of tobacco smoke to the fetal liver has been tested in an animal study. Sister chromatid exchange in the liver cells of fetal mice was analyzed at the 16th day of gestation after short-term exposure (twice, on the 15th and 16th days of gestation), long-term exposure (starting 4 weeks before mating and stopping on the 16th day of gestation), and prepregnancy exposure (4 weeks before mating). The number of sister chromatid exchanges was significantly increased in all exposure groups, and long-term exposure caused a significantly higher increase than did short-term exposure [145].

Most epidemiological studies on the link between exposure to ETS and childhood cancer have focused mainly on pregnant women. While most of studies of smoking by mothers reveal no effects on childhood cancer, many studies of smoking by fathers have shown a significant association with risk of cancer in their children, and when both mothers and fathers are included in the study, the effect appears to be greater for exposure of fathers than of mothers [135]. This effect has been attributed to germ-cell mutations during spermatogenesis caused by tobacco products [146]. Three reports from the Oxford Survey of Childhood Cancers have suggested that paternal but not maternal cigarette smoking is associated with increased risks for the generality of childhood cancers. Some, however, have produced conflicting findings. A large case control study conducted in the UK (the United Kingdom Childhood Cancer Study) concluded that there was no evidence that paternal smoking is a risk factor for childhood cancer in general [147]. A significant association was reported in this study, however, between hepatoblastoma risks and smoking by both parents relative to neither parent smoking. Sorahan and Lancashire speculated that the importance of both parents smoking in the etiology of hepatoblastoma might arise from the combination of oxidative damage to sperm DNA and damage to the fetal liver from carcinogenic metabolites in the blood of the pregnant mother [148]. Further, in a study where both preconception and postnatal smoking by the fathers was quantified, and few of the mothers smoked, the association with childhood cancer related significantly only to preconceptional paternal smoking levels [149]. Thus, second-hand exposure of the infants to smoke was less likely. Transplacental effects of sidestream smoke were one possibility. In rats, sidestream smoke constituents received transplacentally caused oxidative DNA damage in fetal tissues [136]. In one epidemiological study, paternal smoking had a larger possible effect when mothers were nonsmokers [137], suggesting protective effects of detoxification enzymes induced in the placenta and in maternal tissues by maternal smoking.

Some studies have examined the relationship between exposure to environmental tobacco smoke during childhood and cancer risk. Sandler and colleagues [150]

found that the overall cancer risk was greater for individuals with exposures to environmental tobacco smoke during both childhood and adulthood than for individuals with exposure during only one period. When specific cancer sites or types were considered, leukemia and lymphoma among adults were significantly related to exposure to maternal passive smoke before 10 years of age [150].

Pesticides and Cancer

Pesticides are biologically active molecules that are commonly used to destroy unwanted organisms in agricultural and residential environments. The widespread use of these chemicals has raised concerns over the potential of pesticides to cause childhood cancer.

Although the biochemical mechanisms relating pesticide exposures to childhood cancer have not been fully described, some evidence suggests that pesticides may promote the formation of chromosomal aberrations known to be associated with an increased cancer risk [149]. Studies in adult populations suggest that pesticide exposures may have a direct effect on chromosome structure, and therefore a causal relationship between pesticide exposures and childhood cancer is plausible [152].

Epidemiological studies have reported associations between childhood cancer and either parental or child exposures to pesticides. Research reviews have suggested an increase in the risk of brain cancer, leukemia, non-Hodgkin's lymphoma (NHO), Wilms' tumor, Ewing's sarcoma, and germ cell tumors associated with parental occupational and nonoccupational exposure to pesticides [153, 154]. The exposures observed occurred prior to and during pregnancy, as well as after the childbirth, thus involving different potential modes of action. Zahm and Ward [154] concluded that at least some childhood cancer could potentially be prevented by reducing or eliminating pesticide exposure, although methodological limitations common to many studies limit the possibility of making conclusions regarding the role of pesticides in the etiology of childhood cancers [153, 154].

Two extensive reviews were conducted after the Zahm and Ward review [154] that attempted to provide conclusions on the basis of cumulative evidence. In a review that evaluated 18 new studies conducted between 1998 and 2004, it was concluded that while collectively all studies seem to suggest an increase in the risk of different cancer types associated with exposure to pesticides, no conclusions could be drawn with respect to cancer types as well as to specific causative factors across studies [153]. Infante-Rivard and Weichenthal [152] reviewed studies conducted between 1999 and 2004 and critically evaluated the evidence on the associations between pesticide exposures and leukemia (12 studies), brain cancer (10 studies), neuroblastoma (4 studies), non-Hodgkin's lymphoma (3 studies), Wilm's tumor (2 studies), and Ewing's sarcoma (1 study), as in the Zahm and Ward review. The authors found recent studies to be consistent with the suggestion of Zahm and Ward of an association between pesticide exposure and childhood

leukemia, brain tumors, neuroblastoma, and also non-Hodgkin's lymphoma and Wilm's tumor. Specifically childhood exposure to household insecticides and prenatal exposure to pesticides seemed to pose the greatest risks of leukemia and brain tumors. Exposure-response gradients were observed in some studies on pesticide exposure and risk of leukemia. For neuroblastoma, the authors found that all four recent studies reviewed showed an association between exposure of pesticides and risk of neuroblastoma that supported earlier findings by Zahm and Ward. A recent study also indicates that residential use of pesticides, and herbicides specifically, may increase the risk of neuroblastoma in children [153]. The risk of non-Hodgkin's lymphoma was found to be associated with residential exposure to pesticides, and two of the studies reviewed provided evidence of exposure response gradients in two of the three reviewed studies. With respect to Wilm's tumor, recent studies did not provide additional evidence of an association between insecticide exposures and parental pesticide exposure before birth and Wilms' tumor that had been indicated in Zahm and ward's review. The evidence on Ewing's sarcoma was inconclusive.

A systematic review and meta-analysis of studies on childhood leukemia and parental occupational exposure to pesticides concluded that there was not sufficient evidence to affirm an overall association between childhood leukemia and any paternal occupational pesticide exposure among all studies combined or subgroups of studies [155]. An elevated childhood leukemia risk was found in relation to paternal occupational exposure to the broad pesticide classes of insecticides and herbicides, but the authors considered that the small number of studies showing this effect and the lack of exposure-risk relationships did not allow making firm conclusions. However, an association was found between childhood leukemia and prenatal maternal occupational pesticide exposures. The studies also showed associations between childhood leukemia and maternal occupational exposure to insecticides and herbicides. It was concluded that the overall evidence, though limited, warranted exposure prevention measures on the basis of the precautionary principle [152].

Many authors have pointed out the major shortcomings of epidemiological studies on pesticides exposures and childhood cancer [156]. One of the major shortcomings is exposure assessment, as many of the studies use very unspecific measures of exposure, such as "farming" as a measure of "exposures to pesticides." In most of the studies, the specific pesticide/s, timing and other concomitant exposures to which the population was exposed is not known. The authors recommended directing research efforts to the characterization of pesticide exposures in future research. Further they have remarked that "another 40 epidemiological studies similar to the majority of those conducted thus far will not provide clarity."

In spite of the limitations of epidemiological research on pesticide exposures and childhood cancers, many researchers find that there is sufficient evidence to be concerned about the potential role of pesticides in childhood cancers, and to recommend a precautionary approach. Infante-Rivard [152] contrasted the overall evidence against the Bradford Hill's causality criteria (strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and

analogy [157]). The strongest evidence in support of a causal relationship between pesticide exposure and childhood cancer was considered to be the repeated detection of statistically significant increased risks between childhood pesticide exposure and cancer. The authors concluded that there is sufficient evidence to conclude that there is at least some association between pesticide exposure and childhood cancer. In addition, the biological gradients observed in recent studies also suggest that there may be a causal relationship between childhood insecticide exposures and the development of ALL and NHL [158, 159]. Infante-Rivard [152] indicated that the development of childhood cancer probably depends on the presence of many factors, including genetic predisposition, and recommended the use of improved exposure assessments that include separate parental interview, specific pesticide exposure questions, and semiquantitative exposure measures that can be used to confirm exposure information obtained through questionnaires.

Disinfection By-products and Cancer

Disinfection by-products (DBPs), such as trihalomethanes (THMs), are regulated carcinogens in drinking water and have been detected in the blood and breath of swimmers and of nonswimmers at indoor pools. There are a few data on the effects of low doses on humans, particularly infants and children.

Villanueva et al. [160] conducted a pooled analysis of six epidemiological studies and calculated a summary relative risk of bladder cancer equal to 1.18 (95% CI 1.06, 1.32) for exposure above 1 $\mu\text{g/L}$ of trihalomethanes. Boffetta [161] estimated the attributable fraction of bladder cancer on the basis of these figures to be about 10.3%.

Arsenic

Inorganic arsenic is a human carcinogen [162] which causes bladder, skin, and lung cancers in humans. At least in mice, inorganic arsenic is a much more potent carcinogen to the fetus than to adults. The modes of carcinogenic action of inorganic arsenic in rodents and in humans are not yet fully understood, but the possibility exists that inorganic arsenic in drinking water poses a special carcinogenic concern for pregnant women and their unborn infants.

Air Pollution and Childhood Cancer

There have been several studies during the last decade that have linked children's exposure to air pollutants to childhood cancer, leukemia in particular. Infante-Rivard [163] evaluated the results of epidemiological studies conducted between

1998 and 2008 on diverse chemical exposures and childhood leukemia. The review included nine case-control studies and four ecological studies. The latter showed an association between incidence rates of childhood leukemia and levels of air pollution in the area of residence of the population at the time of diagnosis. The lack of information about the place of residence of subjects prior to diagnosis (including during the preconception and gestation period) made it difficult to conclude an association between the exposure levels and risk of childhood leukemia. The review concluded that the weight of evidence from both case-control and ecological studies indicated no increased risk for childhood leukemia associated with exposure to traffic-related residential air pollution. The same conclusion was reached in another review conducted by Raaschou-Nielsen [164].

Endocrine Disruptors and Cancer

Increases in the incidence of cancer in certain parts of the world are often cited as evidence that widespread exposure to endocrine disruptors has adverse effects on human health. Of particular concern are the observed increased incidences of cancer at hormonally sensitive sites, such as breast, uterus, prostate, and testis in Europe and North America. These increases cannot be explained only on the basis of improved diagnostic techniques, and it has been argued that these trends coincide roughly with the increasing use and release of industrial chemicals into the environment. Concerns are also based on plausible mechanisms of action because both human and experimental animal studies show that these cancers are modulated hormonally.

Many epidemiological and experimental animal studies have attempted to evaluate the link between exposure to endocrine disruptors and increased risk of breast cancer. A direct association between these chemicals and increased risk of breast cancer has not been established. However, some researchers claim that the time of life when exposure takes place (e.g., prenatal, neonatal, childhood, adolescence) may have a major influence on the appearance of this and other health effects. The development of the mammary gland occurs in multiple stages. Fetal development of the mammary gland rudiment is governed by tissue interactions in both males and females. In females, the pubertal period drives ductal morphogenesis, and pregnancy results in massive differentiation of the mammary gland. Thus, the perinatal period and the period between age at menarche and age at first full-term pregnancy may be particularly important for breast tumor development and latency [165]. Young girls exposed to carcinogenic agents during puberty may be at high risk of future breast cancer due to susceptibility of rapidly growing breast tissue mediated by hormonal changes during this time. This claim is supported by data from atomic bomb survivors, where an increased risk of breast cancer was found in women exposed before 20 years of age [132]. Similarly, an elevated risk was found for women irradiated during childhood for medical reasons [166].

DES was extensively prescribed in developed countries from the late 1940s through the 1970s to women with high-risk pregnancies to prevent miscarriages and other complications of pregnancy. In the early 1970s, a rare form of female reproductive tract cancer, clear cell adenocarcinoma began to be detected among women whose mothers had taken DES during pregnancy [167]. Although clear cell adenocarcinoma occurs in only 0.1% of women who were exposed to DES in utero, this represents a 40-fold increased risk in comparison with the nonexposed population. In contrast, men who were exposed to DES in utero do not have a clear increased risk of any cancer, although a statistically nonsignificant threefold increased risk of testicular cancer has been reported [168]. While there is no epidemiological evidence for a link between exposure to estrogenic or anti-androgenic compounds and testicular cancer, some authors have hypothesized that the similar increases in the incidence of testicular cancer and in the incidence of cryptorchidism and hypospadias in similar geographical areas, suggest a common cause of similar environmental origin in both health effects [85].

Some studies have shown that women taking DES during pregnancy to prevent miscarriage have been shown to have a slightly increased risk of developing breast cancer 30 years after taking the drug [169]. Data on the risks of breast cancer in daughters of DES-exposed women are not yet available.

Future Directions

During the last 2 decades, there has been an exponential increase of scientific literature about the susceptibility of children to the effects of environmental exposures. Evidence is accumulating that toxic chemicals are responsible for at least some of the changing patterns of disease. Well-studied examples include adenocarcinoma of the vagina in girls exposed prenatally to DES; asthma and pneumonia caused by smoke and particulate air pollutants; neurodevelopmental toxicity in infants exposed to lead, PCBs, methylmercury; and small head circumference at birth in infants exposed in utero to organophosphate pesticides.

Past discoveries of etiologic associations between toxic environmental exposures and diseases in children have led to successful programs of exposure control and disease prevention. Examples include reductions in the use of alcohol and tobacco during pregnancy, minimization during pregnancy of diagnostic x-rays, and removal of lead from gasoline. Sadly, though, the interval between initial recognition or suspicion of effects and their eventual control has been typically been far too long. Early warnings have frequently been ignored. The price of delayed action has been widespread increases in the incidence of certain diseases such as asthma and cancer.

When evaluating the health and social impact of environmental threats on children, it is necessary to take into account, not only their effects on childhood health, but also the long-term potential health effects throughout the lifelong span

of the individual. It has been hypothesized that early exposure to environmental toxicants could affect the brain later in life. Consensus among scientists is based on experimental studies on associations between early life exposures to pesticides and Parkinson's disease, as well as on epidemiologic studies of the toxic and apparently irreversible effects on the developing brain of in utero exposure to lead, methylmercury, and polychlorinated biphenyls. A mechanistic hypothesis proposed that early exposure to neurotoxic chemicals reduce the number of neurons in critical areas of the brain such as the substantia nigra to levels below those needed to sustain function in the face of neuronal attrition associated with advancing age. In addition, as some researchers have pointed out, the effects at population level would add a substantial burden to society, in terms of health, economic, and human costs.

The difficulties in conducting environmental health research have been pointed out by many authors during the last 3 decades. Human populations are exposed to hundreds of chemicals through air, water, and food, under many different exposure situations. Environmental exposures are usually low, and often occur concomitantly with occupational exposures, smoking or naturally occurring agents. And when an association between with an exposure and a disease is found, such as for example, air pollution and asthma, a long path lies ahead to determine the specific causative agent of the disease, and the population and individual susceptibility factors that makes some individuals and not others become ill. The potential for interaction of different pollutant exposures makes the question with respect to the role of environmental exposures impact on health even more difficult to answer. The need for taking into account multiple and cumulative exposures has been clearly affirmed by the EPA and other government and research bodies.

Slowly, evidence is found to confirm or discard certain effects, but it seems that progress is too slow to catch up to the increases in incidence of certain diseases, such as asthma and cancer. It is possible that the statement of Olshan and Daniels [170] with respect to pesticide research, that "another 40 epidemiological studies similar to the majority of those conducted thus far will not provide clarity," should be applied to other groups of chemicals, such as disinfection by-products, or endocrine disruptors, and that we need to think of a more effective way of examining evidence. Many authors have pointed out the need of better exposure assessment methods. In addition to continuing toxicological research, which is essential to elucidate the mechanisms of action, epidemiological research should probably incorporate exposure assessment methods that could enable detection of at least the specific exposures and exposure levels. Exposure assessment can be improved in many ways. In the extreme, if the body burden of a list of suspected carcinogens in the blood or adipose tissue of each child diagnosed with cancer were determined, more specific associations between disease and toxic agent may be determined. The path to confirm and rule out some proposed environmental causes would probably be at least somewhat shorter. While this approach may be costly, it may be cost-efficient in the long run. There have been some efforts to integrate an environmental health perspective in the medical practice. These efforts should be further developed and supported.

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