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**MLS512 QUIZ 1**

**ANSWER**

 **NUMBER ONE**

Poisons are substances that cause harm to organisms when sufficient quantities are absorbed, inhaled or ingested. Some poisons make a person sick, others may result to death and yet others may lead to subtle changes in health that may not be noticed for years. It is defined in biochemistry, as a substance, natural or synthetic, that causes damage to living tissues and has an injurious or fatal effect on the body, whether it is ingested, inhaled, or absorbed or injected through the skin.

Toxicology is the science of poisons. It is the study of harmful effects of chemicals on living organisms. Some people associate the word ‘chemical’ with manufactured poisons.

However, a chemical is not harmful just because it’s manufactured nor is it harmless just because it’s natural. Potentially poisonous chemicals can be synthetic (manufactured) or natural. For example, dioxins, some pesticides and nerve gases are poisonous manufactured chemicals, whereas, belladonna, botulinum and tetrodotoxin are poisonous naturally produced chemicals. There are also poisonous substances that occur naturally in the ground, such as asbestos and lead.

Therefore, Poisoning involves four elements: the poison, the poisoned organism, the injury to the cells, and the symptoms and signs or death. These four elements represent the cause, subject, effect, and consequence of poisoning. To initiate the poisoning, the organism is exposed to the toxic chemical. Whether a drug acts as a therapy or as a poison depends on the dose according to Paracelsus. When a toxic level of the chemical is accumulated in the cells of the target tissue or organ, the resultant injury to the cells disrupts their normal structure or function. Symptoms and toxic signs then develop, and, if the toxicity is severe enough, death may result.

**Classification of poisonous substances**

Poisons are of such diverse nature such that, they are classified according to their origin, physical form, chemical nature, chemical activity, target site, or use.

1. **Based on their toxic effects in the body as:**
* Poisons which cause death by anoxia
* Poisons which make haemoglobin incapable of transporting oxygen
e.g. Carbon monoxide, nitrites
* Poisons which inhibit cellular respiratory enzymes
e.g. Cyanides
* Poisons which destroy haemopoietic organs
e.g. Radioactive substances\
* Poisons, which on contact cause irritation or corrosiveness of the organs (skin) or damage the organ through which they are excreted (GI tract, respiratory tract, urinary tract) e.g. Irritant gases, alkaline corrosives, corrosive inorganic acids, corrosive organic acids and heavy metals
* Poisons, which damage protoplasm or parenchyma. These poisons produce local irritation and after absorption cause damage to the cells and capillaries e.g. phosphorus and carbon tetrachloride
* Poisons, which affect the nerve cells and fibres e.g. Hypnotics, narcotics, anesthetics, alcohol, some alkaloids and glycosides
1. **Based on their origin as plant poisons, toxins, venoms *etc*.**

Poisons are of microbial, plant, animal, or synthetic origin. Microbial poisons are produced by microscopic organisms such as bacteria and fungi. Botulinus toxin, for example, is produced by the bacterium Clostridium botulinum and is capable of inducing weakness and paralysis when present in underprocessed, nonacidic canned foods or in other foods containing the spores. An example of a plant toxin is the belladonna alkaloid hyoscyamine, which is found in belladonna (Atropa belladonna) and jimsonweed (Datura stramonium).

Animal poisons are usually transferred through the bites and stings of venomous terrestrial or marine animals, the former group including poisonous snakes, scorpions, spiders, and ants, and the latter group including sea snakes, stingrays, and jellyfish. Synthetic toxins are responsible for most poisonings. “Synthetic” refers to chemicals manufactured by chemists, such as drugs and pesticides, as well as chemicals purified from natural sources, such as metals from ores and solvents from petroleum. Synthetic toxins include pesticides, household cleaners, cosmetics, pharmaceuticals, and hydrocarbons.

1. **Based on their chemical and physical nature as, organic poisons, inorganic poisons, gaseous poisons, nitrogenous and non-nitrogenous organic poisons *etc*.**

The physical form of a chemical; solid, liquid, gas, vapour, or aerosol, which influences the exposure and absorbability.

Because solids are generally not well absorbed into the blood, they must be dissolved in the aqueous liquid lining the intestinal tract if ingested or the respiratory tract if inhaled. Solids dissolve at different rates in fluids, however. For example, compared with lead sulphate granules, granules of lead are practically nontoxic when ingested, because elemental lead is essentially insoluble in water, while lead sulphate is slightly soluble and absorbable. Even different-sized granules of the same chemical can vary in their relative toxicities because of the differences in dissolution rates. For example, arsenic trioxide is more toxic in the form of smaller granules than is the same mass of larger granules because the smaller granules dissolve faster.

A poison in a liquid form can be absorbed by ingestion or by inhalation or through the skin. Poisons that are gases at room temperature (e.g., carbon monoxide) are absorbed mainly by inhalation, as are vapours, which are the gas phase of substances that are liquids at room temperature and atmospheric pressure (e.g., benzene). Because organic liquids are more volatile than inorganic liquids, inhalation of organic vapours is more common. Although vapours are generally absorbed in the lungs, some vapours that are highly soluble in lipids (e.g., furfural) are also absorbed through the skin.

Aerosols are solid or liquid particles small enough to remain suspended in air for a few minutes. Fibres and dust are solid aerosols. Aerosol exposures occur when aerosols are deposited on the skin or inhaled. Aerosol toxicity is usually higher in the lungs than on the skin. An example of a toxic fibre is asbestos, which can cause a rare form of lung cancer (mesothelioma).

Many liquid poisons can exist as liquid aerosols, although highly volatile liquids, such as benzene, seldom exist as aerosols. A moderately volatile liquid poison can exist as both an aerosol and as a vapour. Airborne liquid chemicals of low volatility exist only as aerosols.

Poisons can be classified according to whether the chemical is metallic versus nonmetallic, organic versus inorganic, or acidic versus alkaline. Metallic poisons are often eliminated from the body slowly and accumulate to a greater extent than nonmetallic poisons and thus are more likely to cause toxicity during chronic exposure. Organic chemicals are more soluble in lipids and therefore can usually pass through the lipid-rich cell membranes more readily than can inorganic chemicals. As a result, organic chemicals are generally absorbed more extensively than inorganic chemicals. Classification based on acidity is useful because, while both acids and alkalis are corrosive to the eyes, skin, and intestinal tract, alkalis generally penetrate the tissue more deeply than acids and tend to cause more severe tissue damage.

1. **Based on their chemical activity**

Electrophilic (electron-loving) chemicals attack the nucleophilic (nucleus-loving) sites of the cells’ macromolecules, such as deoxyribonucleic acid (DNA), producing mutations, cancers, and malformations. Poisons also may be grouped according to their ability to mimic the structure of certain important molecules in the cell. They substitute for the cells’ molecules in chemical reactions, disrupting important cellular functions. Methotrexate, for example, disrupts the synthesis of DNA and ribonucleic acid (RNA).

1. **Based on their target site or use**

There is usually no predictive value in classification by target sites or by uses. However, this is classified to systematically categorize the numerous known poisons. Target sites include the nervous system, the cardiovascular system, the reproductive system, the immune system, and the lungs, liver, and kidneys. Poisons are classified by such uses as pesticides, household products, pharmaceuticals, organic solvents, drugs of abuse, or industrial chemicals.

 **NUMBER TWO**

(2a) Pharmacokinetics is a branch of pharmacology that examines how drug concentrations change with respect to time as a function of absorption, distribution, metabolism and excretion. These are disparate but interrelated processes that occur between drug administration and its irreversible elimination from the body.

The hydrophobic substance Q could be any of the following; acetaminophen, caffeine, theophylline, warfarin, phenytoin, omeprazole, codeine, risperidone, ethanol, midazolam, simvastatin, and pesticides such as gamma‐hexachlorocyclohexane. Hydrophobic substances are well known for both their toxicity and their interference with the structural interactions of cellular macromolecules and lipid bilayers.

**Absorption**

Oral administration is the most common route of drug administration. When drugs are taken orally they can enter the circulation from all parts of the gastro-intestinal tract. One important feature of absorption of drugs from the alimentary tract to the circulation is dissolution. It is generally accepted that substances must dissolve before they can be absorbed by common mechanisms such as diffusion or active transport. Many drugs can undergo aqueous dissolution and lipids undergo emulsification by bile acids.

Bioavailability describes the rate and concentration at which the drug appears in circulation. It is expressed as a percentage of the dose that was initially administered.

Bioavailability is affected by two mechanisms:

• First pass effect: Orally administered drugs are absorbed from the GI tract and reach the liver via the portal circulation. In the liver they undergo first pass metabolism before they enter systemic circulation, which decreases the bioavailability of the drug.

• Ability to pass through lipid membranes: dependent on the nature of the substance, since substance Q is hydrophobic, it undergoes emulsification by bile acids.

**Distribution**

After the drug reaches the bloodstream, it is initially distributed in the most vascularized organs. Drug distribution will be influenced by tissue/organ blood flow, whether the drug is able to passively diffuse across cell membranes or is a substrate for active uptake or efflux transporters, and its extent of binding to plasma protein and tissue sites.

The transfer of many drug compounds from the systemic circulation to various tissues/organs follows the perfusion-rate diffusion process. Here, we assume that cell membranes do not present any barrier to drug transfer. This typically applies to drug compounds that are lipid soluble. Under perfusion-rate diffusion, the rate of delivery from the systemic circulation to a specific tissue/organ is primarily dependent on the blood flow within an organ or tissue. Organs like the liver and the heart are highly perfused with blood. By contrast, the bone and the adipose tissues experience less blood perfusion. Therefore, drugs are likely to distribute more rapidly to tissues/organs that are more richly perfused with blood.

Passive diffusion across cell membranes

A major factor affecting drug distribution is the physicochemical properties of the drug since these would influence the permeability of the drug to various tissues. A drug that is highly lipophilic, such as chloroquine, may readily cross the lipidic bilayer of endothelial cells and most cell membranes to reach into the intracellular space via passive transcellular diffusion. Lipid-soluble drugs, because of their high partition coefficient, can also accumulate in organs or sites with fat deposits

Plasma protein and tissue binding

Another factor influencing drug distribution is the preferential binding to plasma proteins and tissues. It is the unbound or free portion of the drug that diffuses out of the plasma into the tissues/organs. Albumin and α1-acid glycoprotein are the two major proteins in plasma that are responsible for the binding of most drug compounds in the systemic circulation. The extent of plasma protein binding of a drug can be drug- or protein-concentration dependent, based on the affinity and capacity of the plasma protein. A drug’s protein-binding characteristics also depend on its physicochemical properties, with lipophilic drugs more likely to bind to plasma proteins and consequently, less available to the intracellular spaces

• **Distribution coefficient**: measure of hydrophobicity/hydrophilicity of a drug

C (drug concentration in the organic solvent)/ C (drug concentration in water)

• **Volume of distribution**: VD (usually expressed in liters/kg body weight) = M (amount of drug administered)/C (plasma concentration of the drug)

This value measures the tendency of the drug to be distributed in plasma rather than body tissues.

Lipophilic substances tend to have a large volume of distribution

• **Redistribution**: transfer of a drug between the different compartments within the human body

Lipophilic substances (e.g., inhalation anesthetics) are redistributed from plasma into fat tissue → initially decreased action of the applied drug

Drug is stored but over time is released again from fat tissue into plasma → delayed elimination and prolonged action of the specific drug

**Metabolism (biotransformation)**

Biotransformation is the chemical alteration of substances (e.g., drugs) within the body by the action of enzymes and mainly takes place in the liver. Biotransformation detoxifies drugs and facilitates their elimination. In the liver, a wide array of enzymes exists to biotransform drugs, producing less active (or in some cases more active) metabolites. Drug metabolism is defined as the biotransformation of lipid-soluble chemicals into water-soluble forms, so that these can be excreted in the urine. Metabolism is divided into two phases

Phases of biotransformation;

•Phase I reaction: The drug is transformed into a polar metabolite (mostly through oxidation by the cytochrome P450 system) → allows phase II reactions to take place. Such reactions typically involve oxidation, reduction or hydrolysis processes. Often, the by-product of phase I metabolism, called a derivative, is pharmacologically inactive but more chemically reactive than the parent drug, and may be toxic or even carcinogenic. The major liver enzyme system involved in phase I metabolism (oxidation) is the cytochrome P450 (CYP) enzyme system [15]. Thus far, 18 CYP families have been identified in mammals, although only CYP1, CYP2, CYP3 and CYP4 are involved in drug metabolism, with CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 being responsible for the biotransformation of greater than 90% of drugs undergoing phase I metabolism.

In addition to genetic polymorphism, liver CYP enzymes are subject to induction and inhibition by certain drugs. As a consequence, elimination of such CYP enzyme–substrate drugs administered concomitantly may increase or decrease. Additionally, where metabolic pathways involve the production of pharmacologically active or toxic metabolites, induction or inhibition of CYP enzymes could result in unanticipated changes in plasma drug concentrations, with potential clinical relevance to its therapeutic or toxicity profile.

•Phase II reactions (conjugation reaction): involves coupling the metabolite with glucuronic acid (most common coupling reaction), acetyl groups (e.g., metabolism of isoniazid), sulfates, amino acids (e.g., glycine), or glutathione

The derivative from phase I metabolism may be excreted via the urine immediately if high aqueous solubility is achieved. If not, the derivative undergoes a phase II reaction that brings about the conjugation of its functional group(s) to various hydrophilic endogenous compounds [16]. Examples of phase II reactions include sulfation, glucuronidation and glutathione conjugation. Sufficient water solubility is normally achieved in conjugates, which facilitate renal excretion.

**Clinical significance**

• Detoxification: In most cases, the drug is inactivated and modified into a hydrophilic metabolite → allows the drug to be excreted by the kidneys or in bile

• Activation: Certain drugs are transformed in the liver from their inactive prodrug state into active forms.

• Formation of toxic metabolites

**Excretion**

Excretion is the principal mode of termination of drug and metabolite effects. Drugs and their metabolite(s) are most commonly removed from the body via two main routes: renal and biliary excretion.

• Drug clearance: a measure of the rate of drug elimination. It is defined as the plasma volume that can be completely cleared of the drug in a given period of time (e.g., creatinine clearance)

• Half-life (T½): the time required for the plasma concentration of a drug to reach half of its initial value

After 4 half-lives, more than 90% of the drug will be eliminated.

Drugs and/or their metabolites are excreted from the body in one or more of the following ways:

Renal elimination: mostly hydrophilic drugs

• Glomerular filtration

• Tubular secretion

• Tubular reabsorption

Biliary elimination: lipophilic and hydrophilic substances

Biliary excretion is facilitated by active transport systems located in the canalicular membrane of the hepatocyte, and can be an important hepatic elimination pathway for many compounds. Since bile is an aqueous solution, it is suitable for dissolving hydrophilic drugs. In addition, bile acids allow solubilisation of lipid-soluble drugs. Thus, all types of species (anionic, cationic and un-ionised drugs), polar and lipophilic, can be secreted into the bile. These include drug metabolites that have undergone conjugation with glucuronate during phase II metabolism.

• Lipophilic substances that have undergone biliary elimination may be reabsorbed from the gut and then secreted again in bile (enterohepatic circulation).

 (2b) If the substance Q is hydrophilic, the absorption process is the same as the hydrophobic, although it does not undergo biotransformation.

Local blood flow is a strong determinant of the rate of absorption because it continuously maintains the concentration gradient necessary for passive diffusion to occur. For orally administered drugs, remember that the blood supply draining the gut passes through the liver before reaching the systemic circulation. Since the liver is a major site of drug metabolism, this first-pass effect may reduce the amount of drug reaching the target tissue.

**Distribution**

The central compartment includes the well-perfused organs and tissues (heart, blood, liver, brain and kidney) with which drug equilibrates rapidly.

Hydrophilic substance remains mostly in blood compartment until the drug is eliminated. An increase in the volume of distribution of a drug will generally increase its elimination half-life. A decrease in volume of distribution with an increase in elimination clearance will generally decrease elimination half-life.

**Metabolism**

The liver is the major site for drug metabolism, but biotransformation can also occur by the kidney and intestine.

**Excretion**

Polar, hydrophilic drugs may have increased excretion in the urine. Hydrophilic drugs are more likely to be excreted unchanged by the kidney.

• Decrease half-life = Increased glomerular filtration and/or tubular secretion

• Increase half-life = Increased protein binding may reduce glomerular filtration of drug Smaller hydrophilic molecules can diffuse along a concentration gradient through pores in the membrane.

The drugs are eliminated by the kidneys.

Renal excretion incorporates the processes of glomerular filtration, reabsorption from the renal tubular lumen, and tubular secretion as the drug passes through the nephron, the functional excretory unit of the kidney.

As blood passes through the glomerulus, entities within it are filtered to form the renal filtrate in the tubular lumen. The process of filtration is passive in nature and is driven by a combination of the large hydrostatic and concentration gradients present across the glomerulus-Bowman’s capsule junction. Nevertheless, large-sized components cannot be filtered through the glomerular membrane, which implies that large drugs (e.g. heparin), plasma proteins and plasma protein-bound drugs (e.g. warfarin) cannot cross into the tubular filtrate.

Water is reabsorbed along the nephron tubule so that only 1% of the original filtrate is passed out of the body as urine. Approximately 99% of substances filtered at the glomerulus are reabsorbed along the renal tubules. The majority of filtered, unmetabolised drug molecules are also reabsorbed, polar drugs e.g. gentamicin and digoxin, are unable to do this. Such drugs will therefore be excreted unchanged in the urine because they do not need to undergo biotransformation to increase their water solubility.

 **NUMBER THREE**

(3a) Antidotes or cures for particular toxins are produced using the toxin itself. An antidote is a drug, chelating substance, or a chemical that counteracts (neutralizes) the effects of another drug or a poison.Small doses of the toxin are injected into an animal to stimulate the animal’s immune system to produce antibodies to destroy the toxin. Serum (containing the antibodies) is harvested from the animal’s blood, and this serum with the antibodies becomes the antidote for that particular toxin.

|  |  |  |
| --- | --- | --- |
| s/n | Poisonous substance | Antidote  |
|  | Isoniazid | Pyridoxine  |
|  | Valproate | Carnitine  |
|  | Lead poisoning  | Dimercaprol  |
|  | Benzodiazepines | Flumazenil  |
|  | Bupivacaine | Intralipid |
|  | Cyanide  | Cyanocobalamin / Sodium thiosulphate |
|  | Digoxin | Digoxin immune Fab  |
|  | Iron | Desferrioxamine  |
|  | Heparin | Protamine |
|  | Clonidine  | Naloxone  |
|  | Warfarin | Vitamin K |
|  | Opiates | Naloxone |
|  | Beta blockers | Glucagon |
|  | Ethylene glycol | Ethyl alcohol/ Fomepizole |
|  | Methanol  | Ethyl alcohol/ Fomepizole |
|  | Methemoglobinemia  | Methylene blue/Ascorbic acid |
|  | Organophosphate | Atropine / Pralidoxine |
|  | Acetaminophen | Acetylcysteine |
|  | Carbamates | Atropine |
|  | Numerous drug poison | Activated charcoal |

(3b) **Ways Clinical effects of poisons can be studied**.

Toxicology is traditionally defined as "the science of poisons. It is "the study of the adverse effects of chemical, physical, or biological agents on living organisms and the ecosystem, including the prevention and amelioration of such adverse effects."

Toxicology is the study of the adverse effects of chemicals or physical agents on living organisms.

A toxic agent is anything that can produce an adverse biological effect. It may be chemical, physical, or biological in form. For example, toxic agents may be chemical (such as cyanide), physical (such as radiation) and biological (such as snake venom).

These adverse effects can take many forms, ranging from immediate death to subtle changes not appreciated until months or years later. They may occur at various levels within the body, such as an organ, a type of cell, or a specific biochemical.

A toxic substance is simply a material which has toxic properties. It may be a discrete toxic chemical or a mixture of toxic chemicals. For example, lead chromate, asbestos, and gasoline are all toxic substances.

Mechanistic toxicology: The study of how a chemical causes toxic effects by investigating its absorption, distribution, and excretion.

Descriptive toxicology: The toxic properties of chemical agents are systematically studied for various endpoints using a variety of different organisms.

Clinical toxicology: They study of toxic effects of various drugs in the body, and are also concerned with the treatment and prevention of drug toxicity in the population.

Forensic toxicology: A branch of medicine that focuses on medical evidence of poisoning, and tries to establish the extent to which poisons were involved in human deaths.

 Environmental toxicology: The study of the effects of pollutants on organisms, populations, ecosystems, and the biosphere.

Regulatory toxicology: The use scientific data to decide how to protect humans and animals from excessive risk. Public or Private Sector.

Factors determining adverse effects includes;

**Intrinsic toxicity**

Chemical properties; molecular structure & functional groups, solubility – insolubility, volatility, stability (light, water, acids, enzymes), reactivity

 Physical properties gas (density), liquid (vapour pressure), solid (crystal structure, size, shape)

**Dose**

The amount of chemical entering the body. It n is the amount of a substance administered at one time. This is usually given as mg of chemical/kg of body weight = mg/kg.

Types of doses e.g.,

* exposure dose; the amount of a xenobiotic encountered in the environment
* absorbed dose; the actual amount of the exposed dose that enters the body
* administered dose; the quantity administered usually orally or by injection.
* total dose; the sum of all individual doses.

 The dose is dependent upon;

* The concentration
* The properties of the toxicant
* The timing and frequency of exposure
* The length of exposure
* The exposure pathway

The degree of responses depend upon the dose and the organism

• Change from normal state – could be on the molecular, cellular, organ, or organism level--the symptoms

 • Local vs. Systemic

• Reversible vs. Irreversible

• Immediate vs. Delayed

The dose-response relationship is a fundamental and essential concept in toxicology. It correlates exposures and the spectrum of induced effects. Generally, the higher the dose, the more severe the response.



Knowledge of the dose-response relationship:

- establishes causality that the chemical has in fact induced the observed effects

- establishes the lowest dose where an induced effect occurs - the threshold effect

- determines the rate at which injury builds up - the slope for the dose response

**Major Types of Toxicity**

Acute toxicity: It involves lethal concentrations and short-term exposures

The end point is usually death

Dose-response curves are used to derive dose estimates of chemical substances. A common dose estimate for acute toxicity is the LD50 (Lethal Dose 50%). This is a statistically derived dose at which 50% of the individuals will be expected to die. The figure illustrates how an LD50 of 20 mg is derived. Other dose estimates also may be used. LD0 represents the dose at which no individuals are expected to die. This is just below the threshold for lethality. LD10 refers to the dose at which 10% of the individuals will die. For inhalation toxicity, air concentrations are used for exposure values. Thus, the LC50 is utilized which stands for Lethal Concentration 50%, the calculated concentration of a gas lethal to 50% of a group. Occasionally LC0 and LC10 are also used.

Chronic toxicity: It involves Sub-lethal concentration and long-term exposure • Chronic toxicity test is used to derive Effective Dose (ED50): Is the dose by which half of the population has been affected • Effect could be anything but death • ED50 is obtained by plotting, for a given dose the proportion of the population that responded to that dose and all lower doses.

No Observable Adverse Effect Level (NOAEL) – the threshold where no effects are observed. • Lowest Observable Adverse Effect Level (LOAEL) – the concentration level where effects are observed. NOELs and LOELs do not necessarily imply toxic or harmful effects and may be used to describe beneficial effects of chemicals as well. The NOAEL, LOAEL, NOEL, and LOEL have great importance in the conduct of risk assessments.



**Exposure conditions**

* Route of exposure; oral, inhalation, dermal, parenteral, etc
* Frequency and duration of exposure
* Mixed exposures
* Environmental circumstances

 **Response of host**

A target is an organ that is damaged by the xenobiotic or its metabolite. There may be more than one target for toxicity for a particular substance. For example, the targets for alcohol are the central nervous system and the liver.

Toxicity can result from adverse cellular, biochemical, or macromolecular changes. Examples are:

- cell replacement, such as fibrosis

- damage to an enzyme system

- disruption of protein synthesis

- production of reactive chemicals in cells

- DNA damage

Some xenobiotics may also act indirectly by:

- modification of an essential biochemical function

- interference with nutrition

- alteration of a physiological mechanism

The toxicity of a substance depends on the following: form and innate chemical activity dosage, especially dose-time relationship, exposure route, species, age, sex, ability to be absorbed, metabolism, distribution within the body, excretion, presence of other chemicals

**Other Types of systemic toxicity**

1. **Carcinogenicity**

Carcinogenicity is a complex multistage process of abnormal cell growth and differentiation which can lead to cancer. At least two stages are recognized. They are initiation in which a normal cell undergoes irreversible changes and promotion in which initiated cells are stimulated to progress to cancer. Chemicals can act as initiators or promoters. The initial neoplastic transformation results from the mutation of the cellular genes that control normal cell functions. The mutation may lead to abnormal cell growth. It may involve loss of suppresser genes that usually restrict abnormal cell growth. Many other factors are involved (e.g., growth factors, immune suppression, and hormones). A tumor (neoplasm) is simply an uncontrolled growth of cells. Benign tumors grow at the site of origin; do not invade adjacent tissues or metastasize; and generally are treatable. Malignant tumors (cancer) invade adjacent tissues or migrate to distant sites (metastasis). They are more difficult to treat and often cause death.

1. **Developmental Toxicity**

Developmental Toxicity pertains to adverse toxic effects to the developing embryo or fetus. This can result from toxicant exposure to either parent before conception or to the mother and her developing embryo-fetus.

Chemicals cause developmental toxicity by two methods. They can act directly on cells of the embryo causing cell death or cell damage, leading to abnormal organ development. A chemical might also induce a mutation in a parent's germ cell which is transmitted to the fertilized ovum. Some mutated fertilized ova develop into abnormal embryos

1. **Genetic Toxicity (somatic cells)**

Genetic Toxicity results from damage to DNA and altered genetic expression. This process is known as mutagenesis. The genetic change is referred to as a mutation and the agent causing the change as a mutagen.

If the mutation occurs in a germ cell the effect is heritable. There is no effect on the exposed person; rather the effect is passed on to future generations. If the mutation occurs in a somatic cell, it can cause altered cell growth (e.g. cancer) or cell death (e.g. teratogenesis) in the exposed person.

**Types of organ specific toxic effects are**:

4. **Blood and Cardiovascular Toxicity** results from xenobiotics acting directly on cells in circulating blood, bone marrow, and heart.

-hypoxia due to carbon monoxide binding of hemoglobin preventing transport of oxygen - decrease in circulating leukocytes due to chloramphenicol damage to bone marrow cells

- leukemia due to benzene damage of bone marrow cells

- arteriosclerosis due to cholesterol accumulation in arteries and veins

5. **Dermal Toxicity** may result from direct contact or internal distribution to the skin. Effects range from mild irritation to severe changes, such as corrosivity, hypersensitivity, and skin cancer. Examples of dermal toxicity are:

- dermal irritation due to skin exposure to gasoline

- dermal corrosion due to skin exposure to sodium hydroxide

- dermal hypersensitivity due to skin exposure to poison ivy

- skin cancer due to ingestion of arsenic or skin exposure to UV light

6. **Eye (Ocular) Toxicity** results from direct contact or internal distribution to the eye. The cornea and conjunctiva are directly exposed to toxicants. Thus, conjunctivitis and corneal erosion may be observed following occupational exposure to chemicals. Many household items can cause conjunctivitis. Chemicals in the circulatory system can distribute to the eye and cause corneal opacity, cataracts, retinal and optic nerve damage.

- acids and strong alkalis may cause severe corneal corrosion

- corticosteroids may cause cataracts

- methanol (wood alcohol) may damage the optic nerve

7. **Hepatotoxicity** is toxicity to the liver, bile duct, and gall bladder. The liver is particularly susceptible to xenobiotics due to a large blood supply and its role in metabolism. Thus it is exposed to high doses of the toxicant or its toxic metabolites.

8. **Immunotoxicity** realtes to the immune system. It can take several forms: hypersensitivity (allergy and autoimmunity), immunodeficiency, and uncontrolled proliferation (leukemia and lymphoma). The normal function of the immune system is to recognize and defend against foreign invaders. This is accomplished by production of cells that engulf and destroy the invaders or by antibodies that inactivate foreign material. Examples: -

 contact dermatitis due to exposure to poison ivy

- systemic lupus erythematosus in workers exposed to hydrazine

- immunosuppression by cocaine

 - leukemia induced by benzene

9. **Nephrotoxicity** The kidney is highly susceptible to toxicants for two reasons. A high volume of blood flows through it and it filtrates large amounts of toxins which can concentrate in the kidney tubules. Nephrotoxicity is toxicity to the kidneys. It can result in systemic toxicity causing:

- decreased ability to excrete body wastes

- inability to maintain body fluid and electrolyte balance

 - decreased synthesis of essential hormones (e.g., erythropoietin)

10. **Neurotoxicity** represents toxicant damage to cells of the central nervous system (brain and spinal cord) and the peripheral nervous system (nerves outside the CNS). The primary types of neurotoxicity are:

- neuronopathies (neuron injury)

- axonopathies (axon injury)

- demyelination (loss of axon insulation)

- interference with neurotransmission

11. **Reproductive Toxicity** involves toxicant damage to either the male or female reproductive system. Toxic effects may cause:

- decreased libido and impotence

- infertility

- interrupted pregnancy (abortion, fetal death, or premature delivery)

- infant death or childhood morbidity

- altered sex ratio and multiple births

- chromosome abnormalities and birth defects

- childhood cancer

12. **Respiratory Toxicity** relates to effects on the upper respiratory system (nose, pharynx, larynx, and trachea) and the lower respiratory system (bronchi, bronchioles, and lung alveoli). The primary types of respiratory toxicity are:

- pulmonary irritation

- asthma/bronchitis

- reactive airway disease

- emphysema

- allergic alveolitis

- fibrotic lung disease

 - pneumoconiosis

- lung cancer