

# **A Small Dose of Developmental Toxicology Or An Introduction to Pregnancy and Developmental Toxicology**

Chapter 25

*A Small Dose of Toxicology - The Health Effects of Common Chemicals*

By

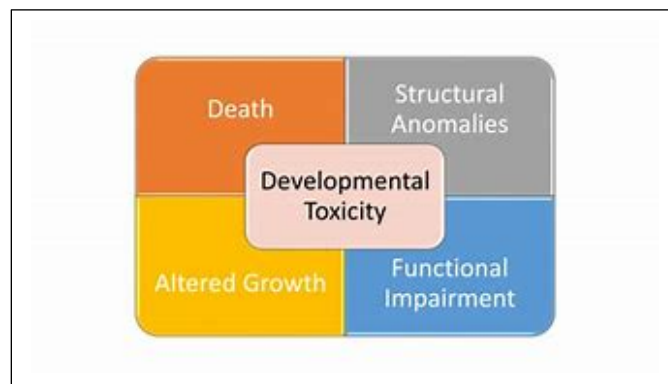
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web: [www.asmalldoseoftoxicology.org](http://www.asmalldoseoftoxicology.org) - "A Small Dose of Toxicology"



## Introduction and History

"Nature creates monsters for the purpose of astonishing us and amusing herself".

Pliny (61–105 AD)

Many organisms, including humans, evolve through sexual reproduction and the sometimes prolonged development of the resulting offspring. It is truly astonishing that male and female germ cells (a sperm and an egg) can merge and develop into an independent organism. In order to facilitate the discussion of this enormous and complex subject, it will be divided into three areas: reproduction – issues associated with the egg and sperm; pregnancy – the critical environment of early development; and development of the infant. The focus will be primarily on humans, but the development of all organisms can be adversely affected by chemical or physical agents. The chapter provides only the briefest examination of the disorders and adverse effects of various agents on reproduction and development. Harmful agents affect the developing organism in dramatic and subtle ways and that can harm a person for a lifetime at enormous cost to the individual and society.

Only in the last 100 years have we begun to understand the mysteries of reproduction and development. Prior to advances in the biological sciences, ancient civilization invoked a fertility goddess to oversee reproduction. Many thought malformed or abnormal infants were a message or warning of future events. A small statue of conjoined twins dating from 6500 BC was discovered in Turkey. A clay tablet (2000 BC) found along the Tigris River described 62 malformations and related the abnormalities to future events. In the 15<sup>th</sup> and 16<sup>th</sup> century, malformed infants were thought to be a product of the devil and both mother and child were killed. Some thought that the development of the child was influenced by what the mother was viewing. Thus, Aristotle recommended that a mother view beautiful statuary to increase her child's beauty. One definition of the word monster is an abnormal animal or plant. Monster is derived from the Latin *monstrum omen*, and from *monere* to warn, reflecting the notion that abnormal infants told of the future. Greek for monster is *teras*, which is the root of teratology, the study of malformations or monsters.

The more scientific investigation of abnormal development began in the 1830s when Etienne Geoffroy Saint-Hilaire studied the effects of different conditions on the development of chicken eggs. But it was not until the late 1800s and early 1900s that it was more widely recognized that genetics played an important role in development. In the 1930s and 1940s experiments by Josef Warkany and others clearly demonstrated that a wide range of agents such as vitamin A deficiency, nitrogen mustard, alkylating agents, hypoxia, and x-rays could cause malformation in rodents. In 1941, the rubella virus infection was linked to malformed infants. However, many thought that the placental

environment protected the infant during pregnancy. This understanding changed dramatically with the discovery that methylmercury was a developmental toxicant and in the 1960s when thalidomide caused severe abnormalities (see below).

While the knowledge that toxic agents can dramatically affect the developing fetus has only developed relatively recently, there is a long and curious history of toxicology and reproduction. Since ancient times, people have sought ways to stop the onset of reproduction by killing the sperm before they meet the egg. A variety of natural products were used with varying degrees of success. Now, more modern chemicals specifically designed to be toxic to sperm, such as nonoxynol-9, are used as spermicides. There is ongoing effort to develop compounds that are not toxic to people but are toxic to the viruses and bacteria that cause sexually transmitted diseases.

Continuing advances in the biological sciences as well as technology provided greater insight into the reproductive process. This research developed into a detailed understanding of the hormones that control the female reproductive process. In the 1950s and 1960s scientists developed “the pill”, which manipulated the natural estrogen and progesterone hormones and thus the onset of the reproductive process. Early versions of “the pill” had a number of undesirable side effects, which decreased when the drug dosage levels were lowered. In essence, “the pill” is an endocrine disruptor and a desirable one. It was subsequently discovered that many different chemicals could affect or disrupt the endocrine system (see Chapter 15). Some of these chemicals, such as DDT, dioxin, and phthalates, were widely distributed in the environment and began to reduce the fertility of wildlife.

We will now examine in more detail some of the physiological and toxicological aspects of reproduction, pregnancy and development

## **Reproduction**

For all species, reproduction is essential, and most cases start with the merging of the egg and sperm cells. In humans, it is estimated that 50% of all pregnancies end in miscarriage or spontaneous abortion, often before the women realizes that she is pregnant. The most common reason for a pregnancy to fail is chromosomal abnormality. Human cells have 46 chromosomes, which are the genes that control cell function and make us unique. The egg and the sperm cells contain only 23 chromosomes each and must correctly combine during reproduction to create a cell with 46 chromosomes and start the development process. Failures in this process and the early stages of cell division are thought to be the primary reason for early loss of pregnancy.

Successful reproduction (and sex) involves many complex chemical processes that can be disrupted at various points to reduce fertility and conception. Part of this process is under the control of the endocrine system, and chemicals that affect the endocrine system are termed endocrine-disruptors. In the 1950s understanding of the endocrine system led to the development of birth control pills as a way to reduce fertility in humans. This is a desirable and planned use of endocrine disruptors. Subsequently, it was discovered that a

number of chemicals released into the environment could disrupt the endocrine system and reduce fertility of wildlife. Some are concerned that exposure to these chemicals at current levels, such as DDT and dioxin (TCDD), may also affect human fertility. Approximately 15% of couples of reproductive age are infertile. Endocrine disruptors may also affect fetal development, causing demasculationization and feminization of the offspring, which in turn cause reduced fertility in the next generation.

Chemicals can also directly affect male reproductive organs or sperm. Decreased sperm count, decreased sperm motility, or abnormalities can result in male sterility or reduced fertility. For example, occupational exposure to lead can result in infertility due to sperm abnormalities. Male sterility can also result from exposure from the fungicide dibromochloropropane (DBCP). Drugs or chemicals, such as alcohol and narcotics that affect the central nervous system, can also reduce sexual activity and thus fertility.

Female reproductive organs are also vulnerable to the effects of chemicals, including changes in ovulation or menstrual cycle, decreased implantation of the fertilized egg, or inability to maintain pregnancy.

### Examples of chemicals that affect reproduction

Class of chemical	Examples
Endocrine disruptors	DDT, Dioxin, phthalates
Heavy metals	Lead (decreased or abnormal sperm)
Organic Solvents	Toluene, benzene, n-Hexane
Drugs	Alcohol, narcotics, hypotensive drugs, chemotherapeutic agents, steroids, diethylstilbestrol
Pesticides	dibromochloropropane (DBCP), methoxychlor, linuron (herbicide)
Disease	Diabetes

### Pregnancy

The female body undergoes a number of significant changes during pregnancy, some of which can increase vulnerability to toxic compounds. A healthy woman readily adapts to the changes of pregnancy, but it is important to be aware of the consequences of some of these changes. As the pregnancy progresses, the heart rate increases and the amount of blood volume circulated increases, and blood pressure increases. The expanded blood volume results in increased urinary output. Antibiotic prescriptions may need to be altered to accommodate the changes in blood volume and urinary excretion. Respiration is affected as oxygen consumption increases by 15 to 20%. Increased nutrients such as iron and calcium are required during pregnancy, and the gastrointestinal tract changes to increase absorption of selected nutrients. An unintended consequence of this change is an increased absorption of lead during pregnancy. Normally, the adult absorbs 10% of

lead following oral exposure, but because lead substitutes for calcium, the lead absorption during pregnancy is increased to levels similar to that of a child. Liver function decreases, resulting in the decreased metabolism of certain drugs (an increase in half-life). For example, the metabolism of caffeine decreases during the second and third trimesters of pregnancy, resulting higher blood caffeine levels for longer periods of time. The half-life of caffeine in a woman approximately doubles during pregnancy. Caffeine and its metabolites readily cross the placenta, exposing the infant to these chemicals.

### Physiological changes during pregnancy

Cardiovascular	Increased - cardiac output heart rate, blood pressure, blood volume expands
Respiration	Oxygen consumption increases 15 to 20%
Urinary output	Increases
Gut absorption changes	Great absorption of iron and calcium (or toxic compounds such as lead)
Liver metabolism	Decreases for some drugs or chemicals – i.e. caffeine (longer half-life)

### Development

One of the great lessons learned in the past 50 years is that the developing organism is more vulnerable than the adult to the effects of many chemicals. This sensitivity begins at the time of fertilization and continues throughout childhood. This knowledge has been reinforced multiple times through tragic experience with thalidomide, alcohol, methylmercury, lead and many other agents. Our knowledge has progressed from concern only over chemicals that cause physical fetal malformation to recognition that chemicals can cause much more subtle but still harmful effects.

A primary reason for the sensitivity of the developing fetus is the rapidly multiplying number of cells. Not only are the cells rapidly dividing, they are changing into organ-specific cells. The nervous system alone ultimately has over 100 billion nerve cells responsible for transmitting information, as well as over 1 trillion glial or connecting cells. Many of these cells will undergo migration to different regions of the brain, formation of synaptic connections with other cells, and some will even die off in a programmed manner. Throughout gestation, different organs or cells within an organ are going through various growth and development phases. Chemicals can interfere with this process in very unexpected and unpredictable ways.

The infant remains vulnerable to exposure to chemicals following birth. The infant's liver only gradually begins to function after about six months of age. This delay has important implications if the infant is exposed to drugs dependent on liver metabolism. For example, an infant cannot metabolize caffeine. The infant can only excrete the caffeine in the urine, resulting in the half-life of caffeine being measured in days rather than hours, as it would be for an adult. Infants are also growing rapidly and require nutrients such as

calcium and iron, which are readily absorbed from the gastrointestinal tract. Lead, a well-established neurotoxicant, is absorbed along with the calcium, making the infant more vulnerable to any lead exposure. Infants will absorb 50% of lead from oral exposure while adults only absorb 10%. Infants are also much smaller than adults, so that even a small amount of exposure represents a large dose. The hand-to-mouth behavior of an infant increases exposure to contaminants that may be in house hold dust or on toys. In addition, infants have a higher respiratory rate and consume more food relative to their body weight. All these and other factors combine to increase an infant's vulnerability to harmful chemicals. The following table list just a few of the compounds know to affect fetal and infant development.

### Agents and chemicals that affect the developing infant

Metals	Lead, Methylmercury, Arsenic (in animals)
Chemicals	Chlorobiphenyls, Solvents (Toluene), Endocrine disruptors (DDT, TCDD)
Radiation	X-rays (therapeutic), Atomic fallout
Infections	Rubella virus, Herpes simplex virus, Toxoplasmosis, Syphilis
Medical Drugs	Antibiotics (tetracyclines), Anticancer drugs, Anticonvulsants (Valproic Acid), Lithium, Retinoids (Vitamin A), Thalidomide, Diethylstilbestrol (DES), Anticoagulants (Warfarin)
Recreational Drugs	Alcohol (ethanol), Tobacco, Cocaine, Solvent abuse
Plants	Many herbs, Skunk cabbage ( <i>Veratrum californicum</i> ) – sheep & cattle, Parasites (frogs)

### Examples

#### Thalidomide

Thalidomide was introduced in 1956 as sedative (sleeping pill) and to reduce nausea and vomiting during pregnancy. It was withdrawn in 1961 after it was found to be a human teratogen. In 1960 researchers in Australia and Germany observed an unusual increase in rare human malformations of missing limbs (amelia) or shortened long bones (phocomelia) particularly of the arms. It was soon realized that these unusual malformation were associated with the consumption of thalidomide by the mother during early pregnancy. Over 5000 infants were affected by thalidomide, primarily in Europe, Canada, and Australia. There were very few cases in the United States because a reviewer at the U.S. Food and Drug Administration, Frances Kelsey, MD, PhD, demanded additional safety data prior to approval of thalidomide. The routine animal safety studies of that period had failed to predict the adverse effects of thalidomide. This event resulted in significant changes to the animal testing requirements to evaluate the possible teratogenic and developmental effects of drugs. Recently, thalidomide was

approved to treat multiple myeloma and leprosy but with extraordinary precautions being taken because of its developmental effects.

### Ethanol (Alcohol)

"You will conceive and bear a son...now then be careful to take no wine or strong drink and to eat nothing unclean".  
Bible - Judges 13:3-4

The Bible (Judges 13:3-4) cautioned against the consumption of alcohol during pregnancy, but it was not until the 1970s that tragic fetal effects of alcohol were described in detail. Fetal Alcohol Syndrome (FAS), characterized by facial malformations, growth retardation, small head, and greatly reduced intelligence, results from maternal consumption of alcohol. FAS affects 4,000 to 12,000 newborn infants in the United States and from 1 to 3 births per 1000 worldwide per year. A milder form of the developmental effects of alcohol is Fetal Alcohol Effect (FAE). FAE infants are slow to develop and have learning disabilities. FAE affects up to 36,000 infants in the United States, while the number of infants affected worldwide is not known. Alcohol consumption during pregnancy is the most common preventable cause of adverse nervous system development. Alcohol should not be consumed during pregnancy in any amounts.

### Methylmercury

Bacteria convert inorganic mercury (quick silver) to methylmercury ( $\text{CH}_3\text{-Hg}$ ) in an effort to detoxify the mercury. Other organisms including fish consume the bacteria along with the methylmercury. Larger fish consume the smaller fish and accumulate methylmercury in fish muscle. Humans and other animals consume the fish and can be poisoned by the mercury. The developing fetus is particularly sensitive to the adverse developmental effects of methylmercury. The tragic effects of fetal methylmercury exposure were first observed in the 1950s in Minamata, Japan. High exposure and severe developmental effects were observed in other unfortunate incidents including the consumption of seed grain coated with organic mercury in Iraq. Further study revealed that even low levels of methylmercury exposure harm the developing fetus. Across the globe there are advisories on fish consumption related to methylmercury for children and women of childbearing age. This is an unfortunate development because fish are an excellent source of protein and essential fats.

### Lead

The use of lead in paint and as a gasoline additive was one of the greatest public health disasters of the 20<sup>th</sup> century. The Greek physician Dioscorides reported in the 2<sup>nd</sup> century BC that "Lead makes the mind give way". In 1922 the League of Nations banned white-lead interior paint, a move which the United States declined to follow, and a year later

leaded gasoline went on sale in the United States. Our experience with lead emphasizes the sensitivity and vulnerability of the developing nervous system. Not only is the developing nervous system more sensitive to lead, but children absorb more lead than adults following oral exposure and their small size means they receive a larger dose of lead. It is now well accepted that even low levels of lead exposure harm the developing nervous system, reducing the IQ for a lifetime. Regulatory authorities around the world are working to reduce lead exposure by removing lead from gasoline and removing lead-based paint.

### Endocrine disrupting chemicals

Depending upon the circumstance and desired effects, endocrine-disrupting chemicals can be either good or bad. The endocrine system is a finely balanced system responsible for fertility and for many of the feminine and masculine traits we are all familiar with. Endocrine disruptors are used by millions of women in the form of “the pill” to control fertility. Chemicals in birth control pills subtly manipulate the endocrine system to reduce fertility. Unfortunately, we now know that many chemicals are capable of influencing the endocrine systems. When these chemicals, such as DDT and TCDD, are released into the environment, they reduce the fertility of wildlife. Exposure to endocrine disruptors is linked to decreased fertility in shellfish, fish, birds and mammals. Endocrine disruptors such as nonylphenol have been shown to feminize male fish, interfering with reproduction. Some studies have also linked exposure to endocrine disruptors to decreases in human male sperm count. Ironically, urinary metabolites of the birth control pill, as well as the female hormone estrogen pass through waste treatment plants and are released into the aquatic environment, where even small concentrations cause feminization of male fish.

### Herbal medicines during pregnancy

Herbal or “natural” remedies are a multibillion-dollar business that is largely unregulated by government agencies. Herbal products are readily available and are often claimed to improve health, but they also contain many physiologically active chemicals. The ingredients have not undergone the rigorous testing required of medical drugs to determine if there are any undesirable effects on the developing fetus or infant. There is a long history of herbal remedies being used as contraceptives, to induce abortions, or to delay or increase uterine contractions. Any of these possible effects indicate that the herbal product should not be consumed during pregnancy. Manufacturers are not required to demonstrate safety of herbal or “natural” products. Given the sensitivity of the developing fetus, consumption of herbal products during pregnancy should be approached very cautiously.

## **Regulatory Issues**

Government regulatory authorities in Europe, North America, and Asia require extensive testing of food additives and new drugs for reproductive and developmental effects. A



significant expansion of drug testing occurred following the tragic experience with thalidomide. Testing requirements have gradually evolved, becoming more sophisticated with our increased understanding of potential effects on the nervous system.

Reproductive and developmental testing is also required of some pesticides and other chemicals that may be released into the environment or have significant human exposure

A variety of cell-based and animal-based studies can be performed to ensure that a new chemical does not cause reproductive or developmental effects. A battery of tests is done to ensure that there are no harmful effects on fertility. Teratogenicity studies are performed to ensure that the chemical does not cause physical malformations in the offspring from exposure during pregnancy. Multiple generations of animals may be continuously exposed to ensure that a compound safe.

There are an estimated 50,000 to 60,000 industrial chemicals in common use. We know very little about the reproductive and developmental effects of the majority of these chemicals. In addition, there are no safety testing requirements for “natural” products. In 1986, the voters of the State of California passed a law requiring that the Governor of the state “to publish, at least annually, a list of chemicals known to the state to cause cancer or reproductive toxicity”. This effort is an excellent source of information on chemicals that can cause birth defects or reproductive harm.

### **Recommendations and conclusions**

Awareness about the potential effects of chemicals on reproduction, pregnancy, and development needs increased attention from individuals as well as society. A growing body of knowledge indicates that the developing organism is more vulnerable to the adverse effects of chemical exposure. Planning for a healthy baby is best started preconception, continue throughout pregnancy and subsequent fetal development. Exposure to hazardous chemicals should be reduced or eliminated to prevent adverse developmental effects.

### **More Information and References**

#### **Slide Presentation**

- Pregnancy and Developmental Toxicology presentation material and references online is available at Toxipedia. Online: [www.asmalldoseoftoxicology.org](http://www.asmalldoseoftoxicology.org)  
Web site contains presentation material related to this book for each chapter.

#### **European, Asian, and International Agencies**

- European Teratology Society (ETS). Online: < <http://www.etsoc.com/>> (accessed: 19 October 2020).  
The society is dedicated to the prevention of adverse effects on reproduction and development.

- The Thalidomide Victims Association of Canada. Online: <<http://www.thalidomide.ca>> (accessed: 19 October 2020). Information on thalidomide in English or French.
- WHO Pregnancy. Online: < <https://www.who.int/health-topics/maternal-health> > (accessed: 19 October 2020). Information from World Health Organization on efforts to improve pregnancy outcome.

### **North American Agencies**

- American College of Obstetricians and Gynecologists (ACOG) <https://www.acog.org> (accessed: 19 October 2020). The scientific evidence over the last 15 years shows that exposure to toxic environmental agents before conception and during pregnancy can have significant and long-lasting effects on reproductive health’
- Center for the Evaluation of Risks to Human Reproduction (CERHR) - The National Toxicology Program. Online: < <https://pubmed.ncbi.nlm.nih.gov/15729732/> > (accessed: 19 October 2020). CERHR web site has “information about potentially hazardous effects of chemicals on human reproduction and development.”
- Developmental & Reproductive Toxicity NTP is located at the National Institute of Environmental Health Sciences, part of the National Institutes of Health. Online: <https://ntp.niehs.nih.gov/whatwestudy/testpgm/devrepro/index.html> - (accessed: 19 October 2020).
- National Agricultural Library - Nutrition During Pregnancy Online: <<http://vm.cfsan.fda.gov/~dms/wh-preg.html>> (accessed: 19 October 2020) This web site contains an extensive for pregnant women.
- US Centers for Disease Control and Prevention (CDC) – Health Topic: Pregnancy. Online: <<http://www.cdc.gov/pregnancy/>> (accessed: 19 October 2020) Site contains information and links on pregnancy and fetal development.
- California – Office of Environmental Health Hazard Assessment – Proposition 65. Online: <<http://www.oehha.ca.gov/prop65.html>> (accessed: 19 2009) Passed in 1986 by the voters of California, Proposition 65 “requires the Governor to publish, at least annually, a list of chemicals known to the state to cause cancer or reproductive toxicity”.

### **Non-Government Organizations**

- The Society for Birth Defects Research and Prevention (BDRP) (was the Teratology Society). Online: < <https://birthdefectsresearch.org/> > Accessed: 19 October 2020).  
BDRP is the premier source for cutting-edge research and authoritative information related to birth defects and other disorders of developmental origin.
- Society for Developmental Biology. Online: < <http://www.sdbonline.org/>> (accessed: 19 October 2020).  
“The purpose of the Society is to further the study of development in all organisms.”
- March of Dimes. Online: <<http://www.modimes.org>> (accessed: 19 October 2020).  
“March of Dimes leads the fight for the health of all moms and babies. We believe that every baby deserves the best possible start. Unfortunately, not all babies get one. We are changing that.”

### **Wikipedia**

- Developmental toxicity – Online:  
[https://en.wikipedia.org/wiki/Developmental\\_toxicity](https://en.wikipedia.org/wiki/Developmental_toxicity). (accessed: 19 October 2020).

### **References**

- Riddle, John M. Eve's Herbs: A History of Contraception and Abortion in the West., Harvard University Press; Cambridge, Mass 1999, 352 pages.
- World Health Organization, Geneva Switzerland. Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals. Environmental Health Criteria 237 (2007). <http://www.who.int/ipcs/publications/ehc/ehc237.pdf>. (accessed: 26 July 2009).
- This volume addresses the unique vulnerability of children to social economic factors, nutrition, environmental chemicals and other hazards.
- Hood, R.D. (2005) Developmental and Reproductive Toxicology: A Practical Approach, 2nd edition CRC Press, Boca Raton, FL