Birth Defects: Peer-Reviewed Analysis

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Birth Defects and the Environment

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May 2004

What Is a Birth Defect?

According to the March of Dimes, "a birth defect is an abnormality of structure, function, or metabolism (body chemistry) present at birth that results in physical or mental disability, or is fatal" (MOD). Another definition (International Classification of Diseases, 9th revision) limits the term to structural malformations and deformations. Minor structural birth defects, such as an extra skin tag, nipple, or a rudimentary extra finger, do not necessarily result in a disability, though they may be unwanted, cosmetically disfiguring, and a sign of abnormal development that signals an underlying cause that should not be ignored. Varying definitions of the term "birth defect" add to the challenges of tracking their incidence and understanding their causes.

Unlike the March of Dimes, many clinicians and scientists do not consider metabolic abnormalities to be birth defects since many can be explained by recessive genetic inheritance. Although that does not make them unimportant, for purposes of studying the incidence and causes of birth defects, it often helps to more narrowly define the conditions being considered.

The March of Dimes definition also includes immune and nervous system abnormalities that are present at birth, though some, for example, mental retardation, autism, and attention deficit hyperactivity disorder (ADHD), may not become apparent for months or years.

Other developmental problems that are sometimes considered related to birth defects include premature birth and low birth weight. They increase the risk of infant mortality and developmental disabilities, like cerebral palsy and mental retardation. Approximately 20% of children with cerebral palsy and 50% of children with mental retardation also have structural birth defects, showing that these conditions often overlap (Goldman, 2001). In this paper, we address structural birth defects and include observations about prematurity, low birth weight, and functional neurological disorders.

Structural birth defects affect the formation of parts of the body and may be apparent at birth, though in many cases they are not diagnosed until later, sometimes even after the first year of life. Historically, structural birth defects have been classified as either major or minor. Most birth

defect research and monitoring efforts have focused on major structural abnormalities such as oral clefts, heart defects, spina bifida, and limb defects. Major birth defects remain the leading cause of infant mortality in the United States (Petrini, 1997). The leading birth defects associated with infant death are heart defects (31%), respiratory defects (15%), nervous system defects (13%), multiple abnormalities (13%), and musculoskeletal abnormalities (7%). Birth defects are also a major cause of miscarriages and fetal death.

Costs of Birth Defects

According to an analysis by the California Birth Defects Monitoring Program, the estimated lifetime costs for children born each year in the US with one or more of 18 of the most significant major birth defects, including cerebral palsy, were approximately $8 billion (in 1992 dollars) (http://www.cbdmp.org/pdf/uscost.pdf). Costs related to other developmental disabilities add substantially to this amount. Special education costs for a child with autism spectrum disorder, for example, are over $8000 annually, with care in residential schools reaching $100,000/year (CDC). Children with ADHD incur medical costs twice those of children without ADHD and are more likely to have major injuries, asthma, and hospital inpatient and outpatient care (Chan, 2002).

How Common Are Birth Defects?

Many pregnancies that are adversely affected end in a miscarriage or a stillborn baby instead of the birth of a child with a structural or functional birth defect. According to a report by the National Academy of Sciences, nearly half of all pregnancies today result in the loss of the baby or a child born with a birth defect or chronic health problem (National Research Council, 2000).

The true incidence of birth defects is difficult to determine because of inconsistent and incomplete data gathering. Not all states have birth defect registries, and in those that do, their quality varies considerably. This issue was recently reviewed by the Pew Environmental Health Commission, which found that, although the incidence of some birth defects is increasing rather dramatically, one-third of all states have no system for tracking birth defects, and systems are inadequate in most others (Goldman, 2001). Moreover, even in states with birth defect registries, most do not include children with defects that become apparent months or years after birth.

Suggested methods for addressing these surveillance deficiencies differ considerably. Although most people support improved state-by-state, nationwide tracking, an alternative view holds that it would be more fruitful to concentrate comprehensive efforts and resources on a few carefully selected geographic areas.

About 3.5 % of all babies will have structural birth defects that are recorded on hospital discharge records (Smulian, 2002). One of the largest studies of structural birth defects, however, shows this to be an underestimate of the true number. The Collaborative Perinatal Project recorded birth outcomes for 50,000 pregnant women at 20 different medical centers (Chung, 1975). Children from these pregnancies were followed up to 7 years after birth. The total rate of structural birth defects was nearly 16%. Half of these (7-8%) were major birth defects and half were less serious.

With the exception of some parts of California and metropolitan Atlanta, GA, no states track conditions such as mental retardation, cerebral palsy, or other functional defects, making it difficult to draw conclusions about their frequency or incidence trends. This problem is complicated by changing and inconsistent criteria for diagnosing a particular disorder. For example, attention deficit hyperactivity disorder (ADHD) is a collection of traits that are present to varying degrees in affected individuals. Similarly, individuals with autism spectrum disorders (ASD) have a wide range of different manifestations and disabilities. Inconsistencies in applying diagnostic criteria and varying reporting patterns make it difficult to draw definitive conclusions about ASD trends, and this remains a topic of considerable debate. (Yeargin-Allsopp, 2003; Fombonne, 2003; Croen, 2003)

What Causes Birth Defects?

The cause of most birth defects is unknown. Genetic, nutritional, infectious, and other environmental factors, such as radiation, pharmaceuticals, and toxic chemicals, contribute to the total incidence of birth defects, but the percentage attributable to each is not known.

A growing number of experts believe that most birth defects result from multiple factors such as an interaction between one or more genes and the prenatal or preconceptual environment (National Research Council, 2000). Gene-environment interactions refer to the circumstance in which certain genes may predispose an individual to a birth defect, but one or more environmental factors are also necessary for the defect to be produced.

A number of instances of this interaction are known. For example, maternal cigarette smoking and genetic variations in production of a growth factor combine to significantly increase the risk of having a child with oral cleft defects (Hwang, 1995). Similarly, fetal alcohol syndrome is a condition in which a child may be born with structural defects of the head and face and later develops evidence of cognitive, learning, and attention problems. The risk of having a child with fetal alcohol syndrome is increased in women who not only drink alcohol during pregnancy but who are also genetically determined to metabolize alcohol in a particular way (Ruttledge, 1994).

Genetic causes of birth defects can occur as a result of one or both parents carrying one or more unfavorable genes or from chromosomal damage in the developing embryo. Environmental agents may play a role by triggering genetic mutations or other chromosomal damage that leads to birth defects. For example, radiation can cause mutations in the DNA of chromosomes of eggs or sperm, and these mutations can, in turn, cause abnormal embryonic development. Some chemicals are mutagenic or cause abnormal chromosome numbers in eggs or sperm and may have a similar effect.

Certain pharmaceuticals or environmental chemical contaminants, however, can cause birth defects without causing mutations in DNA. For example, Dilantin (anti-seizure medication), retinoids (used to treat severe acne), lead, mercury, and polychlorinated biphenyls (PCBs; a family of industrial chemicals that contaminates the general food supply) can cause birth defects by disrupting normal embryonic and fetal development through a number of other mechanisms.

Birth defects have also been linked to maternal infectious illnesses like rubella (German measles) and toxoplasmosis (a parasitic disease). Nutritional deficiencies also play a role. Low levels of folic acid in the mother, for example, have been implicated in the occurrence of neural tube defects (anencephaly, spina bifida and encephalocele). Birth defects are also more frequent in the children of mothers who have diabetes or thyroid disorders. The reasons for these increased risks are not always well understood.

Studying Environmental Causes of Birth Defects

Studying the role that environmental factors play in causing birth defects is extremely challenging and current understanding is evolving. Research approaches include studies in vitro (test tube) and in laboratory animals, wildlife, and human populations.

Laboratory animal and in vitro studies: Animal studies are often used to examine whether or not an environmental agent may disrupt normal development. Such studies are required when a new drug or pesticide is proposed for the market, but these evaluations have significant limits. In general, they tend to emphasize obvious structural defects but are limited in their ability to identify functional defects. Species differences in susceptibility make it necessary to examine effects in at least two separate species. Genetic similarities in laboratory animals of the same species limit the value of this testing strategy for predicting impacts in genetically different populations of people. In short, the combined contributions of genetic, nutritional, and other environmental factors to birth defects in humans are not easily studied in laboratory animals. Nevertheless, animal studies continue to be extremely useful in identifying some agents that cause birth defects, sparing humans from unnecessary harm and suffering. Unfortunately, the developmental impacts of many commonly encountered industrial chemicals have not been studied at all, even in laboratory animals. In vitro screening techniques using dividing, living cells exposed to environmental agents avoid the use of laboratory animals and offer some promise for future directions.

Epidemiologic studies in human populations: Birth defect risks in human populations exposed to pharmaceuticals, drugs of abuse, pesticides, or other industrial chemicals can be studied using several different approaches. Each approach has its strengths and limitations.

1. Case reports may be useful when unusual defects suddenly show up in a cluster of children and are recognized by astute parents or clinicians. Investigation of the use of the drug thalidomide during pregnancy and the resultant severe arm and leg defects in children exposed prenatally is an example of an instance when case reports were helpful. Early suspicions of harmful effects were ignored in some countries, but case reports ultimately lead to case-control studies that confirmed the link, tragically only after a large number of children had been damaged. For a variety of reasons, however, investigations of case reports of clusters of defects may fail to find a cause, though they may generate hypotheses that warrant further study.
2. In another kind of study (cohort study) a large number of people are assigned to groups on the basis of chemical exposure or nutritional status, and pregnancy outcome is monitored. This kind of study is difficult, expensive to conduct, and rarely done. The National Collaborative Perinatal Project, launched in the 1950s, enrolled more than

50,000 pregnant women and followed them until their children were 8 years old. In this kind of study, many factors may contribute to pregnancy outcome and must be controlled for (e.g. family history, diet, occupation, smoking status, alcohol and drug use, etc).

3. Case-control studies are most commonly used to study the relationship between environmental factors and birth defects in people. In this kind of study, a group of children with a particular classification of defect is compared with a control group of children without the defect, but otherwise similar, to see if some difference in previous environmental exposures can be identified. This study design is often limited by inability to estimate accurately exposures that occurred months or years previously. Identification of the control group can also be difficult.

Sources of Uncertainty: Additional Challenges to Studying Environmental Causes of Birth Defects

Identifying, quantifying, and timing exposures: Identifying, quantifying, and timing chemical exposures during fetal development are major challenges to investigating the role of environmental factors in causing birth defects. A large body of scientific research shows that not only the magnitude of exposure but also its timing is an extremely important determinant of risk because of the specific sequencing of developmental events. If the timing of potentially harmful exposures is not known, a link between birth defects and environmental factors may be missed. For example, children exposed to the drug thalidomide during the third to sixth week of gestation often suffered severe limb deformities, while children exposed later had either no or different health effects. Early exposures to thalidomide, approximately 20-24 days after conception, increased the risk of autism (Rodier, 2000).

Classifying birth defects: Regardless of study design, it is often difficult to know how best to group birth defects for analysis. There are tradeoffs among the choices. For example, in an attempt to increase the statistical power of a study to identify causal environmental factors by increasing the number of cases, researchers may "lump together" defects that should not be considered in the same category from the standpoint of developmental biology. "Heart defects", for example, are often considered to be a single category, but within this group are individual kinds of defects that should be considered individually. "Lumping" defects into a single category will tend to "hide" a specific defect that actually is causally related to a specific environmental factor. Yet, because individual defects are relatively rare, statistical power is lost when the number of cases is small.

Multifactorial causes of birth defects: Scientific evidence indicates that not all people are equally susceptible to birth defects. Genetic and nutritional factors may combine with other environmental factors to increase the risk. This combination of factors makes it extremely difficult to conduct epidemiologic studies in populations of people when the entire collection of risk factors is not well understood or identified.

Modest vs. dramatic increases in risks of birth defects: Some environmental agents appear to increase the risk of birth defects moderately but not dramatically. Though extremely important, modest increases in risk are difficult to demonstrate with a high degree of certainty and often remain unidentified. As a result, some reports of chemical agents that are known to cause birth defects are often limited to those that cause a large increase in risk. For example, some people

argue that environmental agents should only be considered relevant and causally related to birth defects if they produce an increased risk of at least 6-fold (Shepard, 1995). However, lesser increases in risks, for example, 1.5-2 fold, are also important and, in large populations, may result in considerable numbers of affected individuals. In numerous studies, many chemicals, or classes of chemicals, are implicated as significant contributors to the risk of birth defects, though the risk is frequently less than 6 times higher than in unexposed groups.

Some Examples of Environmental Exposures That Cause or Are Associated with Birth Defects in Humans

This section is based on published reports showing potential links between environmental agents and classes of birth defects in people. Laboratory animal data are not included in this section. This is an important limitation inasmuch as studies of the developmental impacts of chemical exposures are much more numerous in laboratory animals than in humans. Citations are obtained from searching Medline, Toxline, and medical textbooks.

It is important to recognize that, for some environmental agents, the evidence for a causal role in birth defects is strong whereas for others, the evidence is less consistent or weaker. For example, an increased risk of oral clefts associated with maternal smoking, is much better established than other environmental risks for clefts. In some cases, studies that are not cited do not find the same associations, and additional investigations may or may not confirm the positive study's findings. A series of reports investigating the same agent or class of agents may have inconsistent or conflicting conclusions. For many, the best we can conclude is that available data "implicate" particular agents but further investigations are necessary to confirm the findings. This is the state of the science at the current time, highlighting the need for more systematic and focused attention, while at the same time asking when the weight of evidence is sufficient to act to protect health.

Heart Defects

Heart abnormalities are very common. Approximately 1 in every 400 newborns has a heart defect (CBDMP, 2004). Some heart defects such as holes in the heart wall may be mild and resolve without surgical intervention. Others like hypoplastic left heart syndrome are incompatible with life unless the baby can survive long enough to receive a heart transplant.

Environmental Exposures Associated with Heart Defects

Exposure	References
Maternal medications Hormones, antinauseants, seizure medications, anti-inflammatory drugs, tranquilzers, antibiotics, codeine, ibuprofen	(Cedergren 2002) (Ericson 2001) (Hernandez-Diaz 2000) (Hook 1994) (Loffredo 1993) (Ferencz 1991) (Rubin 1991) (Zierler 1985) (Hendrickx 1985) (Rothman 1979) (Heinonen 1977) (Nora 1975)
Maternal illness Diabetes, rubella, thyroid disease,	(Cedergren 2002) (Vohra 2001) (Loffredo 1993) (Rosenberg 1987) (Freij 1988)

toxoplasmosis, Coxsackie virus B	
Maternal alcohol	(Tikkanen 1992, 1988)
Maternal occupations/exposures Nursing, dye, lacquer, paint	(Loffredo 1997) (Ferencz 1996) (Tikkanen 1992) (Tikkanen 1990)
Paternal occupations/exposures Jewelry making, welding, paint stripping, lead soldering, janitors, forestry and logging, painting, plywood mill work, marijuana use, alcohol, smoking	(Steinberger 2002) (Loffedo 1993) (Correa-Villasenor 1993) (Olshan 1991)
Solvents (e.g. benzene, trichloroethylene, and other organic chemicals used in a variety of consumer products and industrial processes)	(Nurminen 2001) (Loffredo 1997, 1996, 1991) (Loffredo and Beaty 1997) (Tikhonova 1997) (Ferencz 1996, 1992,1991) (Redden 1993) (Tikkanen 1992, 1988) (Correa-Villaseanor 1991) (Bao 1991) (Correa 1990) (Correa-Villaseanor and Loffredo 1990)
Pesticides (may include insecticides, herbicides, fungicides, etc.)	(Sherman 1995) (Ferencz 1992) (Correa-Villaseanor 1991)
Chlorination byproducts	(Cedergren 2002) (Hwang 2002)
Living near hazardous waste sites	(Croen 1997) (Shaw 1992)
Heavy metals Lead, arsenic	(Vinceti 2001) (Engel 1994) (Ferencz 1992, 1991) (Correa-Villaseanor 1991) (Zierler 1988)
Ionizing radiation	(Correa-Villaseanor 1993) (Correa-Villaseanor 1991)
Maternal Smoking	(Ferencz 1996) (Loffredo 1993)

Oral Clefts

Oral clefts are birth defects of the structures that form the mouth. A cleft lip means that the two sides of the upper lip did not grow together properly. A cleft palate is a split or opening in the roof of the mouth. Cleft lip and palate may occur individually or together in the same baby. The opening in the lip or palate may be on one side only (unilateral) or on both sides (bilateral). Oral clefts affect approximately one in every 700-1000 newborns with incidence variations in different racial groups. Families with a history of oral clefts in a parent, another child, or close relative, are more likely to have a baby with an oral cleft. But many families without such a history also have children with oral clefts. This had led researchers to believe that environmental factors can interact with specific genes to interfere with the patterns of normal palate closure and lip development.

Environmental Exposures Associated with Oral Clefts:

Exposure	References
Maternal medications	(Matalon 2002) (Schatz 2001) (Czeizel 2001, 2000) (Arpino 2000) (Park-Wullie 2000)

Antiseizure drugs, oral corticosteroids, antibiotics, folic acid antagonists, retinol, antinauseants, amphetamines, analgesics, chemotherapy, antineurotic drugs	(Hernandez-Diaz 2000) (Rosa 1986) (Golding 1983) (Milkovich 1977) (Saxen 1975)
Maternal illness Diabetes	(Aberg 2001)
Maternal alcohol	(Lorente 2000)
Maternal occupations/exposures Work as a cleaner, work in pelt or leather industry, work as janitors, work with glycol ethers, agricultural work	(Garcaia 1999, 1998) (Cordier 1997, 1992) (Bianchi 1997)
Paternal occupations/exposures Pesticides, dioxins	(Sever 1997) (Sweeny 1994)
Solvents	(Nurminen 2001) (Bove 1995) (Holmberg 1982)
Pesticides	(Sever 1997) (Sherman 1995)
Chlorination byproducts/ public water	(Bove 1995)
Living near hazardous waste sites	(Orr 1999)
Heavy metals Lead	(Vinceti 2001)
Maternal Smoking	(Chung 2000) (Lorente 2000)
Dioxins	(Sweeny 1994)

Neural Tube Defects (Anencephaly, Encephalocele, Spina Bifida)

Neural Tube Defects (NTDs) are serious birth defects that involve incomplete development of the brain, spinal cord and/or the protective coverings of these organs. There are three types of NTDs—anencephaly, encephalocele and spina bifida. Babies born with anencephaly have underdeveloped brains and incomplete skulls. Babies with encephalocele have a hole in the skull allowing brain tissue to protrude and babies with spina bifida have an opening in the spine that may allow part of the spinal cord to protrude. NTDs occur in one or two out of every 1,000 births. A family history of NTDs and maternal folate deficiency each increase the possibility of having a child with one of these defects, but most NTDs are believed to be multifactorial, meaning that they are likely to be caused by one or more genes interacting with an environmental factor.

Environmental Factors Associated with NTDs:

Exposure	References
Maternal medications Antiepileptic drugs, clomid, tetracycline,	(Matalon 2002) (Felkner 2001) (Arpino 2000) (Czeizel 2000) (Kaneko 1995) (Greenland 1995) (Lindhout 1992)

antimicrobials	
Maternal illness Diarrhea	(Felkner 2001)
Maternal occupations/exposures Painting, refinishing furniture, health care, anesthetic gases, gycol ethers, agricultural work	(Brender 2001) (Cordier 1997) (Matte 1993) (Blatter, 1996)
Paternal occupations/exposures Pesticides, dioxins, welding, solvents	(Brender 2001) (Brender 1990)
Solvents	(Brender 2001)
Pesticides	(Shaw 1999) (Kristensen 1991)
Chlorination byproducts/ public water	(Magnus 1999) (Bove 1995)
Living near hazardous waste sites	(Orr 1999) (Dolk 1998) (Croen 1997) (Vrijheid 1997)
Heavy metals Lead	(Irgens 1998)
Dioxins	(Veterans and Agent Orange Update 1996) (Sweeny 1994) (Andrews 1992)
Radiation	(Matte 1993)

Limb Reduction Defects

Limb Reduction Defects (LRDs) involve missing tissue or bone in any part of a limb or limbs. LRDs can range in severity from missing fingers and toes to the complete absence of one or both arms and/or legs. LRDs occur in about one out of every 2,000 births. Upper limb defects are twice as common as lower limb defects. Some LRDs are part of multiple birth defect syndromes that may be inherited. Many researchers believe, however, that the majority of LRDs are caused by the interaction of a susceptible gene and a triggering exposure.

Environmental Factors Associated with LRDs:

Exposure	References
Maternal medications Thalidomide, antiseizure medications, antihistamines, corticoids, thyroid hormones, antinauseants, sex hormones, warfarin, antimigraine drugs, cocaine	(Robert 2001) (Orioli 2000) (Siffel 1997) (Castilla 1996) (Okada 1995) (el-Gindi 1993) (Sharony 1993) (Fries 1992)(Correy 1991) (Kricker 1986) (Hayes 1982) (Cordero 1981)
Maternal illness Diabetes	(Koallaen 1989)

Maternal occupations/exposures Exposure to agricultural chemicals	(Engel 2000) (Kristensen 1991) (Schwartz 1988)
Solvents	(Donald 1991)
Pesticides	(Engel 2000) (Sever 1997) (Munger 1992) (Kristensen 1991) (Schwartz 1988)
Pregnancy Tests Chorionic villus sampling	(Hsieh 1995) (Burton 1992)
Maternal Smoking	(Carr 1997)

Gastroschisis

Gastroschisis is an abdominal wall defect that results in all or part of the small intestine and other internal organs protruding outside of the abdomen. One out of every 3,000 children in California is born with gastroschisis (CBDMP). The defect occurs 5-8 weeks after conception and is thought to be caused by a disruption in the blood flow to the developing abdominal wall. Studies have linked certain medications and environmental chemicals that are known to alter blood flow to increases in gastroschisis.

Environmental Exposures Associated with Gastroschisis:

Exposure	References
Maternal medications/exposures Aspirin, decongestants, marijuana, cocaine, ibuprofen, acetaminophen, oral contraceptives	(Kozer 2002) (Martainez-Frajas 1997) (Torfs 1996, 1994) (Werler 1992) (Drongowski 1991)
Maternal occupations/exposures Printing, exposure to colorants	(Barlow 1982) (Torfs 1996)
Paternal occupations/exposures	(Stoll 2001)
Solvents	(Torfs 1996, 1994)
Living near hazardous waste sites	(Dolk 1998)
Maternal Smoking	(Haddow 1993) (Goldbaum 1989)
Maternal radiation	(Torfs 1994)

Hypospadias

Hypospadias is an abnormality of the penis in which the urinary tract opening is not at the tip. It is a relatively common condition that occurs in about 1 per 300-500 live births. Over the last 25 years, however, the incidence and severity of hypospadias has reportedly doubled in the United States and Europe. (Paulozi, 1999) Hypospadias is more frequent in boys whose fathers have hypospadias and in families where two or more males in the family have the condition. Recent

studies indicate that exposures that affect hormone balance during pregnancy may be associated with increases in hypospadias. (Toppari, 2002; North, 2000; Silver, 1999)

Exposure	References
Maternal medications DES, antiepileptic drugs, cocaine, aspirin	(Klip 2001) (Arpino 2000) (Battin 1995) (Lindhout 1994) (Lindhout 1992) (Correy 1991)
Maternal illness Influenza	(North 2000)
Maternal occupations/exposures In-vitro fertilization using sperm injection into egg, phytoestrogens in vegetarian diet, work in leather industry	(North 2000) (Silver 1999) (Garcaia 1998)
Paternal occupations/exposures Vehicle mechanics	(Irgens 2000)
Pesticides	(Longnecker 2001) (Kristensen 1997)
Living near hazardous waste sites	(Vrijheid 1997)
Dioxins	(Mori 2001) (Fara 1985)

Environmental Exposures Associated with Any Structural Birth Defect

[All birth defect risks listed are significantly elevated, although with only a few exceptions, the increased risk is less than six-fold. The data in this table are limited to major structural defects and do not include premature birth, retarded growth, or other developmental toxicity.]

Agent/exposure	Birth defect	Reference
Solvents		
General solvent exposure	Heart, central nervous system, oral cleft	Tikkanen 1988, 1992; Holmberg, 1979, 1980, 1982; Magee 1993; McMartin 1998
Benzene	Neural tube defect, heart	Bove, 1995; Savitz, 1989
Toluene	Fetal solvent syndrome, urinary tract	Hersh, 1985; McDonald, 1987
Chloroform and trihalomethanes (drinking water disinfectant byproducts)	Central nervous system, oral cleft	Bove, 1995
Glycol ethers	Oral cleft	Cordier, 1997
Trichloroethylene	Central nervous system; heart; oral clefts	Bove, 1995 Goldberg, 1990

Perchloroethylene	Oral cleft	Bove, 1995
Metals		
Mercury	Central nervous system	Harada, 1978
Lead	Abnormal pulmonary blood vessels	Correa-Villasenor, 1991
Other		
Polychlorinated biphenyls (PCBs)	"Yusho" syndrome: Skin lesions, pigmentation, eye swelling, abnormal teeth and gums, abnormal skull calcifications (relatively high dose maternal exposure)	Schatz, 1996; Rogan, 1988.
Residential or occupational factors	**Birth defect**	**Reference**
Maternal residential proximity to pesticide applications	Fetal death from congenital abnormalities	Bell, 2001
Maternal residential proximity to hazardous waste site	Central nervous system, musculoskeletal; Neural tube defect, heart Neural tube defect, heart, hypospadias, anomalies of esophagus, abdominal wall defect	Geschwind, 1993; Marshall, 1997 Shaw, 1992; Croen, 1997 Dolk, 1998
Maternal agricultural work	Oral cleft; neural tube defect	Nurminen, 1995; Blatter, 1996
Maternal farm/garden work	Musculoskeletal	Hemminki, 1980
Paternal pesticide applier	Circulatory or respiratory, urogenital	Garry, 1996
Paternal wood preservative applicator	Eye, neural tube defect, male genital tract	Dimich-Ward, 1996
Paternal solvent exposure	Neural tube defect	Brender, 1990

Premature Birth and Low Birth Weight Associated with Environmental Exposures

Low birth weight (LBW) is defined as birth weight less than 2500 grams, and very low birth weight as less than 1500 grams. Babies can be small either because of premature birth or because of retarded growth in the uterus. In 1997, there were almost 4 million births in the US of which 291,154 were LBW and 54,973 were very low birth weight (Goldman, 2001; NCHS, 2002). Young maternal age and reduced access to medical care increase the risk of having a LBW child. African-Americans also have an increased risk of LBW offspring, (NCHS, 2002)

A number of environmental factors also increase the risk of LBW. They include exposures to cigarette smoke, lead, solvents, pesticides, polycyclic aromatic hydrocarbons (PAHs), and air pollution, including carbon monoxide (Wang X, 2002; Goldman, 2001; Perera, 2003, Ha, 2001 ; Maisonet, 2001; Dejmek, 1999; Bobak, 2000; Ritz, 2000).

The causes of premature birth are not well understood. Strong predictors of prematurity include multiple gestation, prior preterm birth, and African-American ethnicity (Vintzileos, 2002). Several environmental factors have also been implicated, including air pollution, lead, some solvents, the pesticide DDT, and di-ethylhexyl phthalate (DEHP) (Xu, 1995; Goldman, 2001; Wang X, 2000; Longnecker, 2001; Latini, 2003).

Of particular interest is the apparent importance of gene-environment interactions in LBW and prematurity. For both cigarette smoke and benzene exposures, maternal genetic determinants of metabolic enzyme levels significantly influenced the risk of LBW and prematurity, respectively (Wang, 2002; Wang 2000).

Other Kinds of Developmental Abnormalities Associated with Environmental Exposures

Testing for developmental toxicity is an emerging science. Test methods are still undergoing development in laboratory animals and relatively few environmental chemicals have been examined for their ability to alter development in people. As a result, the functional impacts of fetal exposure to the large majority of environmental chemicals on the immune, reproductive, nervous, and endocrine systems are unknown.

Considerable information does exist for a few environmental contaminants, showing that the fetus is commonly more sensitive to exposures than an adult. Exposures during developmental windows of susceptibility can have long-term and even life-long impacts, many of which are not detectable at birth.

The growing human brain, for example, is uniquely vulnerable to exposures to lead, mercury, manganese, polychlorinated biphenyls, alcohol, toluene, various other drugs of abuse, and pesticides (see table). Animal studies confirm the unique susceptibility of the developing brain to these and other commonly encountered chemicals.

Similarly, the immature immune system is vulnerable to long-term disruption after exposure to some industrial and environmental chemicals. The field of developmental immunotoxicology is in its infancy, and there is little consensus surrounding the meaning of various changes in immune system parameters after fetal exposures. Based on available information, however, it is clear that developmental immunotoxicants can alter susceptibility to infection and other diseases, including allergies. For example, in one long-term study, background prenatal exposures to PCBs and dioxin increased the risk of middle ear infections and chicken pox, while lowering the risk of allergic reactions and also lowering the antibody response to mumps and measles vaccine in preschool children (Weisglas-Kuperus, 2000).

Neurologic and Immunologic Defects Associated with Selected Environmental Exposures (human studies):

Neurologic	Associated environmental agent	Reference
Abnormal neurological development, including cognitive impairment, learning, memory, attention disorders, and/or hyperactivity	Lead Mercury Polychlorinated biphenyls (PCBs) Alcohol Manganese Pesticides Tobacco smoke	Needleman, 1990; Bellinger, 1994 Grandjean, 1997 Jacobson, 1996; Weisglas-Kuperus, 2000; Lonky, 1996; Stewart, 2003. Streissguth, 1991 Crinella, 1998 Guillette, 1998 Eskenazi, 1999 (these and others reviewed in Schettler, 2000)
Immune system		
Altered immune system development	Lead Dioxins/furans PCBs Polybrominated biphenyls (PBBs)	Burns, 1996 Vos, 1997 Burns, 1996 Weisglas-Kuperus, 2000 Burns, 1996

An increased risk of an even wider range of health effects may result from fetal or early developmental exposures. For example:

- Maternal use of the synthetic estrogen, diethylstilbestrol, during pregnancy increases the risk of their daughters later developing vaginal, cervical, and breast cancer as well as other abnormalities of the reproductive and immune systems. Their sons are also at increased risk of reproductive tract abnormalities that are not apparent at birth (Herbst, 1970; Giusti, 1995).
- Prostate gland and testicular development in laboratory animals is fundamentally altered by exposure to estrogenic agents during fetal development (National Research Council,

1999). Similar changes in humans would be expected to increase the risk of prostate and testicular cancer later in life.

- Changes in reproductive system function and the behavior of animals can be caused by fetal exposures to hormonally active chemicals during fetal development (National Research Council, 1999).
- The risk of childhood asthma is increased if the mother smoked during pregnancy (Singh, 2003).

Although more research will be necessary to clarify our understanding of details, the weight of current scientific evidence demonstrates the unique vulnerability of embryonic and fetal development to environmental exposures. Accumulated information indicates that the definition of "birth defects" must be expanded to include a much larger spectrum of structural and functional impacts, many of which are not apparent until years or decades after birth.

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