

Three musketeers of genotoxicity: carcinogen, mutagen & teratogen

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ABSTRACT Genotoxicity describes a deleterious action on a cell's genetic material affecting its integrity. Genotoxic substances are known to be potentially mutagenic or carcinogenic, specifically those capable of causing genetic mutation and of contributing to the development of tumors. This includes both certain chemical compounds and certain types of radiation. Typical genotoxins like aromatic amines are believed to cause mutations because they are nucleophilic and form strong covalent bonds with DNA resulting with the formation of Aromatic Amine-DNA Adducts, preventing accurate replication. Genotoxins affecting sperm and eggs can pass genetic changes down to descendants who have never been exposed to the genotoxin. A carcinogen is any substance, radionuclide or radiation that is an agent directly involved in causing cancer. This may be due to the ability to damage the genome or to the disruption of cellular metabolic processes. Several radioactive substances are considered carcinogens, but their carcinogenic activity is attributed to the radiation, for example gamma rays and alpha particles, which they emit. Carcinogens may increase the risk of cancer by altering cellular metabolism or damaging DNA directly in cells, which interferes with biological processes, and induces the uncontrolled, malignant division, ultimately leading to the formation of tumors. Usually DNA damage, if too severe to repair, leads to programmed cell death, but if the programmed cell death pathway is damaged, then the cell cannot prevent itself from becoming a cancer cell. In biology, a mutagen (Latin, literally origin of change) is a physical or chemical agent that changes the genetic material, usually DNA, of an organism and thus increases the frequency of mutations above the natural background level. As many mutations cause cancer, mutagens are typically also carcinogens. Not all mutations are caused by mutagens: so-called "spontaneous mutations" occur due to errors in DNA replication, repair and recombination. Teratology is the study of abnormalities of physiological development. It is often thought of as the study of birth defects, but it is much broader than that, taking in other developmental stages, such as puberty; and other life forms, such as plants.

Keywords: Poly Aromatic Hydrocarbons (PAH), aflatoxins, biomass, radionucleotide, mutation

Introduction

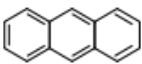
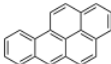
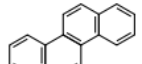

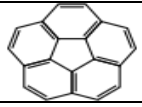

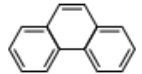

Polycyclic aromatic hydrocarbons (PAHs), also known as poly-aromatic hydrocarbons or polynuclear aromatic hydrocarbons are potent atmospheric pollutants that consist of fused aromatic rings and do not contain heteroatoms or carry substituents. Anthracene is the simplest example of a PAH. PAHs occur in oil, coal, and tar deposits, and are produced as byproducts of fuel burning (whether fossil fuel or biomass). As a pollutant, they

are of concern because some compounds have been identified as carcinogenic, mutagenic, and teratogenic. PAHs are also found in foods. Studies have shown that high levels of PAHs are found in meat cooked at high temperatures such as grilling or barbecuing, and in smoked fish. They are also found in the interstellar medium, in comets, and in meteorites and are a candidate molecule to act as a basis for the earliest forms of life. In graphene the PAH motif is extended to large 2D sheets.

There are many natural carcinogens. Aflatoxin B₁, which is produced by the fungus *Aspergillus flavus* growing on stored grains, nuts and peanut butter, is an example of a potent, naturally-occurring microbial carcinogen. Certain viruses such as Hepatitis B and human papilloma viruses have been found to cause cancer in humans. The first one shown to cause cancer in animals is Rous sarcoma virus, discovered in 1910 by Peyton Rous. Dioxins and dioxin-like compounds, benzene, kepone, EDB, asbestos, and the waste rock of oil shale mining have all been classified as carcinogenic. As far back as the 1930s, industrial smoke and tobacco smoke were identified as sources of dozens of carcinogens, including benzo[a]pyrene, tobacco-specific nitrosamines such as nitrosonornicotine, and reactive aldehydes such as formaldehyde, which is also a hazard in embalming and making plastics. Vinyl chloride, from which PVC is manufactured, is a carcinogen and thus a

hazard in PVC production. Co-carcinogens are chemicals that do not necessarily cause cancer on their own, but promote the activity of other carcinogens in causing cancer. After the carcinogen enters the body, the body makes an attempt to eliminate it through a process called biotransformation. The purpose of these reactions is to make the carcinogen more water-soluble so that it can be removed from the body. But these reactions can also convert a less toxic carcinogen into a more toxic carcinogen. DNA is nucleophilic; therefore soluble carbon electrophiles are carcinogenic, because DNA attacks them. For example, some alkenes are toxicated by human enzymes to produce an electrophilic epoxide. DNA attacks the epoxide, and is bound permanently to it. This is the mechanism behind the carcinogenicity of benzo[a]pyrene in tobacco smoke, other aromatics, aflatoxin and mustard gas.¹

Table 1: Polycyclic aromatic hydrocarbons

Chemical compound	Structure	Chemical compound	Structure
Anthracene		Benzo[a]pyrene	
Chrysene		Coronene	
Corannulene		Naphthalene	
Phenanthrene		Triphenylene	

Radiation

CERCLA identifies all radionuclides as carcinogens, although the nature of the emitted radiation (alpha, beta, gamma, or neutron and the radioactive strength), its consequent capacity to cause ionization in tissues, and the magnitude of radiation exposure, determine the potential hazard. Carcinogenicity of radiation depends of the type of radiation, type of exposure, and

penetration. For example, alpha radiation has low penetration and is not a hazard outside the body, but emitters are carcinogenic when inhaled or ingested. For example, Thorotrast, a (incidentally-radioactive) suspension previously used as a contrast medium in x-ray diagnostics, is a potent human carcinogen known because of its retention within various organs and persistent emission of alpha particles. Marie

Curie, one of the pioneers of radioactivity, died of cancer caused by radiation exposure during her experiments. Not all types of electromagnetic radiation are in fact carcinogenic. Low-energy waves on the electromagnetic spectrum are generally not, including radio waves, microwave radiation, infrared radiation and visible light. Higher-energy radiation, including ultraviolet radiation (present in sunlight), x-rays, and gamma radiation, generally is carcinogenic, if received in sufficient doses. Low level ionizing radiation may induce irreparable

DNA damage (leading to replicational and transcriptional errors needed for neoplasia or may trigger viral interactions) leading to pre-mature aging and cancer. Substances or foods irradiated with electrons or electromagnetic radiation (such as microwave, X-ray or gamma) are not carcinogenic. In contrast, non-electromagnetic neutron radiation produced inside nuclear reactors can produce secondary radiation through nuclear transmutation.²



Figure-1: Danger sign of carcinogens

Carcinogens in prepared food

Cooking food at high temperatures, for example grilling or barbecuing meats, can lead to the formation of minute quantities of many potent carcinogens that are comparable to those found in cigarette smoke (i.e., benzo[a]pyrene). Charring of food resembles coking and tobacco pyrolysis, and produces similar carcinogens. There are several carcinogenic pyrolysis products, such as polynuclear aromatic hydrocarbons, which are converted by human enzymes into epoxides, which attach permanently to DNA.

Pre-cooking meats in a microwave oven for 2–3 minutes before grilling shortens the time on the hot pan, and removes heterocyclic amine (HCA) precursors, which can help minimize the formation of these carcinogens. Reports from the Food Standards Agency have found that the known animal carcinogen acrylamide is generated in fried or overheated carbohydrate foods (such as french fries and potato chips).³ Studies are underway at the FDA and European regulatory agencies to assess its potential risk to humans.

Carcinogens in cigarettes

Tobacco smoke contains over 4000 chemical compounds, many of which are carcinogenic or otherwise toxic. One of these is a compound marketed as a rat poison.

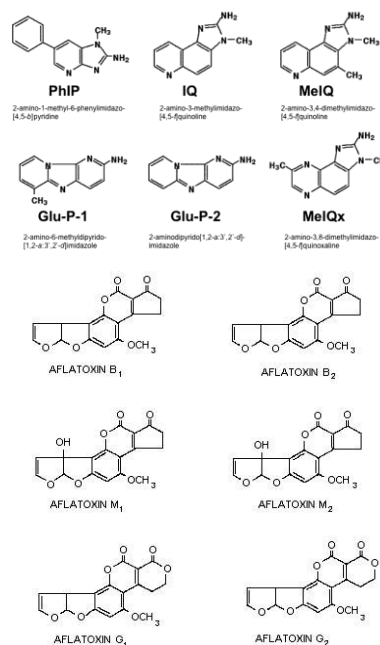


Figure-2: Structures of carcinogens

Circadian disruption

"Shiftwork that involves circadian disruption" was listed, in 2007, as a probable carcinogen by the World Health Organization's International Agency for Research on Cancer. (IARC Press release No. 180). Multiple studies have documented a link between night shift work and the increased incidence of breast cancer.⁴ Circadian disruption by exposure to light at night suppresses the production of the hormone melatonin which leads to reduction in cellular immune defense and surveillance necessary for protection from development of cancers. Melatonin also seems to have a direct protective effect

against cancer, possibly in part because of its strong antioxidant properties.

Mechanisms of carcinogenicity

Carcinogens can be classified as genotoxic or nongenotoxic. Genotoxins cause irreversible genetic damage or mutations by binding to DNA. Genotoxins include chemical agents like N-nitroso-N-methylurea (NMU) or non-chemical agents such as ultraviolet light and ionizing radiation. Certain viruses can also act as carcinogens by interacting with DNA. Nongenotoxins do not directly affect DNA but act in other ways to promote growth. These include hormones and some organic compounds.⁵

Table-2: Approximate equivalences between classification schemes

IARC	GHS	NTP	ACGIH	EU
Group 1	Cat. 1A	Known	A1	Cat. 1
Group 2A	Cat. 1B	Reasonably suspected	A2	Cat. 2
Group 2B	Cat. 2		A3	Cat.3
Group 3	X		A4	
Group 4	X		A5	Group 4

IARC-International Agency for Research on Cancer; GHS-Globally Harmonized System; NTP-National Toxicology Program; ACGIH-American Conference of Governmental Industrial Hygienists; EU-European Union

International Agency for Research on Cancer

The International Agency for Research on Cancer (IARC) is an intergovernmental agency established in 1965, which forms part of the World Health Organization of the United Nations. It is based in Lyon, France. Since 1971 it has published a series of Monographs on the Evaluation of Carcinogenic Risks to Humans that have been highly influential in the classification of possible carcinogens.

- Group 1: the agent (mixture) is definitely carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans.
- Group 2A: the agent (mixture) is probably carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans.
- Group 2B: the agent (mixture) is possibly carcinogenic to humans. The exposure

circumstance entails exposures that are possibly carcinogenic to humans.

- Group 3: the agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.
- Group 4: the agent (mixture) is probably not carcinogenic to humans.

Globally Harmonized System

The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) is a United Nations initiative to attempt to harmonize the different systems of assessing chemical risk which currently exist (as of March 2009) around the world. It classifies carcinogens into two categories, of which the first may be divided again into subcategories if so desired by the competent regulatory authority:

- Category 1: known or presumed to have carcinogenic potential for humans
 - Category 1A: the assessment is based primarily on human evidence

- Category 1B: the assessment is based primarily on animal evidence
- Category 2: suspected human carcinogens

U.S. National Toxicology Program

The National Toxicology Program of the U.S. Department of Health and Human Services is mandated to produce a biennial Report on Carcinogens. As of March 2009, the latest edition was the 11th report (2005). It classifies carcinogens into two groups:

- Known to be a human carcinogen
- Reasonably anticipated to be a human carcinogen

American Conference of Governmental Industrial Hygienists

The American Conference of Governmental Industrial Hygienists (ACGIH) is a private organization best known for its publication of threshold limit values (TLVs) for occupational exposure and monographs on workplace chemical hazards. It assesses carcinogenicity as part of wider assessment of the occupational hazards of chemicals.

- Group A1: Confirmed human carcinogen
- Group A2: Suspected human carcinogen
- Group A3: Confirmed animal carcinogen with unknown relevance to humans
- Group A4: Not classifiable as a human carcinogen

- Group A5: Not suspected as a human carcinogen

European Union

The European Union classification of carcinogens is contained in the Dangerous Substances Directive and the Dangerous Preparations Directive. It consists of three categories:

- Category 1: Substances known to be carcinogenic to humans.
- Category 2: Substances which should be regarded as if they are carcinogenic to humans.
- Category 3: Substances which cause concern for humans, owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment.

This assessment scheme is being phased out in favor of the GHS scheme to which it is very close in category definitions.

Procarcinogen

A procarcinogen is a precursor to a carcinogen. One example is nitrites when taken in by the diet. They are not carcinogenic themselves, but turn into nitrosamines in the body, which are carcinogenic.⁶

Common carcinogens

Occupational carcinogens are agents that pose a risk of cancer in several specific work-locations.



Figure-3: A two-headed calf and structural deformity

Some Drugs may act as carcinogen or promote carcinogen

In some cases, some drug may act as carcinogen or may act to promote carcinogenesis. Di-ethyl-stilbesterol (DES)

is a recognized carcinogen and already withdrawn by physicians from prescribing to pregnant women. Though, the mechanism of the carcinogenesis remains the subject of some controversy. Cunningham and

coworkers suggests that the observed carcinogenic spectrum of DES reflects the activity of metabolic intermediates and the carcinogenicity of DES in mice is due to the presence of a 6 A° geometric descriptor that appears to be related to an estrogen receptor.⁷ Pre-natal exposure to a single dose of DES produced a significant increase in carcinogenic response in hamster. The progeny exposed to DES prenatally developed a greater multiplicity of tumors per tumor bearing animal ($p < 0.001$) and higher rates of neoplasms of the reproductive tract than those treated with 7,12-dimethylbenz(a)anthracene (DMBA) in

post natal conditions. The prenatally DES-exposed progeny also had significantly higher incidences of malignant tumors than the post-natally DMBA treated progenies.⁸ Phenobarbitone, a popular sedative-hypnotic as well as antiepileptic agent, plays a major role in the promotion of hepatocarcinogenesis induced by Diethylnitrosoamine (DEN) or other chemical carcinogens, when administered with diet after cessation of carcinogen feeding. It enhances the persistence of altered foci and increases the incidence of liver tumors by 78-89%.^{9,10}

Mutagen

Effects of mutations

The changes in nucleic acid sequences by mutations include substitution of nucleotide base-pairs and insertions and deletions of one or more nucleotides in DNA sequences. Although some of these mutations are lethal, or cause serious disease, many have minor effects, as the changes they cause in the sequence of encoded proteins are not significant. Many mutations cause no visible effects at all, either because they occur in introns or because they do not change the amino-acid sequence, due to redundancy of codons. On rare occasions they can create beneficial mutations, such as disease resistance, and can spur evolutionary change in a population.¹¹

Genetic drift

The change in a population's genetic material due to the accumulation of random chance mutations is called genetic drift, and serves as a molecular clock. In general, the more nucleotide differences between two organisms, the more time has elapsed since their last common ancestor. Though it is difficult to determine in many organisms, estimates for mutation rates have been made for both *E. coli* and eukaryotes. It was estimated that, in these organisms, about one nucleotide in every 10^{10} is changed,

and continues through reproduction to future generations of cells.

Discovery of mutagenesis

In the 1920s, Hermann Muller discovered that x-rays caused mutations in fruit flies. He went on to use x-rays to create *Drosophila* mutants that he used in his studies of genetics. He also discovered that x-rays not only mutate genes in fruit flies but also have effects on the genetic makeup of humans. The first mutagens to be identified were carcinogens, or cancer-causing substances. Early physicians detected tumors in patients more than 2,000 years before the discovery of chromosomes and DNA. In 500 B.C., the Greek Hippocrates named crab-shaped tumors cancer, meaning crab. In England in 1775, Dr. Percivall Pott wrote a paper on the high incidence of scrotal cancer in chimney sweeps who were typically boys small enough to fit inside chimneys and clean out the soot. Pott suggested that chimney soot contained carcinogens that could cause the growth of the warts seen in scrotal cancer. Over 150 years later, chimney soot was found to contain hydrocarbons capable of mutating DNA. In France in the 1890s, Bordeaux wine workers showed an unusually high incidence of skin cancer on the back of the neck. These workers spend their days bending over in the fields picking grapes,

exposing the back of their necks to the sun.
The ultraviolet (UV) radiation in natural

sunlight was later identified as a mutagen.¹²

Table-3: Occupational carcinogens

Carcinogen	Associated cancer sites or types	Occupational uses or sources
Arsenic and its compounds	<ul style="list-style-type: none"> • Lung • Skin • Hemangiosarcoma 	Smelting byproduct Component of: Alloys, Electrical and semiconductor, devices, Medications (e.g. melarsoprol), Herbicides, Fungicides, Animal dips
Asbestos	<ul style="list-style-type: none"> • Lungs • Mesothelioma • Gastrointestinal tract 	Not in use, but still found in: <ul style="list-style-type: none"> • Constructions Roofing papers, Floor tiles • Fire-resistant textiles • Friction linings
Benzene	<ul style="list-style-type: none"> • Leukemia • Hodgkin lymphoma 	Light fuel oil, Former use as solvent and fumigant, Printing, Lithography, Paint, Rubber, Dry cleaning, Adhesives, Coatings, Detergents
Beryllium and its compounds	<ul style="list-style-type: none"> • Lung 	Missile fuel Lightweight alloys Aerospace applications, Nuclear reactors
Cadmium and its compounds	<ul style="list-style-type: none"> • Prostate 	Yellow pigments, Phosphors Solders, Batteries, Metal paintings and coatings
Hexavalent chromium(VI) compounds	<ul style="list-style-type: none"> • Lung 	Paints, Pigments, Preservatives
Ethylene oxide	<ul style="list-style-type: none"> • Leukemia 	Ripening agent for fruits and nuts Rocket propellant Fumigant for foodstuffs and textiles Sterilant for hospital equipment
Nickel	<ul style="list-style-type: none"> • Nose • Lung 	Nickel plating, Ferrous alloys, Ceramics Batteries Stainless-steel welding byproduct
Radon and its decay products	<ul style="list-style-type: none"> • Lung 	Uranium decay Quarries and mines, Cellars and poorly ventilated places
Vinyl chloride	<ul style="list-style-type: none"> • Hemangiosarcoma • Liver 	Refrigerant, Production of polyvinyl chloride, Adhesive for plastics, Former use in pressurized containers
Shift work that involves circadian disruption	<ul style="list-style-type: none"> • Breast 	
Involuntary smoking (Passive smoking)	<ul style="list-style-type: none"> • Lung 	

Nature of mutagens

Mutagens are usually chemical compounds or ionizing radiation. Mutagens can be divided into different categories according to their effect on DNA replication:

- Some mutagens act as base analogs and get inserted into the DNA strand during replication in place of the substrates.
- Some react with DNA and cause structural changes that lead to miscopying of the template strand when the DNA is replicated.
- Some work indirectly by causing the cells to synthesize chemicals that have the direct mutagenic effect.

The Ames test is one method to determine how mutagenic an agent is.

Examples

- Ionizing radiation, for example X-rays, gamma rays and alpha particles
- Ultraviolet, electromagnetic radiation with a wavelength shorter than that of visible light but longer than x-rays
- Base analog, which can substitute for DNA bases and cause copying errors
- Deaminating agents such as nitrous acid
- Intercalating agents such as ethidium bromide
- Alkylating agents such as ethylnitrosourea
- Transposon, a section of DNA that undergoes autonomous fragment relocation/multiplication
- Alkaloid plants, such as those from *Vinca* species
- Bromine and some compounds that contain bromine in their chemical structure
- Sodium azide, an azide salt that is a common reagent in organic synthesis and a component in many car airbag systems
- Psoralen combined with ultraviolet radiation causes DNA cross-linking and hence chromosome breakage
- Benzene, an industrial solvent and precursor in the production of drugs, plastics, synthetic rubber and dyes

Ames test

The Ames test is a biological assay to assess the mutagenic potential of chemical compounds. A positive test indicates that the chemical might act as a carcinogen (although a number of false-positives and false-negatives are known). As cancer is often linked to DNA damage, the test also serves as a quick assay to estimate the carcinogenic potential of a compound. The procedure described in a series of papers from the early 1970s by Bruce Ames *et al.*, involves the use of several strains of the bacterium *Salmonella typhimurium* that carry mutations in genes involved in histidine synthesis. Such a mutant is coined as “auxotrophic mutant” and they require histidine for growth. The variable being tested is the mutagen's ability to cause a reversion to growth on a histidine-free medium. The tester strains are specially constructed to have both frameshift and point mutations in the genes required to synthesize histidine, which allows for the detection of mutagens acting via different mechanisms. Some compounds are quite specific, causing reversions in just one or two strains. The tester strains also carry mutations in the genes responsible for lipopolysaccharide synthesis, making the cell wall of the bacteria more permeable, and in the excision repair system to make the test more sensitive. Rat liver extract is optionally added to simulate the effect of metabolism, as some compounds, like benzo[a]pyrene, are not mutagenic themselves but their metabolic products.¹³

The bacteria are spread on an agar plate with a small amount of histidine. This small amount of histidine in the growth medium allows the bacteria to grow for an initial time and have the opportunity to mutate. When the histidine is depleted only bacteria that have mutated to gain the ability to produce its own histidine will survive. The plate is incubated for 48 hours. The mutagenicity of a substance is proportional to the number of colonies observed.

Etymology

The term stems from the Greek τέρας (téras, genitive τέρατος- tératos), meaning monster, or marvel and λόγος - lógos, meaning speech or, more loosely, the study of. As early as the 17th century, Teratology referred to a discourse on prodigies and marvels of anything so extraordinary as to seem abnormal. In the 19th century, it acquired a meaning more closely related to biological deformities, mostly in the field of botany. Currently, its most instrumental meaning is that of the medical study of teratogenesis, congenital malformations or individuals with significant malformations. There are many pejorative terms that have historically been used to describe individuals with significant physical malformations. The term was popularized in the 1960s by Dr. David W. Smith of the University of Washington Medical School, one of the researchers who became known in 1973 for the discovery of Fetal alcohol syndrome. With greater understanding of the origins of birth defects, the field of teratology now overlaps with other fields of basic science, including developmental biology, embryology, and genetics.¹⁴

Teratogenesis

Birth defects are known to occur in 3-5% of all newborns. They are the leading cause of infant mortality in the United States, accounting for more than 20% of all infant deaths. Seven to ten percent of all children will require extensive medical care to diagnose or treat a birth defect and although significant progress has been made in identifying the etiology of some birth defects, approximately 65% have no known or identifiable cause.¹¹ It was previously believed that the mammalian embryo developed in the impervious uterus of the mother, protected from all extrinsic factors. However, after the thalidomide disaster of the 1960s, it became apparent and more accepted that the developing embryo could be highly vulnerable to certain environmental agents that have negligible or non-toxic effects to adult individuals. A review published in 2010 identified 6 main teratogenic mechanisms

associated with medication use: folate antagonism, neural crest cell disruption, endocrine disruption, oxidative stress, vascular disruption and specific receptor- or enzyme-mediated teratogenesis.¹⁵

Wilson's 6 principles

Along with this new awareness of the in utero vulnerability of the developing mammalian embryo came the development and refinement of The Six Principles of Teratology which are still applied today. These principles of teratology were put forth by Jim Wilson in 1959 and in his monograph *Environment and Birth Defects*. These principles guide the study and understanding of teratogenic agents and their effects on developing organisms:

1. Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with adverse environmental factors.
2. Susceptibility to teratogenesis varies with the developmental stage at the time of exposure to an adverse influence. There are critical periods of susceptibility to agents and organ systems affected by these agents.
3. Teratogenic agents act in specific ways on developing cells and tissues to initiate sequences of abnormal developmental events.
4. The access of adverse influences to developing tissues depends on the nature of the influence. Several factors affect the ability of a teratogen to contact a developing conceptus, such as the nature of the agent itself, route and degree of maternal exposure, rate of placental transfer and systemic absorption, and composition of the maternal and embryonic/fetal genotypes.
5. There are four manifestations of deviant development (Death, Malformation, Growth Retardation and Functional Defect).
6. Manifestations of deviant development increase in frequency and degree as dosage increases from the No Observable Adverse Effect Level (NOAEL) to a dose producing 100% Lethality (LD100).

Studies designed to test the teratogenic potential of environmental agents use animal model systems (e.g., rat, mouse, rabbit, dog, and monkey). Early teratologists exposed pregnant animals to environmental agents and observed the fetuses for gross visceral and skeletal abnormalities. While this is still part of the teratological evaluation procedures today, the field of Teratology is moving to a more molecular level, seeking the mechanism(s) of action by which these agents act. Genetically modified mice are commonly used for this purpose. In addition, pregnancy registries are large, prospective studies that monitor exposures women receive during their pregnancies and record the outcome of their births. These studies provide information about possible risks of medications or other exposures in human pregnancies.¹⁶

Understanding how a teratogen causes its effect is not only important in preventing congenital abnormalities but also has the potential for developing new therapeutic drugs safe for use with pregnant women.

Teratology education

It is estimated that 10% of all birth defects are caused by prenatal exposure to a teratogenic agent. These exposures include, but are not limited to, medication or drug exposures, maternal infections and diseases, and environmental and occupational exposures. Teratogen-caused birth defects are potentially preventable. Studies have shown that nearly 50% of pregnant women have been exposed to at least one medication during gestation. An additional study found that of 200 individuals referred for genetic counseling for a teratogenic exposure, 52% were exposed to more than one potential teratogen.¹⁷

Teratogenic agents

A wide range of different chemicals and environmental factors are suspected or are known to be teratogenic in humans and in animals. A selected few include:

- Drugs and medications: tobacco, caffeine, drinking alcohol (ethanol) (see fetal alcohol spectrum disorder), isotretinoin

(13-cis-retinoic acid, Roaccutane), temazepam (Restoril; Normisson), nitrazepam (Mogadon), nimetazepam (Ermin), aminopterin, androgenic hormones, busulfan, captopril, enalapril, coumarin, cyclophosphamide, diethylstilbestrol, phenytoin (diphenylhydantoin, Dilantin, Epanutin), etretinate, lithium, methimazole, penicillamine, tetracyclines, thalidomide, trimethadione, methoxyethyl ethers, Flusilazole, valproic acid, and many more.

- Environmental chemicals: polychlorinated biphenyls (PCBs), polychlorinated dibenzodioxins a.k.a dioxin, polychlorinated dibenzofurans (PCDFs), hexachlorobenzene hexachlorophene, organic mercury, ethidium bromide, etc.
- Ionizing radiation: atomic weapons fallout (Iodine-131, uranium), background radiation, diagnostic x-rays, radiation therapy
- Infections: cytomegalovirus, herpes virus, parvovirus B19, rubella virus (German measles), syphilis, toxoplasmosis, Venezuelan equine encephalitis virus. (An easy way to remember maternal infections is TORCH: Toxoplasmosis, Other agents, Rubella, CMV and HSV.
- Metabolic imbalance: alcoholism, endemic cretinism, diabetes, folic acid deficiency, iodine deficiency, hyperthermia, phenylketonuria, rheumatic disease and congenital heart block, virilizing tumors

The status of some of the above substances (e.g. diphenylhydantoin) is subject to debate, and many other compounds are under varying degrees of suspicion. These include Agent Orange, nicotine, aspirin and other NSAIDs. Other compounds are known as severe teratogens based on veterinary work and animal studies, but aren't listed above because they have not been studied in humans, e.g. cyclophosphamide. Teratogenic effects also help to determine the pregnancy category assigned by regulatory authorities; in the United States, a pregnancy category of X, D, or C may be assigned if teratogenic effects (or other

risks in pregnancy) are documented or cannot be excluded.¹⁸

Isotretinoin (13-cis-retinoic-acid; brand name Roaccutane), which is often used to treat severe acne, is such a strong teratogen that just a single dose taken by a pregnant woman may result in serious birth defects. Because of this effect, most countries have systems in place to ensure that it is not given to pregnant women, and that the patient is aware of how important it is to prevent pregnancy during and at least one month after treatment. Medical guidelines also suggest that pregnant women should limit vitamin A intake to about 700 µg/day, as it has teratogenic potential when consumed in excess.¹⁹

Teratogenic outcomes

Exposure to teratogens can result in a wide range of structural abnormalities such as cleft lip, cleft palate, dysmelia, anencephaly, ventricular septal defect. Exposure to a single agent can produce various abnormalities depending on the stage of development it occurs. Specific birth defects are not characteristic of any single agent.²⁰

In plants

In botany, teratology investigates the theoretical implications of abnormal specimens. For example, the discovery of abnormal flowers—for example, flowers with leaves instead of petals, or flowers with staminoid pistils—furnished important evidence for the "foliar theory", the theory that all flower parts are highly specialised leaves.^{21,22}

- Carcinogen
- Congenital abnormalities
- Mutagen

Conclusion

Genotoxicity is a property possessed by some substances that makes them harmful to the genetic information contained in organisms. While there are many different factors that can affect DNA, RNA, and other genetic materials, the property of genotoxicity only applies to those substances that actually cause harm to the genetic information. A substance that has the property of genotoxicity is known as a

genotoxin. There are three primary effects that genotoxins can have on organisms by affecting their genetic information. Genotoxins can be carcinogens, or cancer-causing agents, mutagens, or mutation-causing agents, or teratogens, birth defect-causing agents. Some genotoxins, such as those that affect cancer-suppressing genes, are considered carcinogenic, as they can lead to cancer. Cancer is the uncontrolled growth of cells within the body, and often has genetic causes. Substances with genotoxicity can cause mutations in cells that cause them to divide and grow uncontrollably. They can also have damaging effects on various proteins and other substances that normally prevent such uncontrolled cell growth. When these substances do not act as they should, some cells are much more likely to mutate and divide uncontrollably. In most cases, genotoxicity leads to mutations in various cells and other bodily systems. Mutations can lead to a host of other problems, from cancer to a wide variety of different diseases. Sometimes, mutations caused by genetics are completely harmless and can go completely unnoticed. In many other cases, though, the effects of genotoxins can be deadly. Mutations can come in many different forms; genetic information can be duplicated, deleted, or inserted. Some of these mutations can be teratogenic, meaning that they can cause birth defects. Often, this can occur because of some condition or substance in the parent affects the offspring. Either parent can be responsible, as both parents contribute genetic information to the child. If a genotoxin affects the genetic information in a parent's sex cells (eggs or sperm), a defect can appear in the genetic information of the offspring. Though there are many mechanisms by which genotoxicity can affect genetic information, one of the most common mechanisms involves the formation of strong chemical bonds between the genotoxins and the molecules that compose genetic information, such as DNA and RNA. In some cases, these bonds do not strongly affect the existing genetic

data. They do, however, prevent the proper replication of the genetic information. Such changes in the process of genetic

replication can cause myriad problems, as genes affect nearly every aspect of living organisms.

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