**15/mhs05/003**

**MLS 512**

Question 1

**What is poison?**

“Any substance in relatively small quantities that can cause death or illness in living organisms by chemical action”.

“Any substance that, when relatively small amounts are ingested,

inhaled, or absorbed, or applied to, injected into, or developed within the

body, has chemical action that causes damage to structure or disturbance

of function, producing symptoms, illness, or death.”

**CLASSIFICATION OF POISON**

**Classification based on origin**

Poisons are of microbial, plant, animal, or synthetic origin. Microbial poisons are produced by microscopic organisms such as [bacteria](https://www.britannica.com/science/bacteria) and fungi. Botulinus toxin, for example, is produced by the bacterium [*Clostridium botulinum*](https://www.britannica.com/science/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.

**Classification based on mode of action**

## Corrosives

Corrosives are substances that rapidly destroy or decompose tissues at the point of contact.

GENERAL SYMPTOMS- immediately, if taken orally, there is burning pain in the mouth with severe burning in the esophagus and stomach. This is followed by retching and vomiting; the stomach contents are mixed with dark-colored liquids and shreds of mucous membrane from the mouth, esophagus, and stomach. The inside of the mouth is corroded and the lips present a characteristic stain if an acid has been used. Swallowing is very difficult, respiration is impeded, the abdomen is tender and distended with gas, the temperature is high, and the facial expression shows anxiety and great suffering

1. Acids
2. Inorganic acids: H2SO4, HCl, nitric acid
3. Organic acids: acetic acid, salicyclic acid, oxalic acid, carbonic acid
4. Vegetable: hydrocyanide acid, potassium cyanide
5. Alkali
6. Hydroxides: of sodium, potassium, ammonium
7. Carbonates: of sodium potassium, ammonium

## Irritants

Irritant poisons are those agents that do not directly destroy the body tissues but set up an inflammatory process at the site of application or contact. Some examples are potassium nitrate, silver nitrate, arsenic, and phosphorus.

GENERAL SYMPTOMS- There is usually nausea, vomiting, and purging (frequently the vomitus and stools contain blood), pain, and cramps in the abdomen. In some cases, there is inflammation of the urinary tract.

1. Inorganic: non-metals like phosphorus, chlorine, fluorine, boron, and bromine. Metals like arsenic, lead, mercury, iron, zinc.
2. Organic
3. Vegetables: calotropis, cotron oil, ergot, capsicum
4. Animals: scorpion, snakes, spider and poisonous insects

 3. Mechanical: powdered glass, nails, needles, rust.

## Neurotics

Neurotics are poisons that act on the brain, spinal cord, and the central nervous system. Some examples are opium, ether, chloroform, belladonna, ethyl and methyl alcohol, and the barbiturates.

GENERAL SYMPTOMS- Symptoms may be divided into two subclasses.

Depressants- They produce symptoms characterized by a period of exhilaration, followed by drowsiness and stupor; slow breathing; cold, clammy skin; cyanosis; slow pulse; muscular relaxation; dilated or contracted pupils; and insensibility to external impressions.

Stimulants -These produce symptoms characterized by rapid and feeble pulse; delirium; hot and dry skin; a sense of suffocation and the inability to breathe; shuddering and jerking of muscles; dilated or contracted pupils; distorted vision; and sometimes convulsions and tetany. Examples are strychnine or amphetamines

1. Cerebral nerotoxins
2. Narcotic and somniforus: opium and its alkaloids like morpheine, codeine, noscapine, narcine
3. Inebriants: alcohol, fuel, sedatives and hypnotics, insecticides and coal derivative
4. Deliriants: cannabis, cocaine, camphor, atropa belladonna.
5. Spinal neurotoxins
6. Excitants: Nux vomica and its alkaloid strychnine
7. Depressants: Lathyrus sativus and jasmine.
8. Peripheral neurotoxins: conium and curare

**Cardiac poison**

1. Aconite
2. Digitalis
3. Oleander
4. Tobacco

**Asphyiant (Respiratory poison)**

1. Carbon monoxide
2. Carbon dioxide
3. Sulphur dioxide
4. Tear gas, chlorine, phosphine.

**Miscellenous**

1. Analgesics and Antipyretics
2. Antihistaminics
3. Tranquilizers
4. Stimulants e.g Amphetamines
5. Antidepressants
6. Hallucinogens
7. Food poisoning
8. Drug dependance

QUESTION 2

Hydrophobicity represents the tendency of a substance to repel water and to avoid the complete dissolution in water. The term “hydrophobic” means, “water fearing”, from the Greek words hydro, water, and phobo, fear. Hydrophobic substances are lipid soluble (lipophilic).

**Absorption**

Following oral dosing, drug molecules can cross the luminal membrane through various mechanisms that involve passive diffusion or active transport. In order for a poison to produce toxicity, a sufficient quantity of that chemical must be absorbed into the body. Because the chemical must pass through a number of cell membranes before it can enter the blood, the ability of the chemical to cross these lipid-rich membranes determines whether it will be absorbed, and that ability depends on the chemical’s lipid solubility. The cell membrane the most external layer of all animal cells is composed of two layers of lipid molecules (the lipid bilayer). The lipid molecules each have a hydrophilic (water-loving, or polar) end and a hydrophobic (water-hating, or nonpolar) end. Because an aqueous environment surrounds them, lipid molecules of the cell membrane arrange themselves so as to expose their hydrophilic ends and protect their hydrophobic ends. Suspended randomly among the lipid molecules are proteins, some of which extend from the exterior surface of the cell membrane to the interior surface.

A chemical tends to dissolve more readily in a solvent of similar polarity. Nonpolar chemicals are considered lipophilic (lipid-loving), and polar chemicals are hydrophilic (water-loving). Lipid-soluble, nonpolar molecules pass readily through the membrane because they dissolve in the hydrophobic, nonpolar portion of the lipid bilayer by passive difussion. Although permeable to water (a polar molecule), the nonpolar lipid bilayer of cell membranes is impermeable to many other polar molecules, such as charged ions or those that contain many polar side chains. Polar molecules pass through lipid membranes via specific transport systems.

**Distribution**

Drug distribution can be defined as the movement of drug between blood and extravascular tissues. After absorption into the bloodstream, drugs are disseminated to all parts of the body. As drug absorption occurs, drug transfers to the blood, resulting in a concentration gradient across the capillaries, allowing filtration of drug into the interstitial fluid. The accumulated drug in the interstitial fluid drives its passive diffusion into tissues and organs. Passive diffusion is normally the driving force in drug distribution. In blood drugs can bind reversibly to proteins. Blood cells, in particular erythrocytes when they bind or take up certain drugs, play a role of temporary reservoir.

**Metabolism**

Drugs that are lipid soluble will be passively reabsorbed as urine concentrates in the kidney unless they are converted by enzymatic processes to water-soluble drugs. This is accomplished by drug metabolism. Metabolism and subsequent excretion of drugs together comprise drug “elimination” from the body. Most drug metabolism occurs in the smooth endoplasmic reticulum of the liver. Metabolism generally consists of two phases: Phase I induces a chemical change (most frequently oxidation, but also reduction) that renders the drug more conducive to phase II. Phase II is a conjugative or synthetic addition of a large, polar molecule that renders the drug water soluble and amenable to renal excretion.

Four possible sequelae follow phase I metabolism:

1) Inactivation (eg, most NSAIDs)

 2) Activation from a "pro-drug" to the active form of the drug (eg, enalapril to enalaprilat)

3) Modification of activity, ie, formation of active metabolites that may be characterized by activity greater than (eg, tramadol), less than (eg, diazepam), or equal to that of the parent compound.

 4) Formation of toxic metabolites, which is generally due to direct cell damage (eg, acetaminophen). In some instances the toxic metabolite acts as an antigen, causing immune-mediated toxicity (eg, sulfonamides). Because phase II drug metabolism almost exclusively inactivates drugs (the notable exception being some acetylated and methylated drugs), it often protects the organ of metabolism from drug-induced toxicity. This is particularly true with the addition of glutathione, which scavenges oxygen radicals; in the face of drug toxicity, *N*-acetylcysteine will increase intracellular glutathione. Multiple isoforms of phase II drug-metabolizing enzymes exist. Glucuronide (the addition of which is catalyzed by glucuronide transferase) is the most common phase II reaction; cats are deficient in some, but not all, glucuronyl transferases. Other important phase II enzymes include sulfation (deficient in swine), acetylation (deficient in dogs), and methylation. Amino acid conjugations are particularly important in avian species.

Heme-containing enzymes referred to as cytochrome P450 (CYP450) largely, but not exclusively, accomplish phase I drug metabolism. More than 20 super families have been identified, with some being specific for some drug or drug classes but others characterized by broad substrate specificity. Among the major super families are CYP3A, which in people has been demonstrated to be responsible for the larger proportion of drug metabolism. Others important to drug metabolism are CYP2C and CYP2D. CYP enzymes are responsible for synthesis (eg, adrenal steroids, fatty acids) and metabolism of many endogenous compounds.

**Elimination**

The body can clear itself of drugs either by metabolism or excretion. Excretion irreversibly removes drugs or metabolites from the body. The kidneys are the principal organ of excretion, but the liver, GI tract, and lungs also may play important roles. Renal excretion of foreign compounds is accomplished either by glomerular filtration, passive diffusion into and out (e.g., resorption) of the tubular lumen, and carrier-mediated secretion (eg, active transport or facilitated diffusion).

**Renal elimination:** The kidney, which receives with high pressure approximately 1400 ml/mn of blood, about a quarter of the cardiac output, eliminates drugs and various other compounds from the body. From the physiological point of view, the nephron, basic unit of the kidney, acts by three different mechanisms: glomerular filtration, tubular secretion and tubular reabsorption. There are approximately 1 million nephrons per kidney.

**Digestive elimination of drugs** The digestive tract is a location of exchanges where, of course, absorption is predominant after oral administration, but secretion is far from being negligible. Actually, very often absorption is followed by secretion, itself followed by reabsorption. The entero-hepatic cycle of biliary salts and of a certain number of drugs is a particular case of this general process.

The secretion of the drugs can occur along the digestive tract: in saliva, gastric fluid, bile, and intestinal secretions. This secretion is not necessarily elimination, because the secreted drugs can be reabsorbed. The final elimination in stools results from the difference between secretion into the intestinal lumen and reabsorption. Moreover, during their transfer in the digestive tract, drugs can undergo biotransformation under the effect of digestive or microbial enzymes or because of their instability according to pH.

**Pulmonary elimination:** The pulmonary elimination (in expired air) concerns only a low number of drugs, but for which it can represent the main route of elimination. The concerned drugs are volatile products like some general anesthetics, halothane for example, from which 60% is eliminated in the expired air. .

The elimination of ethyl alcohol by the pulmonary route is used to measure its plasma concentration. The expired air constitutes also a route of elimination of volatile solvents (ether, hexane, benzene, trichloroethylene, etc), which can be at the origin of poisoning by pulmonary absorption. Absorption or elimination depends on the relative concentrations of these products in the expired air and blood.

**2b.**

Hydrophilic drugs are “water loving” substances. A hydrophilic [molecule](https://en.wikipedia.org/wiki/Molecule) is one whose interactions with water and other polar substances are more thermodynamically favorable than their interactions with oil or other hydrophobic surfaces. They are typically charge-polarized and capable of hydrogen bonding. This makes these molecules soluble not only in water but also in other polar solvents.

**Differences between hydrophilic and hydrophobic drugs.**

|  |  |
| --- | --- |
| **Hydrophilic**  | **Hydrophobic**  |
| Usually polar | Usually non polar |
| Aqueous diffusion | Lipid diffusion |
| Require pores or transporters to get across the lipid bilayer | Can cross lipid bilayer by passive difussion  |
| Usually don’t cross the blood-brain barrier and blood-uterine barrier | Usually cross the blood-brain barrier and blood-uterine barrier |

Absorption: Polar molecules pass through lipid membranes via specific transport systems. Drugs that are water soluble and polar, such as aminoglycosides, do not distribute well into most tissues/organs. For such drug molecules, entry into the tissue spaces may rely on either paracellular diffusion via gaps in-between cells or carrier-mediated uptake transport processes.

Elimination: Hydrophobic drugs, to be excreted, must undergo metabolic modification making them more polar. Hydrophilic drugs, on the other hand, can undergo excretion directly, without the need for metabolic changes to their molecular structures. Therefore hydrophilic drugs are rapidly excreted from the body.

QUESTION 3a.

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| --- | --- |
| **Toxin** | **Antidote**  |
| Anticholinergic substances | Physostigmine  |
| Aluminium  | Deferoxamine  |
| Benzodiazepines | Flumazenil |
| Barbiturates  | Charcoal hemoperfusion, multiple oral dose activated charcoals. |
| Beta-blockers | Glucagon  |
| Carbamazepine  | Multiple dose oral activated charcoal |
| Carbon monoxide | Oxygen  |
| Cyanide  | Amyl nitrite, sodium nitrite |
| Digoxin  | Digibind  |
| Ethylene glycol, methanol | Ethanol  |
| Iron  | Deferoxamine  |
| Isoniazide  | Pyridoxine  |
| Lead  | Calcium disodium edetate, dimecaprol |
| Mercury  | Dimercaprol, 2,3-dimercaptosuccinic acid |
| Nitrites, nitrate | Methylene blue |
| Opiods  | Naloxone  |
| Organophosphate  | Atropine |
| Salicylates  | Bicarbonate  |
| Tricyclic antidepressant  | Sodium bicarbonate |
| Theophylline | Multiple dose oral activated charcoal |

3b.

The clinical effect of poison is **toxicity.** Toxicity studies investigate the safety profile of the candidate compound. They also provide important information about the absorption, distribution, metabolism, and excretion (ADME) of the compound in the body. A candidate compound must be assessed in many different kinds of non-clinical toxicity study before it can be administered to the first human volunteer; even more toxicity studies are required thereafter before the medicine receives marketing authorization.

**Types of Toxicology Studies**

The following kinds of toxicology studies must be performed during non-clinical testing:

### Systemic toxicity studies

Systemic toxicology studies investigate the toxicity profile of the candidate compound in all of the tissues and organs. Systemic toxicology studies can be either single-dose or repeated-dose studies.

### Reproductive toxicity studies

Reproduction toxicity studies investigate the effect of the drug on the ability to reproduce and develop normally. These studies should be conducted as is appropriate for the population to be exposed to the drug, and according to the following considerations:

* Men can be included in Phase I and II clinical trials before the conduct of the male fertility study, as an evaluation of the male reproductive organs is performed in the repeated-dose toxicity studies, although these studies should happen early in the process whenever possible. In any case, a male fertility study should be completed before the initiation of large scale or long duration clinical trials (for instance, Phase III trials).
* Women not of childbearing potential (for instance, permanently sterilized or postmenopausal women) can be included in clinical trials without reproduction toxicity studies, if the relevant repeated-dose toxicity studies (which include an evaluation of the female reproductive organs) have been conducted.
* If women of childbearing potential are identified as a potential user population of the medicine, reproduction toxicity studies need to be done as early as possible.

### Local tolerance studies

Local tolerance studies investigate the effect of the compound on the skin or eyes. These local toxicity studies are usually part of the general toxicity studies. To support limited human administration by non-therapeutic routes, e.g. a single intravenous dose for determination of absolute bioavailability, a single dose local tolerance study in a single species is usually sufficient.

### Genotoxicity studies

Genotoxicity studies investigate the effect of the candidate drugs on the chromosomes and genes, and are generally needed to support human safety. Assessment of gene mutation is considered sufficient to support all single-dose clinical trials. For multiple-dose clinical trials, an additional assessment of chromosomal damage in mammalian systems is needed, and a full battery of tests for genotoxicity should be completed before initiation of Phase II clinical trials. If positive findings are observed in genotoxicity tests, the need for additional testing must be considered.

### ****Carcinogenicity studies****

Carcinogenicity studies assess the effect that the candidate compound has on cancer generation. Carcinogenicity studies are generally conducted to support the marketing application of a new medicine. However, if there is a significant cause for concern, carcinogenicity studies should be conducted to bolster safety within clinical trials. In this case, a longer-term clinical trial duration with frequent monitoring can be carried out. Generally, for medicines indicated for serious diseases in adults or pediatric patients, carcinogenicity testing may be concluded post-approval, based on the assumption that the early access to the medicines for patients outweighs the possible risk, although the earlier these tests can be completed, the better.