



## Review Article

### HUMAN TERATOGENS AND THEIR EFFECTS: A CRITICAL EVALUATION

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#### ABSTRACT

Although prescription drug use is common during pregnancy, the human teratogenic risks are undetermined for more than 90% of drug treatments approved in the USA during the past decades. A particular birth defect may have its origins through multiple mechanisms and possible exposures, including medications. A specific pathogenic process may result in different outcomes depending upon factors such as embryonic age at which a drug is administered, duration and dose of exposure and genetic susceptibility. This review focuses on the teratogenic mechanisms with their effects associated with varieties of natural as well as synthetic substances. Mechanisms were included only if they are associated with major structural birth defects and medications that are used relatively frequently by women of reproductive age. Identifying teratogenic mechanisms may not only be relevant for etiologic and post-marketing research, but may also have implications for drug development and prescribing behavior for women of reproductive age, especially since combinations of seemingly unrelated prescription and over the counter medications may utilize similar teratogenic mechanisms with a resultant increased risk of birth defects.

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#### INTRODUCTION

Teratogenesis refers to the production of defects in the fetus. A teratogenic agent is responsible for producing such a defect. The term teratogen is cited in the context of causing anatomical defects in an embryo that was previously differentiating normally (Im Zomerdijk, *et al.*, 2014). Teratogens are substances that may produce physical or functional defects in the human embryo or fetus after the pregnant woman is exposed to the substance. Alcohol and cocaine are examples of such substances. Exposure to the teratogen affects the fetus or embryo in a variety of ways, such as the duration of exposure, the amount of teratogenic substance, and the stage of development the embryo or fetus is in during the exposure (Yoav Mayshar, 2011). They affect the embryo or fetus in a number of ways, causing physical malformations, problems in the behavioral or emotional development of the child, and decreased intellectual quotient (IQ) in the child. Additionally, teratogens may also affect pregnancies and cause complications such as preterm labors, spontaneous abortions, or miscarriages.

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Teratogens are classified into four types: physical agents, metabolic conditions, infection, and finally, drugs and chemicals (Lim *et al.*, 2011).

##### History

The word teratogen originates from the Greek word for monster, teratos. Isidore Geoffroy Saint-Hilaire, a physician from Paris, France, defined it in 1932 in *Histoire générale et particulière des anomalies de l'organisation chez l'homme et les animaux* (General and Particular History of Structural Monstrosities in Man and Animals). People had sought explanations for abnormal human and animal development, however, for centuries, and they had developed different theories about the causes for the abnormalities. In Babylon, many said that infants with congenital malformations, or structural abnormalities present at birth, were constellations in human forms as well as fortune-tellers (Allen *et al.*, 2014). Hebrews said that abnormal development resulted from the deformed person's association with the devil. Aristotle, who lived in Athens, Greece in the fourth century, B.C., deemed birth defects as disturbances in reproduction rather than supernatural occurrences. Aristotle and Hippocrates, a physician who practiced in Greece in the fifth century B.C., claimed that a pregnant woman's experiences or emotions, which became

called maternal impressions, can affect the formation of the fetus. The theory of maternal impressions persisted until the early 1900s, despite evidence to the contrary by John Hunter, a surgeon in Scotland in the late eighteenth century (Angles *et al.*, 1990). At the beginning of the 19th century, Johann Friedrich Meckel, the Younger, an anatomist from Halle, Germany, asserted that deviations from the normal developmental process caused malformations. Meckel wrote his doctoral thesis on an anatomical study of heart disease in 1802 and founded a journal dedicated to teratology, *Journal für anatomische Varietäten, feinere und pathologische Anatomie*. Meckel examined anatomical defects and their causes. Because he asserted that to understand abnormal development, one must first understand normal development, he documented his observations of normal embryological development of mammals in a sequence of forms.<sup>[6]</sup> Meckel also categorized abnormal development into four basic types: reduced or absent body parts (insufficient generative energy), enlarged or multiple body parts (excessive energy), aberration of form and of position, and hermaphroditism, which included deformities such as ambiguous genitalia (Barrow and Mark, 1971).

Following Meckel, scientists in the nineteenth century began experimental studies to detect teratogens. Etienne Geoffroy Saint-Hilaire in Paris, France, experimented on chick eggs by subjecting them to pricking, inversion, jarring, and abnormally high or low temperatures to study the resulting malformations; he believed that certain manipulations could invoke specific deformations. Although deformities materialized, Saint-Hilaire didn't identify their exact causes. His son Isidore then reported the results of the experiments between the years of 1832 and 1837 in his three-volume *Traité de Tératologie* (Treatise on Teratology). Other scientists following Saint-Hilaire also experimented with teratogens, notably Camille Dareste in France, who successfully produced abnormalities in chick embryos during twenty-two years of experiments until his death in 1899 (Brown-Woodman *et al.*, 1988). Since approximately half of the pregnancies in the USA are unintended, many women expose their unborn children to drugs before they know they are pregnant. Furthermore, prescription drug use is common during pregnancy in many other countries as well, with prevalence estimates ranging from 44 to 79% in several European countries.

Because pregnant women were often excluded from clinical trials and data from animal studies are not always predictive for a teratogenic effect in humans, drug use by pregnant women can be considered experimental in most instances. Nevertheless, the use of medication is sometimes inevitable in the treatment of women of reproductive age and during pregnancy (<http://www.cdc.gov/cmrv/index.html>, 2012). Although it has clearly been shown that some drugs, e.g. thalidomide and isotretinoin, can produce birth defects, the teratogenic risks in human pregnancy are undetermined for more than 90% of drug treatments approved in the USA in the last decades. Birth defects are the leading cause of infant mortality and the etiologic pathways are largely unknown for many defects. A particular birth defect may be caused by many different factors (e.g. genetics, environmental agents, medications, physical conditions) as well as by different mechanisms, whereas a specific pathogenic process may result in different outcomes for chemical or drug exposures depending upon such factors as embryonic age, duration and dose of exposure and genetic

susceptibility (<http://www.cdc.gov/parasites/toxoplasmosis/>, 2012). In addition, maternal determinants, including drug administration, distribution, metabolism, and excretion, may also play an important role. Identifying these mechanisms may be relevant for drug development, (post-marketing) research and prescribing of medications to women in their reproductive years.

**Behavioral teratogens:** Teratogens that tend to harm the prenatal brain, affecting the future child's intellectual and emotional functioning (Chambers *et al.*, 1997). Although all teratogens increase the risk of harm to the developing child, none always cause damage; the ultimate impact depends on the complex interplay of many factors.

### Principles of Teratology

Teratology is the study of environmentally induced congenital anomalies. A teratogen is an agent, which by acting on the developing embryo or foetus, can cause a structural anomaly. To date, very few drugs are proven teratogens. However, malformations induced by drugs are important because they are potentially preventable (<http://www.chw.org/display/PPF/DocID/22924/router.asp>, 2012). Teratogens act with specificity in that they produce specific abnormalities at specific times during gestation. For example, thalidomide produces limb phocomelia, while valproic acid and carbamazepine produce neural tube defects. Other teratogens are associated with recognizable patterns of malformations, for example, phenytoin with foetal hydantoin syndrome and coumarin anticoagulants with foetal warfarin syndrome. Teratogenic specificity also applies to species, for example, aspirin and corticosteroids have been found to be teratogenic in mice and rats but appear to be safe in humans. Thalidomide, on the other hand, was not shown to be teratogenic in rats, a tragic fact that resulted in significant human morbidity (Clark and Owen, 1969).

Teratogens may demonstrate a dose-effect relationship. At low doses there can be no effect, at intermediate doses the characteristic pattern of malformations will result, and at high dose the embryo will be killed. A dose-response may be considered essential in establishing teratogenicity in animals, but is uncommonly demonstrated in sufficient data among humans. A threshold dose is the dosage below which the incidence of adverse effects is not statistically greater than that of controls. With most agents, a dose threshold for teratogenic effects has not been determined; however they are usually well below levels required to cause toxicity in adults (Cockroft *et al.*, 1975). Teratogens must reach the developing conceptus in sufficient amounts to cause their effects. Large molecules with molecular weights greater than 1,000 do not easily cross the placenta into the embryonic-foetal bloodstream to exert potential teratogenic effect. Other factors influencing the rate and extent of placental transfer of xenobiotics include polarity, lipid solubility and the existence of a specific protein carrier (Cockroft *et al.*, 1978).

### Causes

#### Causes of teratogenesis can broadly be classified as

- Toxic substances, such as, for humans, drugs in pregnancy and environmental toxins in pregnancy.
- Vertically transmitted infection

- Lack of nutrients. For example, lack of folic acid in the nutrition in pregnancy for humans can result in spina bifida (Cockroft *et al.*, 1978).
- Physical restraint. An example is Potter syndrome due to oligohydramnios in humans.
- Genetic disorders (Cockroft *et al.*, 1978).

### Factors influencing the effect of teratogens

- **Timing:** the effect of a teratogen on the developing organism depends on what period in the pregnancy (in development) the child is exposed to the teratogen.
- some teratogens cause damage only during specific days or weeks in early pregnancy
- other teratogens are harmful at any time during the pregnancy---for example, for behavioral teratogens, there is no safe period---the brain and nervous system can be harmed throughout the pregnancy (Cohlan and Sidney, 1953).
- **critical period:** in prenatal development, the time when a particular organ or other body part is most susceptible to teratogenic damage.
- **Exposure:** the effect of a teratogen on the developing organism also depends on the dose and/or frequency of exposure of/to the teratogen.
- **Threshold effect:** the phenomenon in which a particular teratogen is relatively harmless in small doses but becomes harmful when exposure reaches a certain level (the threshold).
- **Interaction effect:** the phenomenon in which a particular teratogen's potential for causing harm increases when it is combined with another teratogen or another risk factor.

**Genetic variability:** another factor that determines whether a specific teratogen will be harmful is the genetic make-up of the developing organism (Dareste and Camille, ?).

- possessing and not possessing certain genes may make the developing child more susceptible to the effect of a teratogen.

### Cellular Action of a Teratogen

A teratogen may potentially affect embryogenesis by causing gene mutation, chromosome breakage or nondisjunction, depletion or inhibition of precursors or substrates, depletion of energy sources, inhibition of enzymes, or changes in intracellular milieu secondary to changes in membrane integrity (Edwards and Marshall, 1986). These lead to cell death, reduced cell division, failure of expected interaction between cells, disruption of cell migration, or mechanical disruption. Regardless of the initial mechanism or the intermediary effect, the ultimate result usually is an organ with too few cells. The critical mass necessary for induction or continuation of differentiation is lacking; thus, the particular organ system fails to develop (Finnell and Richard, 1999). Of course, a few anomalies (e.g., polydactyly or labioscrotal fusion) could result either from increased cell proliferation or from failure of localized cell degeneration.

### Variables Affecting Teratogenesis

**Specificity of Agent:** Some agents are more teratogenic than others. Less obvious is the axiom that an agent may be teratogenic in only certain species.

For example, thalidomide produces phocomelia in primates but not in rodents. Within a given species, however, a given teratogen may affect many organ systems. Some organ systems are preferentially affected, but the pattern of anomalies also reflects the organ systems differentiating at the time the agent was administered. For example, administering thalidomide between days 35 and 37 causes ear malformations; administering the agent between days 41 and 44 causes amelia or phocomelia (Friedman and Jan, 2010).

**Dosage:** Although high doses of a proven teratogen usually are more deleterious than low doses, this is not always true. At any given time, an embryo can respond to a teratogen in one of three ways: (1) at a low dose, there is no effect; (2) at an intermediate dose, a pattern of organ-specific malformations can result; and (3) at a high dose, the embryo may be killed, causing the organ-specific teratogenic action to go unrecognized. In animals, teratogens exert their action within a relatively narrow dose range, usually one-fourth to one-half the average dose that would kill the mother (Garfield and Eugene, 1986). The effect also depends on the developmental stage during which the drug is administered. That is, an agent may be teratogenic only at a higher or lower dose at a different stage. Similarly, at one dose level an agent might be lethal yet not teratogenic, whereas at another level it could be either lethal or teratogenic.

**Stage of Embryonic Development:** The time during embryogenesis when the fetus is exposed to a potential teratogen is crucial. Three stages of susceptibility may be identified, with these times varying from one organ system to another: (1) the embryo is relatively resistant to teratogenic insults during the first few weeks of life, perhaps 2 weeks after conception in humans (Germain *et al.*, 1985). A large insult might kill the embryo, but surviving embryos usually manifest no organ-specific anomalies. Presumably, the explanation is that early embryonic cells have not differentiated irrevocably. If one cell is destroyed, a surviving cell may be able to assume its function; (2) organogenesis, the process of organ differentiation, occurs in most human organ systems between embryonic weeks 3 to 8 (menstrual weeks 5–10); however, differentiating occurs later in the brain and gonads. During organogenesis, susceptibility to teratogens is maximal. Teratogens act in an organ-specific fashion; a teratogen may affect one organ system at one stage of development but another system at another stage. Development of the brain and gonadal tissues continues in the second and third trimesters of pregnancy. Therefore, drug use at this time in pregnancy is a concern, although the effects may not be recognized until later in life. Some of the uterine anomalies resulting from diethylstilbestrol occurred with exposure as late as 20 weeks but were not recognized until after puberty. The brain continues to develop throughout pregnancy and the neonatal period (Goldstein *et al.*, 1929).

**Genotype:** The genotype of the mother and the fetus influences the efficacy of a teratogen. For example, genotype determines the prevalence of cleft palate in inbred strains of mice whose mothers are administered cortisol during pregnancy (Graham *et al.*, 1989). Daily administration of 10-mg cortisol during days 11 through 14 produced cleft palate in 100% of offspring of A/Jax parents, in 68% of offspring of C3H parents, and in only 12% of offspring of CBA parents.<sup>[24]</sup> Differences in frequencies of anomalies between various strains presumably are genetic.

In humans, only 18% of girls had clitoral hypertrophy after administration of norethindrone to their mothers during a specific time and at a specific dose (Graham *et al.*, 1998). Another example in humans involves a woman who received diphenylhydantoin during a pregnancy in which she carried dizygotic twins sired by different men (Gregg and Norman McAlister, 1941). The infant sired by a white man showed the hydantoin embryopathy; the infant sired by the black man was normal. Because the environment was identical for the co-twins, any differences in teratogenic effects must reflect genetic differences in susceptibility.

**Drug Interactions:** Simultaneous administration of two teratogens may produce a different effect from that existing when the two are administered separately. For example, folic acid reduces the frequency of cortisol-induced teratogenesis in mice (Hale and Fred, 2014), possibly because of induction of enzyme systems that catabolize the teratogen or compete for binding sites. Conversely, one agent may enhance the teratogenic potential of another. For example, the food preservative benzoic acid enhances aspirin teratogenicity in rats (Hellmann and Wilhelmine, 1977). Possible mechanisms include enzyme inhibition, destruction of enzyme-producing cells, and saturation of binding sites on carrier proteins that, if available, would decrease levels of the unbound active teratogen.

**Other Factors:** Variability in teratogenic response sometimes is associated with other environmental or morphologic factors: maternal or fetal weight, in utero position of the fetus, proximity to other affected litter mates, uterine vasculature, and diet. However, further investigation usually reveals that these factors are correlated with other factors already cited. For example, the inverse correlation between maternal weight and susceptibility of the fetus to cortisol-induced cleft palate is related not to weight per se but to dose per unit mass (Hill and Robert, 1983).

### Timing of Embryonic and Foetal Development

The effect produced by a teratogenic agent depends upon the developmental stage in which the foetus is exposed to the agent. Several important phases in human development are recognized: The time from conception until implantation known as the "all or none" period, when insults to the embryo are likely to result in death of the conceptus and miscarriage (or resorption), or in intact survival. At this stage, the embryo is undifferentiated and repair and recovery are possible through multiplication of the still totipotent cells to replace those which have been lost. Exposure of embryos to teratogens during the preimplantation stage usually does not cause congenital malformations, unless the agent persists in the body beyond this period (Kalter and Harold, 2003). The embryonic period, from 18 to 54-60 days after conception is the period when the basic steps in organogenesis occur. This is the period of maximum sensitivity to teratogenicity since not only are tissues differentiating rapidly but damage to them becomes irreparable. Exposure to teratogenic agents during this period has the greatest likelihood of causing a structural anomaly. Since teratogens are capable of affecting many organ systems, the pattern of anomalies produced depends upon which systems are differentiating at the time of teratogenic exposure (Lary *et al.*, 1982).

The foetal phase, from the end of the embryonic stage to term, is the period when growth and functional maturation of organs and systems already formed occurs. Teratogen exposure in this period will affect foetal growth (e.g., intrauterine growth retardation), the size of a specific organ, or the function of the organ, rather than cause gross structural anomalies. The term foetal toxicity is commonly used to describe such an effect. Of particular interest is the potential effect of psychoactive agents (e.g., antidepressants, antiepileptics, alcohol and other drugs of abuse) on the developing central nervous system, which has led to a new field of behavioural teratology (Lary, 1983).

### Evaluation of Drugs for Potential Teratogenicity in Humans

All new drug applications filed with the United States Food and Drug Administration (FDA) include data from animal developmental and reproductive-toxicologic studies. Although major new teratogenic drugs in humans have been predicted from animal studies, there are problems in extrapolating animal data to humans. Animals have a different "gestational clock" to humans, there is marked interspecies variability in susceptibility to teratogens and no experimental animal is metabolically and physiologically identical to humans (Lenz *et al.*, 1962). Animal studies are important because, in some instances, they have shed light on mechanisms of teratogenicity and because when an agent causes similar patterns of anomalies in several species, human teratogenesis should also be suspected. For obvious ethical considerations no studies of teratogenicity are conducted during embryogenesis in humans. The studies are, therefore, either retrospective in nature (case reports, case-series and case-control studies), or prospective cohort studies, where a specific maternal exposure in question is ascertained during pregnancy and the pregnancy outcome is evaluated and compared to a control group. Retrospective case-control studies are less costly and easier to conduct but they have other weaknesses such as the inaccuracy of data collected from medical records and recall bias (Lipson *et al.*, 1988). For the rare malformation/rare exposure, the case report method is commonly used to suggest association, but case reports are unable to prove or disprove teratogenicity, nor can they give estimation of teratogenic risk. Human teratogenicity is supported by:

- A recognizable pattern of anomalies.
- A statistically higher prevalence of a particular anomaly in patients exposed to an agent than in appropriate controls.
- Presence of the agent during the stage of organogenesis of the affected organ system.
- Decreased incidence of the anomaly in the population prior to the introduction of the agent (Schardein, 1986).
- Production of the anomaly in experimental animals by administering the agent in the critical period of organogenesis.

### Proof of Teratogenicity

Teratogens usually are first identified by alert clinicians. Unfortunately, many agents are falsely implicated, requiring case reports to be assessed critically. Retrospective case-control designs thus are commonly used. Such an experimental design is efficient in identifying teratogens but vulnerable to false-positive conclusions, because recall biases and memory biases render control and subject (mothers of affected infants) unequal in incentive.

That is, normal controls have less incentive to recollect events than women having anomalous infants (an “anomaly control,” a woman having an abnormal outcome, but not that being tested, can be used to minimize this problem) (Rubin *et al.*, 1986). However, definitive cohort (prospective) studies are expensive and complex. Thus, there is no ideal way of assessing teratogens. A variety of approaches can be used, usually leading to a scientific consensus eventually. Confounding any study is knowledge that similar congenital anomalies occur in women not exposed to teratogens. Given these caveats, it is not surprising that proof of teratogenicity is difficult. Observations such as the following can implicate a particular agent: (1) the agent was associated more often with subjects having a particular anomaly than with suitable controls; (2) an anomaly or pattern of anomalies is consistently associated with the suspected teratogen; (3) the agent was presented during the stage of organogenesis when the anomaly would have been likely to occur; (4) the anomaly was less common before the time the potential teratogen was available (e.g., phocomelia was almost unreported before the time thalidomide was introduced); and (5) the anomaly can be produced in experimental animals by administration of the agent during a stage of organogenesis comparable with that believed to be involved in causing the anomaly in humans (Wilson, 1973). Epidemiological pitfalls in assessing human teratogens are myriad, and several different surveillance methods are used. No single method or design is universally reliable (Shepard, 1979; Teratology Society Public Affairs Committee, 1994 and Shepard, 1994).

### Harmful Teratogens

**Ionizing Radiation-** High dose of ionizing radiation over a short period of time leads to abnormal brain development, mental retardation, and leukemia in children. This information has come from studies of consequences the atomic bomb explosions over Hiroshima and Nagasaki. However, medical diagnostic x-ray procedures have much smaller dose of radiation and appear to be safe even with several performed procedures during pregnancy. There is a different situation with a computer tomography (CT) diagnostic procedure (Briggs *et al.*, 1998). Even a single computer tomography scan (CT-scan) creates a radiation exposure dose that equals to tens of x-rays and should be avoided during pregnancy.

**Chemicals:** Organic mercury (methylmercury) compounds can be extremely dangerous for the developing fetus in a small dose that would not bring any symptoms to an adult human. Pregnant women should not eat some type of fish with possible high methylmercury levels as this mercury compound would be easily delivered to the baby's body (Koren, 1994). Organic mercury exposure can lead to damage of neural system, mental retardation, behavioral and cognitive problems, and blindness in a baby. Lead exposure, received through some leaded glass products and pottery that have contact with food, can be a culprit of spontaneous abortions, delayed fetal development, increased risk of infant death, or abnormal mental or physical development of the child. Large doses of potassium iodine, found in anti-cough syrups or medical cocktails for x-ray diagnostic, can be a cause of abnormal thyroid development and function in a fetus. This effect will lead to mental retardation or cretinism in a child (Shiota, 1982). Polychlorinated biphenyls (PCBs) were linked to delayed fetal growth, abnormal neural system development, and impaired behavioral and cognitive functions in a child.

Products containing PCBs were banned in the late 1970s. Since that time level of PCBs in the environment is gradually declining. Pregnant women should avoid PCBs exposure by not consuming some types of fish, washing and possibly peeling fruits and vegetables before eating them, and not handling old fluorescent lamps or old mechanisms with hydraulic or heat transfer fluids (Fisher and Smith, 1980). **Toxoplasma-** *Toxoplasma* is a single-celled protozoa—“pre-animal”—that can be an infection of other animals. Cats are known hosts of *Toxoplasma* and a human might be infected after handling the infected cat's feces and not washing hands properly after that action. *Toxoplasma* may also be contracted by eating undercooked meats, trying raw minced meat while cooking, or not washing hands or utensils properly after meat handling. If a pregnant woman was never exposed to *Toxoplasma* before pregnancy and had not developed the immunity, the obtaining of *Toxoplasma* infection during pregnancy can be extremely dangerous to the baby (Edwards, 1969). It can lead to spontaneous abortion or delivery of the dead infant; or the baby might have underdevelopment of the brain, brain calcifications, blindness, and seizures.

**Syphilis Bacteria-** Syphilis is a sexually transmitted disease caused by very small, corkscrew shaped bacteria—*Treponemes*. If left untreated, this disease progresses through three clinical stages, causing severe damage to a person's health. If a pregnant woman has syphilis and is not treated quickly, these tiny bacteria travel with her blood to the baby's body. Syphilis infection can be a cause of fetal death and spontaneous abortion, or can result in the delivery of the dead baby, or the baby can die within several days of life. If the baby survives, there is a high risk that this baby will have copious nasal discharge (snuffles) packed with *Treponemes* and severe inflammatory reaction as a consequence, destroying nasal cartilages and bones (Edwards, 1967). The baby will likely suffer from liver and spleen enlargement and dysfunction, meningitis or meningoencephalitis, and inflammatory skin rash—all of these are symptoms of early congenital syphilis. Some babies will not develop signs of early congenital syphilis, but around eight years of age or older they will demonstrate symptoms of late congenital syphilis: their vision will become deteriorated due to inflammatory changes in eyes, some of their central permanent teeth will have unusual conic shape and notching, and they may become deaf with complaining of vertigo and ringing in the ears. Their bones will be deformed, resulting in the look of “saddle” nose and “saber” shins (Edwards, 1971).

**Viruses-** Viruses are incredibly small live particles composed of RNA or DNA that cannot produce their own energy for multiplication. In fact, they are parasites that live on certain cells of other creatures, called viral hosts. A virus penetrates the host's cell and uses the host's cellular mechanism for its own multiplication by millions of viral copies inside of the cell. Finally, millions of new viruses will leave the cell either killing it or creating certain damage (Jones *et al.*, 1995). These new millions of viruses will target other cells of the viral host, one virus per one cell, to produce more viral copies and create more damage on the host's cells. Most of the time, the host's immune system will defeat these invaders. However, loss of certain cells or their damage in a growing fetus can be catastrophic. Certain types of viruses are well-known to create birth defects. Rubella or German measles virus exposure to the fetus can be a culprit of congenital heart defects, deafness, and blindness.

Rubella virus can also be a cause of abnormal brain development and other internal organs, and creates characteristic bluish-red skin lesions known as “blueberry muffin spots.” (Wang *et al.*, 2009) Fortunately, if the mother had rubella in the past or was vaccinated against the rubella virus before pregnancy, her immune system will eliminate the rubella virus before it can reach the fetus. Cytomegalovirus (CMV) is the most common type of fetal infection because of the ubiquitous nature of this virus. Fortunately, 90% of the babies born with CMV exposure have no symptoms. However, in some babies, CMV can be a cause of underdevelopment of the brain, calcifications inside of the brain, blindness, deafness, dysfunction of the liver and spleen, jaundice or lesions on the skin known as “blueberry muffin spots.” (Gomaa *et al.*, 2002; Rischitelli *et al.*, 2006 and Goldhaber *et al.*, 1988). Herpes virus infection, in about 5% of cases, can infect a baby in the uterus. The consequences are catastrophic—from fetal death to permanent problems like underdevelopment and/or calcification of the brain, blindness, or abnormal limb formation. If the herpes virus was acquired by the baby during or just after the delivery, the baby will get herpetic pneumonia or meningoencephalitis (AMA, 1985). Varicella zoster virus is a cause of chickenpox (mostly in children), and herpes zoster or shingles (mostly in seniors). If a pregnant woman would contract varicella zoster virus for the first time during the pregnancy, there is a 25-40% risk that the fetus will have underdeveloped limbs, brain or eye malformations, and specific zig-zag skin scarring (Levine and Muenke, 1991). If varicella zoster virus was transmitted to the baby just before the delivery, an infant can suffer from severe varicella zoster pneumonia. Like with rubella virus, if the mother had chickenpox in the past or was vaccinated against the rubella virus in her childhood or before pregnancy, her immune system will eliminate the rubella virus before it can reach the baby (Levine, 1991). Congenital cytomegalovirus infection is the most common viral infection of the fetus. Infection of the early embryo during the first trimester most commonly results in spontaneous termination. Exposure later in the pregnancy results in intrauterine growth retardation, micromelia, chorioretinitis, blindness, microcephaly, cerebral calcifications, mental retardation, and hepatosplenomegaly (Murakami, 1971).

### Thermodisruptions

Hyperthermia is defined as a body temperature of at least 38.9°C and is an antimitotic teratogen after exposure between weeks 4 and 14 (Amin-zaki *et al.*, 1979; Murata *et al.*, 2007 and Warkany, 1988). In a retrospective study, Smith *et al* (Cohen, 1994) presented 21 patients who had been exposed during pregnancy to hyperthermia caused by infections or by sauna bathing. Severe mental deficiency, seizures in infancy, microphthalmia, midface hypoplasia, and mild distal limb abnormalities were associated with hyperthermia (Lipson *et al.*, 1988). Infants exposed to maternal hyperthermia at 7 to 16 wk of gestation have hypotonia, neurogenic arthrogryposis, or CNS dysgenesis (Jacobson, 1992). Shiota (Berkowitz, 1986) studied 100 embryos with CNS defects and found that 18% of mothers of anencephalic infants had experienced hyperthermia at the critical embryonic stage (Schardein, 1986). Occipital encephalocele has also been related to hyperthermia (Berkowitz, 1986). Embryonic studies in guinea pigs and rats have highlighted the sensitivity of brain growth to elevated temperatures (Schou, 1968; Giles *et al.*, 2006 and Cohen *et al.*, 1994).

Hypothermia is defined as a core body temperature of less than 35°C. Cardiopulmonary bypass in a pregnant patient is associated with a fetal mortality rate of 16% to 33%. One infant with multiple congenital defects has been described. Another infant had severe disruptive defects of the brain and distal spinal cord, suggesting hypoperfusion injuries related to hypothermia (Longo, 1980).

### Toxic Metals

**Lead:** A woman who has had lead poisoning can pass lead on to her fetus if she becomes pregnant, even if she no longer is exposed to lead. This happens because more than 90% of the lead may be stored in bone and released into the bloodstream years later. Blood Pb levels of  $\geq 10$   $\mu\text{g}/\text{dl}$  are considered to be elevated but not dangerously high. The term “lead poisoning” refers to blood Pb levels  $\geq 50$   $\mu\text{g}/\text{dl}$ . Deleterious effects of lead exposure have not been convincingly shown to occur at blood Pb levels  $\leq 20$   $\mu\text{g}/\text{dl}$ . Lead crosses the placenta as early as the 12th to 14th weeks of gestation and accumulates in fetal tissue (Beckman and Brent, 1984; Jacobson and Jacobson, 1997; Arnold and Wilkens-Haug, 1990). The adverse effects of lead include spontaneous abortion and stillbirth. A small but significant increase in minor malformations, including hemangiomas, lymphangiomas, hydroceles, skin tags, skin papillae, and undescended testes, was seen in infants with high lead levels in the umbilical blood (Beckman and Brent, 1984; Jacobson and Jacobson, 1997; Arnold and Wilkens-Haug, 1990 and Hersh *et al.*, 1985). The VACTERL (vertebral, anal, cardiac, tracheoesophageal fistula, renal and limb abnormalities) association has been reported with prenatal exposure to high lead levels, similar to animal models of lead teratogenicity (Jacobson and Jacobson, 1997).

**Mercury:** Organic forms of mercury are more toxic than the inorganic forms. Methylmercury, the most toxic organic form, causes severe brain damage, as in Minamata disease, which occurred in epidemic proportions on the Japanese island of Minamata after maternal ingestion (by both humans and cats) of methylmercury-contaminated shellfish (Arnold and Wilkens-Haug, 1990). A similar exposure occurred in Iraq after the ingestion of bread prepared from wheat treated with methylmercury that was used as a fungicide (Costa *et al.*, 2002). The blood Hg assay measures exposure to all types of mercury, but because mercury remains in the bloodstream for only a few days after exposure, the test should be done soon after exposure. Most non-exposed people have blood Hg levels of 0 to 2  $\mu\text{g}/\text{dl}$ . Levels  $> 2.8$   $\mu\text{g}/\text{dl}$  are required to be reported to the state health department. The assay can be influenced by eating fish that contain mercury. Early effects of mercury toxicity have been found when the blood Hg level exceeds 3  $\mu\text{g}/\text{dl}$  (deSilva *et al.*, 1990). Methylmercury poisoning produces atrophy of the granular layer of the cerebellum and spongiose softening in the visual cortex and other cortical areas of the brain (Donald *et al.*, 1991); polyneuritis can also occur.

**Lithium:** it is used in the treatment of bipolar disorder. If possible lithium should be withheld during the first trimester of pregnancy and women taking lithium should not breast feed their infants. The ratio of lithium concentrations in umbilical cord blood to maternal blood is uniform (mean  $1.05 \pm 0.13$ ). Infants with high lithium concentrations ( $> 0.64$  mmol/L) at delivery have significantly lower Apgar scores.

High lithium concentrations at delivery are associated with perinatal complications, and lithium concentrations can be reduced by brief suspension of therapy proximate to delivery. Cardiovascular malformations, in particular Ebstein anomaly and tricuspid atresia, have been related to lithium exposure (Utidjian, 1974; McDonald, 1987; Hersh, 1989 and Pearson *et al.*, 1994). Infants exposed in utero to lithium may experience transient lethargy, hypotonia, cyanosis, poor feeding, and poor respiratory efforts during the early neonatal period (McDonald, 1987). Other defects that have been noted in infants exposed to lithium in utero include malformations of the CNS, ear, and ureter, altered thyroid and cardiac function, and congenital goiter (Hersh, 1989). Some abnormalities (mainly heart defects such as Ebstein malformation) in the newborn occur in 6% to 10% of pregnancies involving first trimester exposure to lithium (Naeye, 1990 and Stephansson *et al.*, 2001).

### Maternal Conditions

**Obesity:** During pregnancy, obesity is associated with adverse outcomes that include macrosomia, hypertension, pre-eclampsia, gestational diabetes mellitus (GDM), and fetal death (Miller and Hare, 1981; Zhao and Reece, 2005; Loeken, 2006; Reece *et al.*, 2006 and de Vigan, 2000). In addition, many investigators have reported an increased risk of birth defects.

**Diabetes mellitus:** Although hyperglycemia may be key in the pathogenesis of diabetic embryopathy, other factors contained in diabetic serum may also contribute to the embryopathy<sup>[79]</sup>. Hyperglycemia leads to inhibition of the myoinositol uptake that is essential for embryonic development during gastrulation and neurulation stages of embryogenesis (Zhao and Reece, 2005; Loeken, 2006). Deficiency of myoinositol appears to cause perturbations in the phosphoinositide system that lead to abnormalities in the arachidonic acid-prostaglandin pathway. The gastrulation and neurulation stages of development are particularly sensitive to hypoglycemia and result in growth retardation as well as cranial and caudal neural tube defects (NTDs). Obesity that occurs with a number of metabolic abnormalities, including abnormal glucose metabolism, is associated with a higher risk of malformations. A possible role of free oxygen radicals in diabetic teratogenicity has been suggested. The pathogenesis of diabetic embryopathy is heterogeneous (Reece *et al.*, 2006; de Vigan, 2000) maintenance of glucose homeostasis is important for the prevention of diabetic embryopathy.

**Hypothyroidism:** in infants occurs when the fetal thyroid gland has been suppressed by antithyroid drugs (propylthiouracil, carbimazole, iodides), radioactive iodine (Bunn *et al.*, 1976) or possibly maternal antibodies (Dunn *et al.*, 1979). Transfer of maternal thyroxine to the fetus is negligible during early pregnancy. During the final weeks of pregnancy, thyroidbinding globulin (TBG) may compete for thyroxine. Triiodothyronine is less bound by TBG and can more freely cross the placenta.

**Hyperthyroidism:** during pregnancy is usually due to Graves disease. The presence of thyroidstimulating globulins may result in thyrotoxicity in the fetus and newborn regardless of the treatment of maternal disease. Neonatal thyrotoxicosis is usually a transient phenomenon lasting several months. Affected infants have goiter, exophthalmos, restlessness, tachycardia, periorbital edema, ravenous appetite, hyperthermia, cardiomegaly, cardiac failure, and hepatosplenomegaly (Nielsen *et al.*, 1997).

**Hyperparathyroidism:** Infants of mothers with untreated hypoparathyroidism may have transient hyperparathyroidism during the fetal and neonatal periods (Kucera, 1971). The fetal parathyroid hyperplasia that occurs in response to low maternal and fetal serum calcium concentration is mediated by the maternal parathyroid dysfunction. Bone demineralization and subperiosteal reabsorption occurs in the long bones. IUGR, pulmonary artery stenosis, VSD, and muscle hypotonia also occur.

**Cretinism and iodine deficiency:** Iodine deficiency is the cause of endemic goiter and cretinism due to deficiency or of insufficient availability of thyroxine at the feto-placental level. There is a role of maternal T4 in neurological embryogenesis, before the onset of fetal thyroid function and, therefore, its protective role in fetal thyroid failure. In early pregnancy, iodine deficiency induces a critical decrease of T4 levels with consequent TSH increase responsible for hypothyroidism in about 50% of iodine-deficient pregnant women (Kucera, 1971).

**Myotonic dystrophy:** The myotonic dystrophy gene contains a segment of CTG repeats that tends to amplify in each generation (Passarge, 1965). Infants born of women with myotonic dystrophy may show fetal hypokinesia and generalized weakness, and may experience difficulty in respiration and feeding. The facies characteristically shows tenting of the upper lip, ptosis, absence of movement, and anterior cupping of the pinnae. Clubfoot is often present and postnatal growth is slow.

**Phenylketonuria:** Maternal phenylketonuria (PKU) leads to defects that include intrauterine and postnatal growth retardation, cardiovascular defects, dislocated hips, and other anomalies (Burrow *et al.*, 1968). Infants of mothers with PKU are heterozygous, and because phenylketonuric heterozygotes are generally normal, the defect in the fetus must be attributed to the maternal metabolic disturbance. These effects are directly related to the maternal phenylalanine level. When the level exceeds 20 mg/ml, 92% of infants have mental retardation; 73%, microcephaly; 40%, IUGR; and 12%, cardiac malformations. One-fourth of pregnancies abort spontaneously.

**Mechanical forces:** can also act as teratogens. Malformations of the uterus may restrict fetal movements and be associated with congenital dislocation of the hip and clubfoot. Oligohydramnios can have similar results and mechanically induce abnormalities of the fetal limbs. These abnormalities would be classified as deformations or abnormal forms, shapes, or positions of body parts caused by physical constraints.<sup>[88]</sup> Amniotic bands are fibrous rings and cause intrauterine amputations or malformations of the limbs as well. These abnormalities would be classified as disruptions or defects from interference with a normally developing organ system usually occurring later in gestation.

### Proven Teratogenic Drugs in Humans

**Thalidomide:** More than any other event, the thalidomide tragedy alerted the world to the teratogenic potential of drugs. Thalidomide was marketed in 1956 and was available for four years before its teratogenicity was recognized. Thalidomide produced malformations limited to tissues of mesodermal origin, primarily limbs, ears, cardiovascular system, and gut musculature.

The types of malformations could be related to the developmental stage of the embryo at the time of ingestion. Malformations resulted from repeated use as well as from single ingestions during the critical period from the 27th day to the 40th day of gestation (Sutherland *et al.*, 1960). In women, a single dose of less than 1 milligram per kilogram has produced the syndrome. Abnormal development of long bones produced a variety of limb reduction defects. Typically the upper limbs were more severely involved than the lower limbs. However, any of the bones could be defective or, in severe cases, totally absent. Phocomelia, polydactyly, syndactyly, oligodactyly were all reported. Lower extremities could be similarly affected, although less frequently and less severely.

**Alcohol:** The foetal alcohol syndrome is a clinical pattern of anomalies characterized by intrauterine growth retardation which commonly continues postnatally (Polak, 1998). These include: microcephaly, developmental delay, and dysmorphic facies consisting of low nasal bridge, midface hypoplasia, long featureless philtrum, small palpebral fissures and thin upper lip. Cleft palate and cardiac anomalies may also occur. Full expression of this syndrome occurs with chronic daily ingestion of at least 2 grams alcohol per kilogram (eight drinks per day). The full syndrome is present in about one third of these mothers and partial effects occur in approximately three quarters of offspring (Polak, 1998).

#### **Angiotensin converting enzyme inhibitors (ACEI) (captopril, enalapril, lisinopril)**

ACEI are potent anti-hypertensive drugs. Their use in late pregnancy has been associated with foetal toxicity including intrauterine renal insufficiency. Reports of neonatal hypotension, oliguria with renal failure, and hyperkalemia have been reported with ACEI use in pregnancy. Complications of oligohydramnios (i.e., foetal limb contractures, lung hypoplasia, and craniofacial anomalies), prematurity, intrauterine growth retardation, and foetal death have also been reported with the use of these agents late in pregnancy (Landing and Kamoshita, 1970). The adverse effects are related to the haemodynamic effects of ACEI on the foetus, teratogenic risk with first trimester exposure to these agents appears to be low.

**Carbamazepine:** Exposure to carbamazepine in utero carries a 1% risk of neural tube defects (10 times their baseline risk). A pattern of malformations similar to those described with the foetal hydantoin syndrome has also been associated with carbamazepine exposure in pregnancy (Landing and Kamoshita, 1970).

**Cocaine:** Cocaine use during pregnancy has been associated with abruptio placentae, prematurity, foetal loss, decreased birth weight, microcephaly, limb defects, urinary tract malformations, and poorer neurodevelopmental performance. The contribution of cocaine to the incidence of congenital malformations is difficult to assess because of methodological problems, which make the results difficult to interpret. Cocaine abuse is often associated with poly-drug abuse, alcohol consumption, smoking, malnutrition, and poor prenatal care (Potter and Phillips, 2006). Experimental animal studies and human epidemiology indicate that the risk of major malformation from cocaine is probably low, but the anomalies may be severe.

**Coumarin anticoagulants:** First trimester exposure to coumarin derivatives is associated with a characteristic pattern of malformations termed the foetal warfarin syndrome. Clinical features consist of nasal hypoplasia and calcific stippling of the epiphyses. Intrauterine growth retardation and developmental delay due to central nervous system damage, eye defects, and hearing loss have also been described. The critical period of exposure for the foetal warfarin syndrome appears to be between 6 and 9 weeks of gestation. A prospective study found evidence of warfarin embryopathy in about one third of the cases where a coumarin derivative was given throughout pregnancy (Connolly *et al.*, 1979). Oral anticoagulants are also associated with a high rate of miscarriage. Exposure to oral anticoagulants after the first trimester presents a risk of central nervous system damage due to haemorrhage. Unlike heparin, oral anticoagulants readily cross the placental barrier.

**Diethylstilbestrol:** Diethylstilbestrol was used in the 1950s and 1960s for the diagnosis of recurrent miscarriage. Clear cell adenocarcinoma of the vagina was found to be associated with diethylstilbestrol treatment of the patient's mother during the first trimester of pregnancy. Over 90% of the cancers occurred after 14 years of age (Connolly *et al.*, 1979). Clear cell carcinoma has not occurred in women exposed in utero after the 18th week of gestation. A high incidence of benign adenosis of the vagina was found in women prenatally exposed to this nonsteroidal estrogen analogue. In a prospective study, exposure starting at 4 weeks was associated with adenosis in 56% of the offspring, decreasing later to 30% at 16 weeks and 10% at 20 weeks. Miscarriage rate and preterm delivery were significantly more common in women exposed in utero to diethylstilbestrol compared to matched controls. In 134 males exposed in utero to the agent no signs of malignancy were found but 27% had genital lesions (epididymal cysts, hypotrophic testes, or capsular induration of the testes). In 29%, pathologic changes were found in spermatozoa (Connolly *et al.*, 1979).

#### **Folic acid antagonists: Aminopterin and methotrexate**

Aminopterin has been known since 1950 to result in foetal death, which led to its use as a human abortifacient. The foetal aminopterin syndrome was described based on anomalies observed in aborted fetuses and infants born following unsuccessful abortions. Malformations include central nervous system defects (hydrocephalus, meningomyelocele), facial anomalies (cleft palate, high arched palate, micrognathia, ocular hypertelorism, external ear anomalies), abnormal cranial ossification, abnormalities in first branchial arch derivatives, intrauterine growth retardation and mental retardation (Hetzel and Hay, 1979). Infants have been born with features of the aminopterin syndrome after pregnancy exposure to methotrexate (methylaminopterin). It was suggested that the maternal dose necessary to induce defects is above 10 mg per week with a critical period of 6 to 8 weeks post conception being postulated.

**Hydantoins (phenytoin and trimethadione):** Hydantoins have been associated with a recognizable pattern of malformation termed the foetal hydantoin syndrome. The clinical features include craniofacial dysmorphism (wide anterior fontanelle, ocular hypertelorism, metopic ridge, broad depressed nasal bridge, short anteverted nose, bowed upper lip, cleft lip, cleft palate),

as well as variable degrees of hypoplasia of the distal phalanges, nail hypoplasia and low arch dermal ridge patterning (Yu and O'Halloran, 1970). Growth retardation, mental deficiency and cardiac defects are additional features of the syndrome.

**Isotretinoin (13-cis-retinoic acid):** Isotretinoin is a synthetic vitamin A derivative, prescribed for severe cystic acne, that has been proven to be a potent human teratogen as well as a behavioural teratogen when given systemically. A pattern of anomalies termed retinoic acid embryopathy has been associated with isotretinoin (and other retinoic acid derivatives such as etretinate and megadoses of vitamin A) exposure in pregnancy (Rogers and Kavlock, 1996). The clinical features include craniofacial anomalies (microtia or anotia, accessory parietal sutures, narrow sloping forehead, micrognathia, flat nasal bridge, cleft lip and palate, and ocular hypertelorism), cardiac defects (primarily conotruncal malformations), abnormalities in thymic development, and alterations in central nervous system development. The risk for associated miscarriage was 40%.

**Misoprostol:** Misoprostol is a synthetic prostaglandin E1 analogue, prescribed for duodenal and gastric ulceration, also used as an abortifacient by women in Brazil. A Brazilian case-series suggested an association between first trimester exposure to misoprostol and limb defects with or without Moebius' sequence. The association was further supported by a case-control study comparing the frequency of misoprostol use during the first trimester by mothers of 96 infants with Moebius' syndrome and mothers of infants with neural tube defects. Among the mothers of infants with Moebius' syndrome, 49% had used misoprostol, as compared with 3% of the mothers of infants with neural tube defects (odds ratio, 29.7; 95% confidence interval 11.6 to 76.0) (Rogers and Kavlock, 1996). Despite the strong association between misoprostol exposure during the first trimester and Moebius' syndrome, its absolute teratogenic risk is probably not high.

**Tetracyclines:** Yellow-brown discolouration of teeth may occur due to deposition of the antibiotic in calcifying teeth with tetracycline use in late pregnancy. The risk is apparent only after 17 weeks of gestation when the deciduous teeth begin to calcify. Generally, only the deciduous teeth are involved, although with administration of the drug close to term the crowns of the permanent teeth may be stained (Jones *et al.*, 1973). Oxytetracycline and doxycycline are associated with a lower incidence of enamel staining.

#### Possible Teratogenic Drugs in Humans

**D-penicillamine:** Based on several case reports, high dose treatment of the pregnant woman with D-penicillamine has been associated with connective tissue disorders (cutis laxa).

**Methimazole:** Methimazole treatment during pregnancy has been associated with scalp defects (aplasia cutis congenita) based on case reports and on an epidemiological study in which methimazole had been added to animal feeds as a weight enhancer, and in those areas a higher incidence of cutis aplasia congenita was found (Birth Defects, 2014).

**Diazepam:** First trimester exposure to diazepam has been associated in small studies with a small increase in the incidence of cleft lip and palate. Larger studies did not confirm the association (Birth Defects, 2014).

#### Teratogenic Counselling

In counselling the pregnant patient exposed to a potential human teratogen, it is important to emphasize the significance of exposure to the patient. Ascertaining the clinical facts regarding the nature of the exposure: the length, dosage, and timing of exposure during pregnancy, as well as other exposures of concern about which the patient may not ask (e.g., alcohol, cigarette smoking). All available current data regarding the agent are then collected, and conclusions regarding the risks of exposures are drawn. Counselling should include the background human baseline risk for major malformations, whether the foetus is at increased risk, which anomaly has been associated with the agent in question, a risk assessment, methods of prenatal detection, when available, limitations in our knowledge, and limitations of prenatal diagnostic capabilities (James G. Wilson, 1973). Additional aspects include the potential risk of the medical condition for which a drug is prescribed, known interactions (in both directions) between the disease state and the pregnancy and preventive measures, when applicable (e.g., folic acid supplementation in the case of carbamazepine exposure). Because more than 50% of pregnancies in North America are unplanned, teratogenic risk assessment should be started prior to pregnancy.

#### Some Recent Findings

Dispensing of potentially teratogenic drugs before conception and during pregnancy: a population-based study (Lozano, 2012). "To study the dispensing of potentially teratogenic drugs in the 12-month period before as well as during pregnancy in the Netherlands. Drug-dispensing information was identified from the PHARMO Database Network for the 12-month period before conception and during pregnancy. Drugs with either a Swedish FASS 'D' classification, an Australian ADEC or American FDA 'D' or 'X' classification were considered potentially teratogenic (n = 202). ...Five percent of the pregnancies received a potentially teratogenic drug during pregnancy and 0.66% received a drug from the risk category X. It may be possible to reduce these proportions when reasons for prescription have been explored."

Teratogen Screening Using Transcriptome Profiling of Differentiating Human Embryonic Stem Cells (Kumar, ?). "Teratogens are substances that may cause defects in normal embryonic development while not necessarily being toxic in adults. Identification of possible teratogenic compounds has been historically beset by the species-specific nature of the teratogen response. To examine teratogenic effects on early human development we performed non-biased expression profiling of differentiating human embryonic and induced-pluripotent stem cells treated with several drugs; ethanol, lithium, retinoic acid, caffeine and thalidomide, which is known to be highly species specific. Our results point to the potency of specific teratogens and their affected tissues and pathways. Specifically, we could show that ethanol caused dramatic increase in endodermal differentiation, retinoic acid caused misregulation of neural development, and thalidomide affected both these processes. We thus propose this method as a valuable addition to currently available animal screening approaches." Maternal exposure to multi-wall carbon nanotubes does not induce embryo-fetal developmental toxicity in rats (Molnar, 2001).

"The results show that repeated oral doses of multi-wall CNTs (MWCNTs) during pregnancy induces minimal maternal toxicity and no embryo-fetal toxicity at 1,000 mg/kg/day in rats. The no-observed-adverse-effect level of MWCNTs is considered to be 200 mg/kg/day for dams and 1,000 mg/kg/day for embryo-fetal development. In this study, the dosing formulation was not analyzed to determine the degree of reaggregation (or not), nor were blood levels of CNT's measured in the dosed animals to verify or characterize absorption."

## Conclusions

Drugs that can cause birth defects are said to be 'teratogenic drugs'. Medical science cannot always predict how exposure to a teratogenic drug will affect a developing fetus. It can be dangerous for a pregnant woman to stop taking prescription drugs if she has a medical condition or becomes ill. Without treatment, the health and welfare of both the mother and her unborn baby could be at risk. Today, the FDA monitors teratogen exposures to pregnant women in the US with a number of regulations and risk management programs. For example, the retinoic acid isotretinoin which is commonly used for acne treatment cannot be given to any patient unless they are enrolled in iPLEDGE, a risk management program designed to prevent fetal exposure to isotretinoin.

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