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Chapter 2. Children's Exquisite Vulnerability to Environmental Exposures - RUTH ETZEL and PHILIP LANDRIGAN

Chapter Overview. Children are uniquely sensitive to toxic chemicals and other hazards in the environment. This vulnerability is based on four factors:

+ Children have proportionately greater exposures than adults to toxic chemicals and other environmental hazards.

+ Children's metabolic pathways are immature. They are therefore not well able to metabolize and excrete toxic compounds.

+ Children's exquisitely delicate developmental processes are easily disrupted. The great complexity of early human development creates *windows of vulnerability*, periods of heightened sensitivity to toxic chemicals that exist only in early life and have no counterpart in adulthood.

+ Children have many more future years than most adults to develop chronic, multi-stage diseases that may be triggered by environmental exposures in early life.

Understanding of children's unique vulnerabilities to environmental exposures had its origins in a series of tragic episodes in the 1950s and 1960s. In each of these cases women took a medication or experienced an environmental exposure during pregnancy that caused no physical injury to the women, but produced terrible and lasting damage to their infants in the womb. These tragedies – the thalidomide disaster, the DES episode and Minamata Disease – documented the extreme vulnerability of developing children to environmental hazards. They showed that the placenta does not protect against toxic injury during pregnancy and that toxic chemicals in a pregnant woman's body can pass freely into the body of her unborn child to cause damage to developing organs.

More recent research has shown that even extremely low-level exposures to toxic chemicals during pregnancy – lead, phthalates and organophosphate insecticides - can cause fetal injury. This injury becomes evident during childhood or young adult life as diminished cognition (loss of IQ), shortened attention span, disordered behavior or decreased reproductive capacity.

It is necessary in light of these findings to consider amending the ancient toxicological principle attributed to Paracelsus that "The Dose Makes the Poison" with a new corollary, that "In Early Development, the Timing Makes the Poison".

Keywords. Children's environmental health; developmental vulnerability; subclinical toxicity; low-dose effects Minamata Disease; phthalate toxicity; organophosphate toxicity; Paracelsus.

A fundamental maxim of pediatrics is that children are not "little adults" (1). Children are far more sensitive than adults to toxic chemicals and other harmful exposures in the environment. This sensitivity reflects the combination of children's disproportionately greater exposures to toxic materials in the environment plus their exquisite biological sensitivity.

Children's susceptibility is especially great during periods in early development – unique "windows of vulnerability" - when their vital organs are forming and rapidly developing

(2). Most of these windows occur in embryonic and fetal life and some in early childhood. Exposures to even minute quantities of toxic chemicals during these sensitive periods of very rapid development can lead to permanent and irreversible injury to the brain, reproductive organs, immune system and other organ systems. These windows of vulnerability have no counterpart in adult life.

Recognition of the vulnerability of children, infants, and fetuses to toxic chemicals in the environment was a watershed event. This discovery catalyzed development of the academic discipline of children's environmental health. It also triggered two further insights that have now themselves become cornerstones of children's environmental health:

- Exposures to toxic chemicals in early life are important causes of disease and dysfunction in children and also in adults, *and*
- Diseases caused by chemicals can successfully be prevented, thus saving lives; enhancing the quality of life; reducing health care and education costs; and increasing national productivity (see Chapter 1 for further discussion).

Historical Background. Current understanding of children's vulnerability to environmental hazards had its origins in a series of seminal clinical observations and epidemiological studies (3). Among these early reports were:

- Thalidomide and Phocomelia. In the 1950s and 1960s, pediatricians in Europe began to see large numbers of newborn babies with a previously rare birth defect of the limbs termed "phocomelia". (The term comes from Greek: *phokos* = seal [the marine mammal] and *melia* = limb; these babies' vestigial limbs were thought to resemble a seal's flippers.) Clinical and epidemiological studies found that virtually all of these babies had been exposed in the womb to thalidomide, a newly invented sedative that had been prescribed to women during the first trimester of pregnancy to alleviate morning sickness. Thalidomide was most harmful when it was taken between days 34 and 50 of pregnancy, which is precisely the time when the limbs are forming (4). In addition to interfering with limb formation, thalidomide was subsequently found to be associated also with deformed eyes, ears, hearts, alimentary, and urinary tracts, blindness, deafness and increased risk of autism (5). The drug was never licensed in the United States, but more than 10,000 cases of phocomelia were reported worldwide (8,000 in Germany alone) before thalidomide was removed from the market and the epidemic halted. The mothers who took the medication were physically unaffected.

Figure 2.1. Infant with Phocomelia following exposure *in utero* to Thalidomide.

- Leukemia and Microcephaly in Atomic Bomb Survivors. An epidemic of leukemia was reported in the 1940s and 1950s among children in Hiroshima and Nagasaki who had been exposed to ionizing radiation in the atomic bombings (6). Cases of leukemia began to be seen in these children in the first 2-3 years after the attacks. Incidence peaked approximately 7 years after the bombing and then declined. Risk of leukemia was highest in the children who had been most heavily irradiated. Risk was much greater in children than in adults with similar radiation doses. This study and subsequent studies of leukemia in children exposed to X-rays *in utero* (7) established that infants and children are much more sensitive than adults to ionizing radiation.

An additional finding in these studies was that infants who were exposed *in utero* to ionizing radiation had an increased incidence of microcephaly. This presumably reflected radiation injury to their developing brains. There was no comparable neurological damage observed in adults.

- Minamata disease (Congenital Methyl Mercury Poisoning). An epidemic of microcephaly, cerebral palsy, mental retardation, blindness, spasticity and convulsions was reported in the 1960s among children living in the fishing village of Minamata, Japan. Investigation revealed that the epidemic was caused by the ingestion by pregnant women of fish and shellfish contaminated with methyl mercury. Investigators traced the source to a plastics factory that had discharged metallic mercury into Minamata Bay. The mercury was transformed to methyl mercury by microorganisms and biomagnified along the food chain, eventually reaching high levels in people who ate local fish and shellfish. Children exposed to the methyl mercury *in utero* experienced the most devastating health effects. The mothers were at most only minimally affected (8). Minamata disease is also described in Chapter 1.

- The DES episode. Diethylstilbestrol (DES), a synthetic estrogen, was prescribed to as many as five million pregnant women in the US in the 1960s and early 1970s to block spontaneous abortion and promote fetal growth. A decade later, gynecologists began observing cases of a rare malignancy, adenocarcinoma of the vagina, in young women. Peak incidence was in the years immediately after puberty. Epidemiologic analysis found that the great majority of the young women with vaginal cancer had been exposed *in utero* to DES. Their mothers were physically unaffected. Further long-term follow-up studies have shown that after age 40 DES daughters have a 2.5-fold increased incidence of breast cancer (9).

These tragic episodes marked the beginning of the academic discipline of children's environmental health. They showed clearly that infants are far more sensitive to toxic chemicals than their mothers. They demonstrated that toxic chemicals from the environment can enter women's bodies, cross the placenta from mother to baby and cause disease in the child. They destroyed forever the myth that the placenta is an impenetrable barrier that protects infants in the womb against toxic chemicals.

These episodes occurred in the era when concern about the environment and about links between the environment and human health was just beginning to emerge in America. They occurred during the time in which Rachel Carson was writing her transformative book, *Silent Spring.* The publication of *Silent Spring* in 1962 is widely considered to mark the birth of the American environmental movement (10).

In response to these episodes, the American Academy of Pediatrics (AAP), the professional association of American pediatricians, established a Committee on Radiation Hazards and Epidemiology of Malformations. The purpose of this Committee, formed in 1957, was to advise pediatricians about the diagnosis, treatment, and prevention of environmental hazards. Robert W. Miller, an American pediatrician, who had led epidemiologic studies of children's health in Hiroshima and Nagasaki after the atomic bombings, was instrumental in establishing this Committee. Dr. Miller is profiled in Chapter 3. This Committee still exists today and has now grown to become the AAP Council on Environmental Health. This council has been an important source of authoritative reports and important recommendations on a wide range of environmental hazards to children. It has been central to establishment of the academic discipline of children's environmental health, and for two generations, it has been an incubator of leaders in children's environmental health.

Report on Pesticides in the Diet by the US National Academy of Sciences. A key event that that crystallized findings from earlier studies, built on the growing environmental movement in the United States, and greatly accelerated understanding of the vulnerability of infants and children to toxic hazards in the environment was publication in 1993 of a report by the US National Academy of Sciences (NAS) on *Pesticides in the Diets of Infants and Children*. (1)

The NAS report found that children have unique patterns of exposure and unique susceptibilities to hazardous exposures in the environment that have no counterparts in adult life. The report recommended that children must have special protections against environmental threats to health in law, regulation, and risk assessment. The central conclusion of this report was that "Children Are Not Little Adults".

This report was commissioned by the Committee on Agriculture of the United States Senate. It was catalyzed by growing concern about potential risks to children's health of pesticides in fruits and vegetables, concern that stemmed from the recognition that nearly all fruits and vegetables sold in commercial markets in industrialized countries, except those certified "organic", contain measurable levels of one of more pesticides (1).

Prior to publication of the NAS report, virtually all research in toxicology and all risk assessment and policy formulation in environmental health had focused on protection of the "average adult". That research took little cognizance of the unique exposures or the special susceptibilities of fetuses, infants and children.

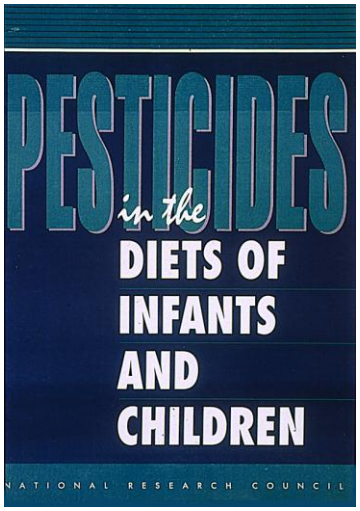

Fig 2.2. National Academy of Sciences Report on Pesticides in the Diets of Infants and Children, 1993.

The old approach to regulation of pesticides in food provides an example. Prior to publication of the NAS report, the levels of pesticides, termed "tolerance levels", that were permitted on fruits and vegetables sold in markets were set at levels considered to be safe for adults. However, those older tolerances had two fundamental shortcomings. A first problem was that they were not health-based. Instead the tolerance-setting process weighed the protection of human health against the costs of regulation to agricultural producers and tried to strike a balance between the two, often to the detriment of public health. A second even more serious shortcoming was that the older pesticide tolerances paid no attention to the unique exposures or special susceptibilities of infants and children. They assumed that the population was comprised solely of adults and that a single tolerance level would protect people of all ages against pesticides in agricultural products.

The NAS report fundamentally changed that paradigm. It built on parents' age-old understanding that children are exquisitely sensitive to hazards in the world around them. It built on research into children's vulnerabilities that had begun with the founding of the specialty of pediatrics in the 1850s by Dr. Abraham Jacobi. The report's main finding was that children are uniquely vulnerable to pesticides and other toxic chemicals in the environment (1).

The findings of the NAS report produced a profound shift in public policy. For the first time ever, it brought the issue of children's sensitivity to toxic chemicals to the attention of national policy-makers and elected officials in the United States and other countries. This increase in policy makers' attention to children catalyzed the recent exponential growth of children's environmental health that is discussed in Chapter 1.

The NAS report identified four differences between children and adults that contribute to children's heightened susceptibility to pesticides and other toxic chemicals:

1. Children Have Proportionately Greater Exposures than Adults to Toxic Chemicals on a Body-Weight Basis. Children's increased exposures are due in part to their disproportionately large intakes of air, food and water. Infants, for example, have respiratory rates that are twice as great as those of adults, and on a body weight

basis they inhale twice as much air (11). Thus they are at increased risk of absorbing airborne toxins. Likewise, children eat more food and drink much more water per pound of body weight than do adults. For example, children take in three to four times more calories per Kg than adults, and a six-month-old infant drinks seven times more water per Kg body weight than an adult. Children's diets are very different than those of adults. Children also consume more milk, more fruits, and often more vegetables. Moreover children have unique food preferences and eat a much less varied diet than most adults. For example, an average 1-year-old drinks 21 times more apple juice and 11 times more grape juice than an adult. The consequence of all these differences is that they place children at much greater risk of ingesting any pesticides or toxic chemicals that may be present in those favored foods.

The differences between children and adults in dietary exposure to toxic chemicals become especially striking when one moves beyond consideration of average exposures to examination of the full range of exposures to infants and children. Some children consume extraordinary amounts of certain foods such as milk, juices and fruits for certain periods of time in early infancy and childhood. If those foods happen to be contaminated with relatively high levels of pesticides, and worse yet if they are contaminated by multiple pesticides, the cumulative dose delivered to certain infants in the population can be quite significant. The NAS report presented quantitative analyses of the full range of children's exposures to benomyl, aldicarb and combinations of organophosphate pesticides (1). These analyses demonstrated that several thousand children in the US are exposed each day to levels of these pesticides sufficiently high to cause toxic injury.

Another physiologic difference between children and adults is that children have a larger surface-to-volume ratio and more permeable skin, two factors that lead to greater dermal absorption of toxic chemicals. A classic example is an epidemic of skin cancer in among young boys described in 1775 by the English surgeon, Sir Percival Pott. These boys were employed as chimney sweeps in Victorian England (11). They were placed in rope harnesses and lowered naked into chimneys that were too narrow for adults. This work led to heavy dermal exposure to soot containing carcinogenic polycyclic aromatic hydrocarbons. Soot was trapped in the skin folds of the scrotum and absorbed. Repeated exposures over many years led to the formation of squamous cell carcinomas.

Children's age-related behaviors further magnify their intake of toxic chemicals from the environment. Children behave differently from adults, and their behaviors change as they develop. Most children actively explore their environments, and young children engage in frequent hand-to-mouth and object-to-mouth behavior. This normal oral exploratory behavior can lead to significant ingestion of toxic substances.

Children spend their time in different physical locations than adults, and these differences magnify their exposures. Infants and young children, for example, spend much of their time on the floor. They are therefore at disproportionate risk of exposure to house dust that may be contaminated by lead or pesticides. And toddlers, because of their short stature, breathe air that is much closer to the ground than that inhaled by adults. They are therefore at increased risk of inhaling vapors of solvents or pesticides that may form layers near the floor. In addition, children are exposed to pre-school or school classroom environments and playgrounds. Schools

and playgrounds are two often built on relatively undesirable lands and the facilities may be old, poorly maintained and poorly ventilated.

> Case Study. Children's Disproportionate Exposure to Airborne Mercury. Mercury vapor, is heavier than air, and thus the highest concentrations of airborne mercury vapor occur near the floor. Before 1991, many brands of interior latex paint sold in the US contained mercury as a preservative. Also paint stores sold mercury salts that could be added to paint for the control of mildew. During the first several months after this mercury-containing paint was applied to a wall, mercury vapor was released from the paint into the indoor air, sometimes exposing people to high levels of mercury. Acrodynia, a form of pediatric mercury poisoning was a result (12). In one case, a 4-year-old boy became poisoned after the entire interior of his fire-damaged home had been painted with 17 gallons of paint containing mercury. (13). Remarkably, four adult family members living in the same house under the same conditions remained unaffected, although urine tests documented that they too had been exposed to elevated levels of mercury (14).

2. Children's Metabolic Pathways Are Immature. One manifestation of this metabolic immaturity is that children's ability to metabolize and excrete toxic chemicals is different from that of adults. In some instances, infants are at lower risk than adults because they cannot convert chemicals to their toxicologically active forms. But in many other cases, they are more vulnerable, because children are less able than adults to detoxify and excrete toxic compounds. As a result, many toxic chemicals have prolonged half-lives in children's bodies. Organophosphate pesticides provide an example. The half-life of the widely used organophosphate chlorpyrifos in the bloodstream of an adult is about 6 hours. But in an infant the half-life of chlorpyrifos is 36 hours, which means that in an infant, this biologically active molecule has much more time to cause cellular injury (15).

Another manifestation of children's immaturity is the rapidity of their metabolism. This can result in increased risk following exposure to certain toxic materials as is illustrated by the disproportionate occurrence of carbon monoxide poisoning in children as compared to adults. Children are more susceptible to carbon monoxide because their developing organ systems have high metabolic rates and high oxygen demand. They are therefore severely affected by the oxygen deprivation that results when carbon monoxide combines with hemoglobin and blocks oxygen transport (16). There have been cases reported in which a snowbound automobile containing high levels of carbon monoxide was found with adults in the front seat, unconscious, but children in the back seat dead (17). A fetus is also more vulnerable than an adult to carbon monoxide poisoning. Fetal blood has a higher affinity for carbon monoxide than adult blood, and the fetus eliminates carboxyhemoglobin more slowly than the adult.

3. Children's Extremely Rapid, but Exquisitely Delicate Developmental Processes are Easily Disrupted. Rapid, complex, and highly choreographed growth and development take place in embryonic and fetal life, as well as in the first years after birth, as is illustrated in Figure 2.3. This great complexity creates *windows of vulnerability*, periods of heightened sensitivity to toxic chemicals that exist only in early development and have no counterpart in adult life (2).

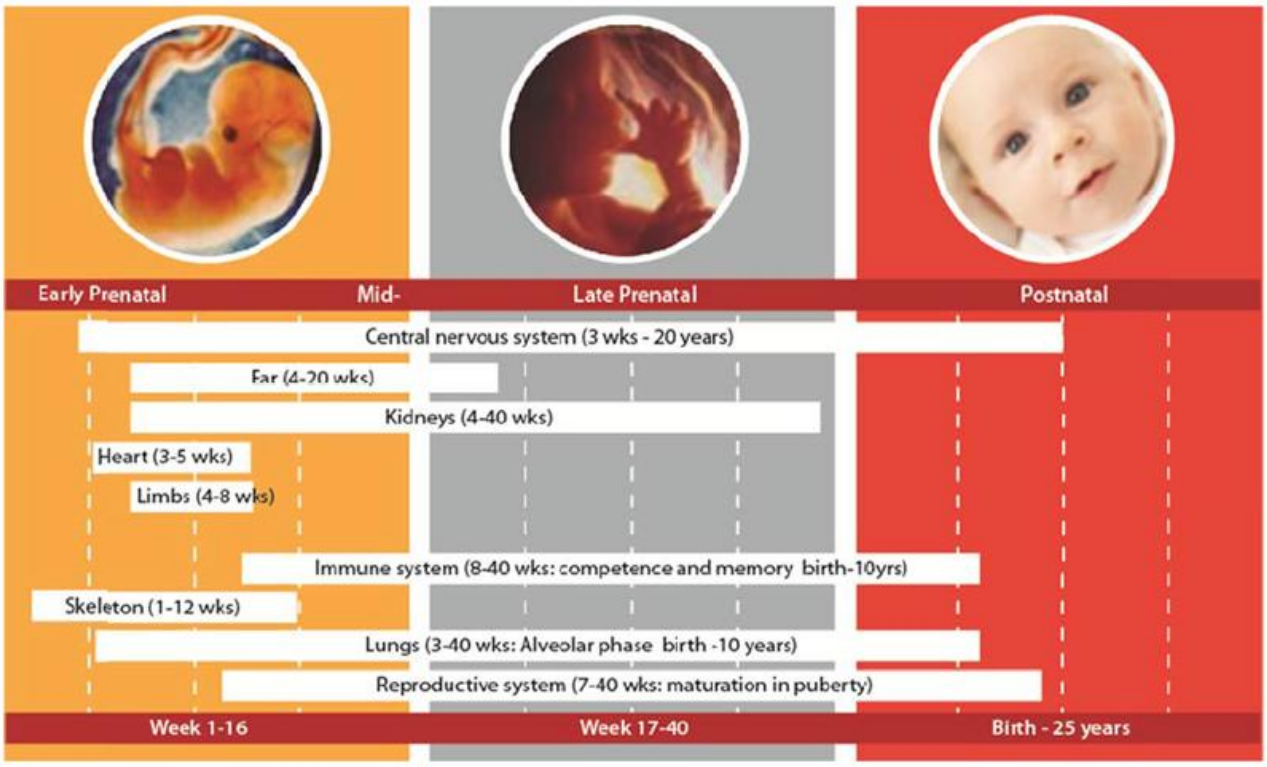

Figure 2.1. Stages of Human Development (courtesy of Dr Jerrold Heindel, US National Institute of Environmental Health Sciences)

The developing brain, for example, is very vulnerable to radiation injury during pregnancy. Mental retardation and microcephaly occurred in children born to women who were pregnant when the atomic bomb was dropped on Hiroshima. (18). The increased vulnerability of the infant respiratory tract is largely due to the prolonged development of the infant lungs. The lungs are growing rapidly during the first year of life and develop more air sacs continue to form up until the fourth year of life. Exposure to second-hand smoke during this time has harmful effects on the developing lungs of young infants. Because the adult lung and respiratory tract are mature, second-hand smoke does not have these same effects. Similarly, outdoor pollutants such as airborne particulates and nitrogen dioxide have been linked to significant deficits in lung growth in fourth graders, but less significant deficits were noted in 7^{th} and 10^{th} graders living in the same polluted area (19).

4. Children Have More Time Than Adults to Develop Chronic Diseases That May Be Triggered by Environmental Exposures in Early Life. Many diseases triggered by toxic chemicals, such as cancer and neurodegenerative diseases, are now understood to evolve through multistage, multiyear processes over the course of many years or even decades. Because children have more years of future life than most adults, they have much more time to develop chronic diseases that may be initiated by early exposures (20). This understanding builds on the landmark observations of Barker and his colleagues who found that the nutritional environment *in utero* can influence health across the entire human life span even into extreme old age (21).

Case Studies in Vulnerability. The unique vulnerability of infants and children to toxic chemicals in the environment is illustrated by two case studies:

1. Examination of the impacts on brain development of early exposures to neurotoxic chemicals; *and*
2. Examination of the effects on multiple organ systems of early exposures to endocrine disrupting (ED) chemicals.

Neurotoxic Exposures in Early Development. Exposures to even minute quantities of neurotoxic chemicals during early brain development can cause devastating damage to the brain and nervous system that have no counterpart in adult life. This vulnerability of the developing human brain to toxic insult is a direct consequence of the extraordinary complexity of early brain development (22). In the nine months of pregnancy, the human brain and spinal cord must develop from a thin strip of cells along the dorsal surface of the embryo into a complex organ comprised of billions of precisely located, highly interconnected and specialised cells. Brain development requires that neurons move along precise pathways from their points of origin to their assigned locations, 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. Redundant connections need to be pruned away through programmed cell death, apoptosis. All of these processes must take place within a tightly controlled time frame, in which each developmental stage must be reached on schedule and in the correct sequence.

Because of its extraordinary complexity, brain development is highly sensitive to toxic environmental exposures. 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 (23). If a developmental process in the brain is halted or inhibited, if cells fail to migrate in the proper sequence to their assigned locations, if synapses fail to form, or if pathways are not established, there is only limited potential for later repair and the consequences can be permanent.

Postnatally, the human brain continues to develop, and the period of heightened vulnerability therefore extends throughout infancy and into childhood. While most neurons have been formed by the time of birth, growth of support cells and development of axons continue through adolescence (23).

Example: Early Life Exposures to Organophosphate Pesticides (OP's) Can Cause Developmental Retardation and Possibly Autism. Organophosphate insecticides are the most commonly utilized class of pesticides in the world. They are well known to be acutely toxic to the brain and nervous system at high doses. They kill insects and also cause acute human poisoning by inhibiting the enzyme acetyl-cholinesterase, an enzyme found in the nervous systems of both insects and mammals. Acetyl-cholinesterase inhibition leads to accumulation of acetylcholine in the brain and nerves, which in turn causes nausea, vomiting, diarrhea, excessive salivation, meiosis, coma, convulsions and in extreme cases, death by respiratory failure. The "nerve gas", sarin, is a member of the OP family.

The developmental toxicity of the OP pesticides has come to be recognized only in recent years. It appears to be quite distinct from acute OP toxicity and to be mediated via different cellular mechanisms (24). Studies of the developmental toxicity of OP pesticides have focused especially on chlorpyrifos, a member of the OP family

extensively used until a few years ago to control insects in schools and homes in the US and still used in agriculture. Studies of the developmental toxicity of chlorpyrifos in newborn baby rodents (whose developmental stage is roughly equivalent to that of a 7-month human fetus) have shown that even very low doses of chlorpyrifos can disrupt the basic cellular machinery in the developing brain that controls neural cell maturation and synapse formation (25). The consequences are reduced numbers of neurons in the brains of newborn rodents followed by learning deficits and behavioral abnormalities.

Recent prospective epidemiological studies have found that chlorpyrifos is also linked to developmental neurotoxicity in human infants. Infants exposed *in utero* to chlorpyrifos have been found to have smaller head circumference at birth than unexposed babies. Reduced head circumference at birth is an indicator of delayed brain growth during pregnancy and a predictor of delayed development and learning disabilities. This effect is most pronounced among infants born to mothers with low expression levels of the enzyme paraoxonase, an enzyme critical to the metabolic breakdown of OP pesticides in the body (26). This effect disappeared after a ban on residential use of chlorpyrifos was imposed in the United States in 2001 (27).

Follow-up studies of children with biochemically documented exposures to chlorpyrifos *in utero* have found evidence for developmental delays. These children also had increased prevalence of attention deficit/hyperactivity disorder (ADHD) (28-30). Most recently, a prospective epidemiological follow-up study suggests that prenatal exposure to chlorpyrifos may be associated with Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS), a form of Autism Spectrum Disorder (31).

Although residential use of chlorpyrifos has now been banned in the US, dozens more OP's are approved for home and school use, and many more OP's are used extensively in agriculture. Their potential impacts on brain development in early childhood are largely unexplored.

Developmental neurotoxicity is discussed in detail in Chapter 45.

Endocrine Disruption and Early Development. Endocrine disruptors are synthetic chemicals that can mimic, alter, magnify and block the effects of naturally occurring hormones, such as estrogen, testosterone, growth hormone, insulin and thyroid hormone (32). Synthetic endocrine disruptors are manufactured in volumes of millions of pounds per year. They include phthalates, bisphenol A, perchlorate, certain pesticides, brominated flame retardants, certain metals and dioxins. These chemicals are widespread today in consumer products such as soaps, shampoos, perfumes and plastics. They are common contaminants in air, food and drinking water.

Exposures to even minute quantities of endocrine disruptors during windows of vulnerability *in utero* and in early childhood have been shown to be capable of producing serious effects on health.

Example: The Effects of Phthalates on Reproductive Function and Brain Development.
Phthalates are a widely used family of chemicals used as plasticizers to confer flexibility to rigid plastics and also used in personal-care products, lacquers, varnishes, and timed-release coatings for some medications.

Phthalates are endocrine disruptors, and several phthalates possess anti-androgenic activity and reduce testosterone levels. In animal studies, evidence of anti-androgenic effects associated with phthalate exposure in early life include impaired Leydig cell function, hypospadias and undescended testicles. In humans, prenatal exposure to phthalates has been linked to lower serum testosterone levels in newborn and adult males and with adverse effects on adult sperm. Prenatal exposure to phthalates has also been linked to shortening of the ano-genital distance in baby boys, a finding indicative of *in utero* feminization (33).

Phthalates appear to be toxic to the developing brain and nervous system. Childhood exposure to phthalates appears to be associated with lower IQ scores (34). Prenatal exposures to phthalates appear also to be linked to behavior problems in 5-9 year olds (35) and with reduced masculine play in boys (36). Baby boys exposed in the womb to phthalates appear to be at increased risk of behavioral abnormalities that resemble attention deficit hyperactivity disorder (ADHD) (37, 38).

Endocrine Disruptors and their effects on child health and development are discussed in detail in Chapter 35.

A New Paradigm for Toxicology. Understanding has become widespread in the past two decades that children are highly sensitive to toxic chemicals and other hazardous exposures in the environment. Exposures in early life, even to extremely low levels of toxic materials can cause lasting damage to embryos, fetuses and young children (39). It is now understood that children have susceptibilities in early development – unique "windows of vulnerability" – that have no counterpart in adult life.

It has also come to be understood that timing of exposure is critically important in early development. The level of lead or methylmercury that can injure the developing brain of a fetus is far lower than the level that causes injury to a 5-year-old, and that level in turn is much lower than the level that can injure an adult. Careful studies of birth defects in children exposed prenatally to thalidomide have shown that exposures between days 34 and 27 of pregnancy can cause defects of the ears, while exposures between days 34 and 50 cause phocomelia and exposures between days 20 and 24 are associated with increased risk of autism. These effects have no parallel in toxicological studies in adults.

In light of these new findings, it is necessary to reconsider the ancient toxicological principle that "The Dose Makes the Poison". This principle, which is attributed to Paracelsus, the "Father of Toxicology," states that the greater the level of exposure to a toxic chemical (the "dose") the more severe will be its effects on health (40).

Paracelsus' principle has been a powerful organizing principle in toxicology for five centuries. It still has enormous validity today. But it fails to explain how very small exposures to toxic chemicals in early development can have profound and lasting impacts on health. Tthese findings ttherefore suggest the need for a new corollary principle in toxicology that "In Early Development, The Timing Makes the Poison".

In the years ahead, this new understanding of the vulnerability of infants and children to environmental hazards will need to be translated into pediatric and public health practice, risk assessment, regulation and legislation. The protection of children's health demands no less.

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