INTRODUCTION TO TOXICOLOGY

History

- **Paracelsus** determined that specific chemicals were actually responsible for the toxicity of a plant or animal poison.
- He also documented that the body's response to those chemicals depended on the dose received. His studies revealed that small doses of a substance might be harmless or beneficial whereas larger doses could be toxic.
- This is now known as the dose-response relationship, a major concept of toxicology. Paracelsus was one of the founders of modern toxicology. His best known quote: *All substances are poisons;* it is the dose that makes the poison.

Continue History

- **Orfila**, a Spanish physician, is often referred to as the **founder of toxicology**. Orfila who first prepared a systematic correlation between the chemical and biological properties of poisons of the time.

- He demonstrated effects of poisons on specific organs by analyzing autopsy materials for poisons and their associated tissue damage.

- The 20th century is marked by an advanced level of understanding of toxicology. DNA *(the molecule of life)* and various biochemicals that maintain body functions were discovered. Our level of knowledge of toxic effects on organs and cells is now being revealed at the molecular level. It is recognized that virtually all toxic effects are caused by changes in specific cellular molecules and biochemical.

Toxicology Terminology

- **Toxicology** is the study of the harmful effects of chemicals or physical agents on living organisms.
- A **toxicologist** is a scientist that determines the harmful effects of agents and the cellular, biochemical, and molecular mechanisms responsible for the effects.
- **Toxicant, toxin, and poison** are often used interchangeably in the literature; however, there are subtle differences as indicated in the table.

Toxicology Terminology

Toxins	refers to toxic substances that are produced by biological systems such as plants, animals, fungi, or bacteria. E.g. zeralanone, produced by a mold, is a toxin.
Toxicants (Poisons)	is used in speaking of toxic substances that are produced by or are a by-product (human-made) activities. E.g. dioxin" [2,3,7,8-tetrachlorodibenzo-*p*dioxin (TCDD)], produced during the production and/or combustion of certain chlorinated organic chemicals, is a toxicant.
venom	Is special category of toxins it must injected by one organism to another .
Toxicity (Poisoning)	Is the harmful effect of chemicals on the exposed biological system.
Toxicosis	It describe the disease state resulted from the exposure to chemicals.

Toxic agent or substance

- **Toxic agent** is anything that can produce a harmful biological effect. It may be chemical, physical, or biological in form.

Toxic agents may be:

- Chemical *(such as cyanide)*,
- Physical *(such as radiation)* and
- Biological *(such as snake venom)*.

Toxic agents

- Some **toxicants** can be produced by both natural and anthropogenic activities.
- For example, polyaromatic hydrocarbons are produced by the combustion of organic matter, which may occur both through natural processes (e.g., forest fires) and through anthropogenic activities (e.g., combustion of coal for energy production; cigarette smoking).
- Arsenic, a toxic metalloid, may occur as a natural contaminant of groundwater or may contaminate groundwater secondary to Industrial activities.

Toxicological Chemistry

Toxicological chemistry relates chemistry to toxicology. It deals with the chemical nature of toxic substances, how they are changed biochemically, and how xenobiotic substances and their metabolites react biochemically in an organism to exert a toxic effect.

Specialized Areas of Toxicology

Given the huge variety of toxic substances and their toxic effects, it is obvious that toxicology is a large and diverse area. Three specialized areas of toxicology should be pointed out.

Clinical toxicology

is practiced primarily by physicians who look at the connection between toxic substances and the illnesses associated with them. For example, a clinical toxicologist would be involved in diagnosing and treating cases of poisoning.

Forensic toxicology

deals largely with the interface between the medical and legal aspects of toxicology and seeks to establish the cause and responsibility for poisoning, especially where criminal activity is likely to be involved

.

Environmental toxicology

is concerned with toxic effects of environmental pollutants to humans and other organisms. Of particular importance are the sources, transport, effects, and interactions of toxic substances within ecosystems as they influence population dynamics within these systems. This area constitutes the branch of environmental toxicology called ecotoxicology

CLASSIFICATION OF TOXIC AGENTS

Toxic agents are classified in a variety of ways, depending on the interests and needs of the classifier.

Toxic agents are classified according to:

- **Target organs** (liver, kidney, hematopoietic system, etc.),
- **Use** (pesticide, solvent, food additive, etc.),
- **Source** (animal and plant toxins),
- **Effects** (cancer, mutation, liver injury, etc.).

Toxic agents may also be classified in terms of

- **Physical state** (gas, dust, liquid), their chemical stability or reactivity (explosive, flammable, oxidizer),

- General **chemical structure** (aromatic amine, halogenated hydrocarbon, etc.),

Or **poisoning potential** (extremely toxic, very toxic, slightly toxic, etc.).

Classification of toxic agents on the basis of their

- **Biochemical mechanisms of action** (e.g., alkylating agent, cholinesterase inhibitor, methemoglobin producer) is usually more informative than classification by general terms such as irritants and corrosives.

- But more general classifications such as **air pollutants**, **occupation-related agents**, and **acute and chronic poisons** can provide a useful focus on a specific problem.

Toxic substances may be organic or inorganic in composition

Organic toxins	substances that were originally derived from living organisms *(thus named organic)* contain carbon and often are large molecules can be synthesized *(that is man-made)* as well as be obtained from natural sources
Inorganic toxins	specific chemicals that are not derived from living organisms *(minerals)* generally small molecules consisting of only a few atoms *(such as nitrogen dioxide)*

Toxic substances may be **systemic toxins** or **organ toxins**.

- A **systemic toxin** is one that affects the entire body or many organs rather than a specific site. For example, **potassium cyanide** is a systemic toxicant in that it affects virtually every cell and organ in the body by interfering with the cell's ability to utilize oxygen.

- Toxicants may also affect only specific tissues or organs while not producing damage to the body as a whole. These specific sites are known as the **target organs** or **target tissues**.

- Some examples: Benzene is a **specific organ toxin** in that it is primarily toxic to the blood-forming tissues.
- Lead is also a **specific organ toxin**; however, it has three **target organs** *(central nervous system, kidney, and hematopoietic system).*

Target tissue

- A **toxicant** may affect a specific type of tissue ***(such as connective tissue)*** that is present in several organs. The toxic site is then referred to as the **target tissue**.
- There are many types of cells in the body and they can be **classified in several ways**.
- basic structure (e.g., cuboidal cells)
- tissue type (e.g., hepatocytes of the liver)
- germinal cells (e.g., ova and sperm)
- somatic cells (e.g., non-reproductive cells of the body).

Germ and Somatic cells

Germ cells are those cells that are involved in the reproductive process and can give rise to a new organism. They have only a single set of chromosomes peculiar to a specific sex. Male germ cells give rise to sperm and female germ cells develop into ova. **Toxicity** to germ cells can cause effects on the developing fetus ***(such as birth defects, abortions)*.**

Somatic cells are all body cells except the reproductive germ cells. They have two sets *(or pairs)* of chromosomes. **Toxicity** to somatic cells causes a variety of toxic effects to the exposed individual *(such as **dermatitis, death, and cancer**)*.

Reversible versus Irreversible Toxic Effects

- Some toxic effects of chemicals are **reversible**, and others are **irreversible**.
- If a chemical produces pathological injury to a tissue, the ability of that tissue to regenerate largely determines whether the effect is reversible or irreversible.
- Thus, for a tissue such as liver, which has a high ability to regenerate, most injuries are reversible, whereas injury to the CNS is largely irreversible because differentiated cells of the CNS cannot divide and be replaced.

- Carcinogenic effects of chemicals, once they occur, are usually considered irreversible toxic effects.

Factors determining adverse effects

- Several factors will be discussed determining the harmful effects of toxic agents.

1-Related to poison

- **Intrinsic toxicity**
- Dose
- Exposure conditions

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, …)

- The **form** of a substance may have a profound impact on its toxicity especially for metallic elements. For example, the toxicity of mercury vapor differs greatly from methyl mercury.
- Another example is chromium. Cr^{3+} is relatively nontoxic whereas Cr^{6+} causes skin or nasal corrosion and lung cancer.

- The **essential chemical activity** of substances also varies greatly.
- Some can quickly damage cells causing immediate cell death. Others slowly interfere only with a cell's function.

- For example: 1- hydrogen cyanide binds to cytochrome oxidase resulting in cellular hypoxia and rapid death

  2- nicotine binds to cholinergic receptors in the CNS altering nerve conduction and inducing gradual onset of paralysis.

Dose

- The **dose** is the amount of a substance administered at one time.
- However, other parameters are needed to characterize the exposure to xenobiotic.
- The most important are the **number of doses**, **frequency**, and **total time period of the treatment.**

Some examples:

- 500 mg Asperin as a single dose
- 500 mg Penicillin every 8 hours for 10 days
- 15 mg DDT per day for 60 days

Types of doses

- **e.g.,** exposure dose, absorbed dose, administered dose and total dose

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

Fractionating dose

- **Fractionating** a total dose usually decreases the probability that the total dose will cause toxicity.
- The reason for this is that the body often can repair the effect of each sub-toxic dose if sufficient time passes before receiving the next dose.

- In such a case, the total dose, harmful if received all at once, is non-toxic when administered over a period of time.
- **For example,** 30 mg of strychnine swallowed at one time could be fatal to an adult **whereas** 3 mg of strychnine swallowed each day for ten days would not be fatal.

Units used in toxicology

- The units used in toxicology are basically the same as those used in medicine. **The gram** is the standard unit. However, most exposures will be smaller quantities and thus the **milligram (mg)** is commonly used.

- **For example,** the common adult dose of Tylenol is 650 milligrams. The clinical and toxic effects of a dose must be related to **age** and **body size**.

- **For example**, 650 mg is the adult dose of Tylenol. That would be **quite toxic to young children**, and thus Children's Tylenol tablets contain only 80 mg.

- A better means to allow for comparison of effectiveness and toxicity is the amount of a substance administered on a **body weight basis**.

- A common dose measurement is **mg/kg** which stands for mg of substance per kg of body weight.

Dose units

• Another important aspect is **the time** over which the dose is administered. This is especially important for exposures of several days or for chronic exposures.

• The commonly used time unit is one day and thus, the usual dosage unit is **mg/kg/day**. Since some xenobiotics are toxic in much smaller quantities than the milligram, smaller fractions of the gram are used, such as microgram (µg). Other units are shown in the slide.

Unit	Gram Equivalents	Exp. Form
Kilogram (kg)	1000.0 g	10^{3} g
Gram (g)	1.0 g	1 g
Milligram (mg)	0.001 g	10^{-3} g
Microgram (µg)	0.000,001 g	10^{-6} g
Nanogram (ng)	0.000,000,001 g	10^{-9} g
Picogram (pg)	0.000,000,000,001 g	10^{-12} g
Femtogram (fg)	0.000,000,000,000,001 g	10^{-15} g

In the environmental sciences Environmental exposure units are expressed as the amount of a xenobiotic in a unit of the media.
mg/liter (mg/l) for liquids
mg/gram (mg/g) for solids
mg/cubic meter (mg/m3) for air

Smaller units are used as needed, e.g., µg/ml.

Other commonly used dose units for substances in media are parts per million (ppm), parts per billion (ppb) and parts per trillion (ppt).

The dose level at which a toxic effect is first encountered is known as the **threshold dose**. Doses below the threshold dose are often referred to as "**subthreshold doses**."

ppm

- This is a way of expressing very dilute concentrations of substances.
- Parts per million - ppm - is commonly used as a measure of small levels of pollutants in air, water, body fluids, etc.

- Parts per million is the mass ratio between the pollutant component and the solution and ppm is defined as

ppm = 1,000,000 mc / ms

ppb - parts per billion (1 / 1,000,000,000 or 10-9)

ppt - parts per trillion (1 / 1,000,000,000,000 or 10-12)

- Parts per million or ppm means out of a million.

- Usually describes the concentration of something in water or soil.

- One ppm is equivalent to 1 milligram of something per liter of water (mg/l) or 1 milligram of something per kilogram soil (mg/kg) .

1 mg/kg = 1 part per million

EXPOSURE

- The major factors that influence toxicity as it relates to the exposure situation for a specific chemical are the route of exposure, the duration, and frequency of exposure.

Exposure conditions

- Routes of exposure
- Frequency & duration of exposure
- Mixed exposures

Routes of exposure

- Oral
- Inhalation
- Dermal
- Parenteral

- **Parenteral means**: application outside the gastro-intestinal tract by e.g. intramuscular, intravenous application of medicines.

Route and Site of Exposure

- The major routes (pathways) by which toxic agents gain access to the body are the gastrointestinal tract (ingestion), lungs (inhalation), skin and other parenteral (other than intestinal canal) routes.

- Toxic agents generally produce the greatest effect and the most rapid response when given directly into the bloodstream (the intravenous route).

- An approximate descending order of effectiveness for the other routes would be inhalation, intramuscular, intradermal, oral, and dermal.

- In addition, **the route of administration** can influence the toxicity of agents. For example, an agent that acts on the CNS, but is efficiently detoxified in the liver, would be expected to be less toxic when given orally than when given via inhalation, because the oral route requires that nearly all of the dose pass through the liver before reaching the systemic circulation and then the CNS.

Duration and Frequency of Exposure

- **The chemicals classified into four categories:**

- Acute, subacute, subchronic, and chronic.

Acute exposure is defined as exposure to a chemical for less than 24 hours, and examples of exposure routes are intravenous, and injection; oral intubation; and dermal application

. **Whereas** acute exposure usually refers to a single administration, repeated exposures may be given within a 24-hours period for some slightly toxic or practically nontoxic chemicals. Acute exposure by inhalation refers to continuous exposure for less than 24 hours, most frequently for **4 hours**.

- **Repeated exposure is divided into three categories:** subacute, subchronic, and chronic.

Subacute exposure

refers to repeated exposure to a chemical for 1 month or less.

Subchronic

for 1 to 3 months.

Chronic for more than 3 months, although usually this refers to studies with at least 1 year of repeated dosing.

- These three categories of repeated exposure can be by any route, but most often they occur by the oral route, with the chemical added directly to the diet.

Mixed exposure to more than toxicant

Interaction of Chemicals

- The effects of two chemicals given simultaneously produce a response that may simply be additive of their individual responses or may be greater or less than that expected by addition of their individual responses. The study of these interactions often leads to a better understanding of the mechanism of toxicity of the chemicals involved. A number of terms have been used to describe pharmacologic and toxicologic interactions.

- **An *additive* effect** occurs when the combined effect of two chemicals is equal to the sum of the effects of each agent given alone (example: 2 + 3 = 5). The effect most commonly observed when two chemicals are given together is an additive effect. For example, when two organophosphate insecticides are given together, the cholinesterase inhibition is usually additive.

- **A *synergistic* effect** occurs when the combined effects of two chemicals are much greater than the sum of the effects of each agent given alone (example: 2 + 2 = 20).

For example, both carbon tetrachloride and ethanol are hepatotoxic compounds, but together they produce much more liver injury than the mathematical sum of their individual effects on liver at a given dose would suggest.

- ***Potentiation*** occurs when one substance does not have a toxic effect on a certain organ or system but when added to another chemical makes that chemical much more toxic (example: 0 + 2 = 10).
- Isopropanol, **for example,** is not hepatotoxic, but when it is administered in addition to carbon tetrachloride, the hepatotoxicity of carbon tetrachloride is much greater than when it is given alone.

Antagonistic effects

Antagonism occurs when two chemicals administered together interfere with each other's actions or one interferes with the action of the other .

- Antagonistic effects of chemicals are often very desirable in toxicology and are the basis of many antidotes.

- **There are four major types of antagonism:**

functional, chemical, dispositional, and receptor.

Functional antagonism:

occurs when two chemicals counterbalance each other by producing opposite effects on the same physiologic function.

Advantage is taken of this principle in that the blood pressure can markedly fall during severe barbiturate intoxication, which can be effectively antagonized by the intravenous administration of a vasopressor agent such as norepinephrine or metaraminol.

Similarly, many chemicals, when given at toxic dose levels, produce convulsions, and the convulsions often can be controlled by giving anticonvulsants such as the benzodiazepines (e.g., diazepam).

Chemical antagonism or inactivation is simply a chemical reaction between two compounds that produces a less toxic product. For example, dimercaprol (British antilewisite, or BAL) chelates with metal ions such as arsenic, mercury, and lead and decreases their toxicity.

The use of antitoxins in the treatment of various animal toxins is also an example of chemical antagonism.

The use of the strongly basic low-molecular-weight protein protamine sulfate to form a stable complex with heparin, which abolishes its anticoagulant activity, is another example.

Dispositional antagonism occurs when the disposition—that is, the absorption, distribution, biotransformation, or excretion of a chemical—is altered so that the concentration and/or duration of the chemical at the target organ are diminished.

Thus, the prevention of absorption of a toxicant by ipecac or charcoal and the increased excretion of a chemical by administration of an osmotic diuretic or alteration of the pH of the urine are examples of dispositional antagonism.

Receptor antagonism occurs when two chemicals that **bind** to the **same receptor** produce **less of an effect** when given together than the addition of their separate effects (example: 4 + 6 = 2).

OR when one chemical **antagonizes** the effect of the second chemical (example: 0 + 4 = 1).

Receptor antagonists are often termed ***blockers***. This concept is used to advantage in the clinical treatment of poisoning.

For example, the receptor antagonist **naloxone** is used to treat the respiratory depressive effects of **morphine** and other morphine-like narcotics by **competitive binding to the same receptor**.

Treatment of **organophosphate insecticide** poisoning with **atropine** is an example not of the antidote competing with the poison for the receptor (cholinesterase) but involves **blocking the receptor (cholinergic receptor)** for the excess acetylcholine that accumulates by poisoning of the cholinesterase by the organophosphate.

Tolerance

- **Tolerance** is a state of decreased responsiveness to a toxic effect of a chemical resulting from prior exposure to that chemical or to a structurally related chemical.
- Two major mechanisms are responsible for tolerance:

one is due to a decreased amount of toxicant reaching the site where the toxic effect is produced (dispositional tolerance),

and the other is due to a reduced responsiveness of a tissue to the chemical.

- Two chemicals known to produce dispositional tolerance are carbon tetrachloride and cadmium.
- Carbon tetrachloride produces tolerance to itself by decreasing the formation of the reactive metabolite (trichloromethyl radical) that produces liver injury.

- Cadmium tolerance is explained by induction of metallothionein, a metal-binding protein. Subsequent binding of cadmium to metallothionein rather than to critical macromolecules decreases its toxicity.

Habituation

- It may developed in animals given small doses of some poisons for long time.
- Such case can tolerate greater amounts of poisons than would normally cause toxic or lethal effects.
- Arsenic, common salt, morphine as atypical examples of poisons may habituate.