

Al Mustaqbal University
College of pharmacy
4th stage
General Toxicology
Lecture: 1

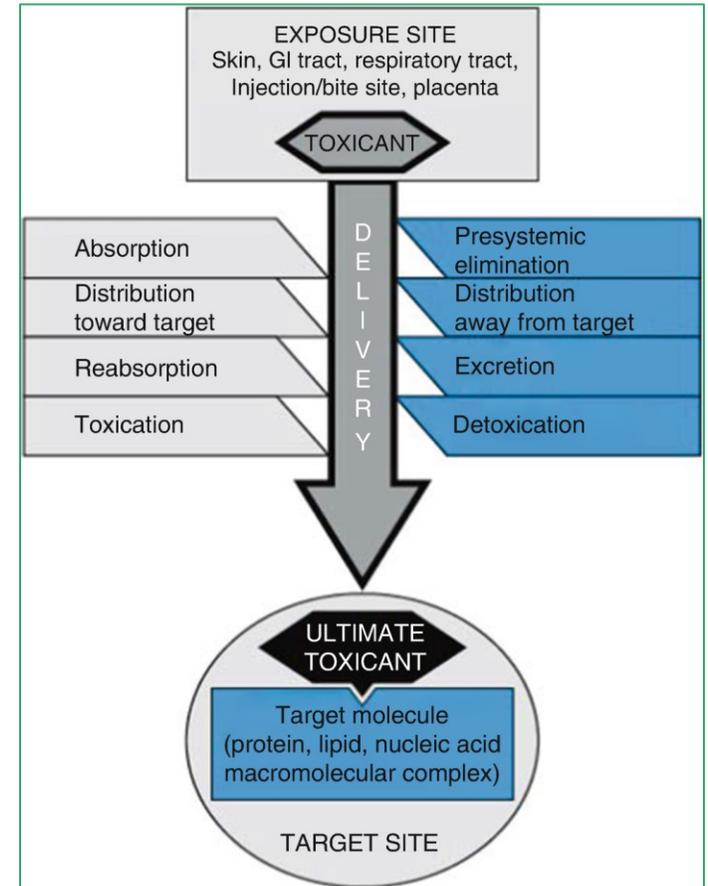
Introduction to General Toxicology

WEAAM JASIM ABBAS

Definition

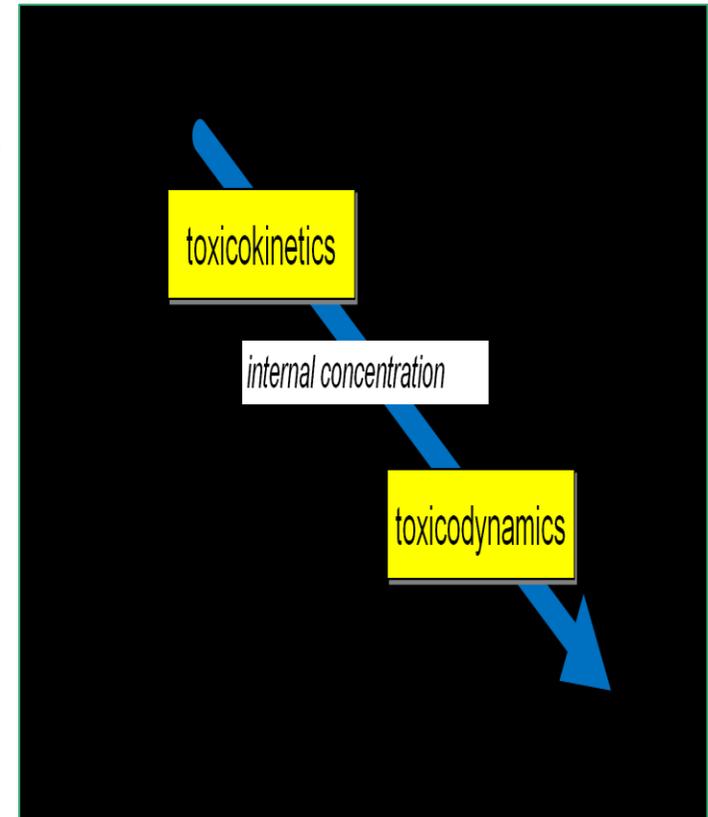
✓ Toxicology focuses on the study of:

1. The **agents** responsible for adverse effects
2. The **mechanisms** involved
3. The **damage** that may occur
4. Testing **methodologies** to determine the extent of damage, and ways to avoid or repair it.



Toxicodynamic and Toxicokinetic

- ✓ Toxicology is largely concerned with the **interaction** of toxicants and biological systems.
- ✓ While **toxicodynamic** investigates the effect of the toxicant on the organism.
- ✓ **Toxicokinetic** looks at how the organism affects the toxicant (e.g., absorption, biotransformation, distribution, and elimination).



Classification of Toxicology

Descriptive Toxicology

Mechanistic Toxicology

Clinical Toxicology

Forensic Toxicology

Environmental Toxicology

Occupational Toxicology

Regulatory Toxicology

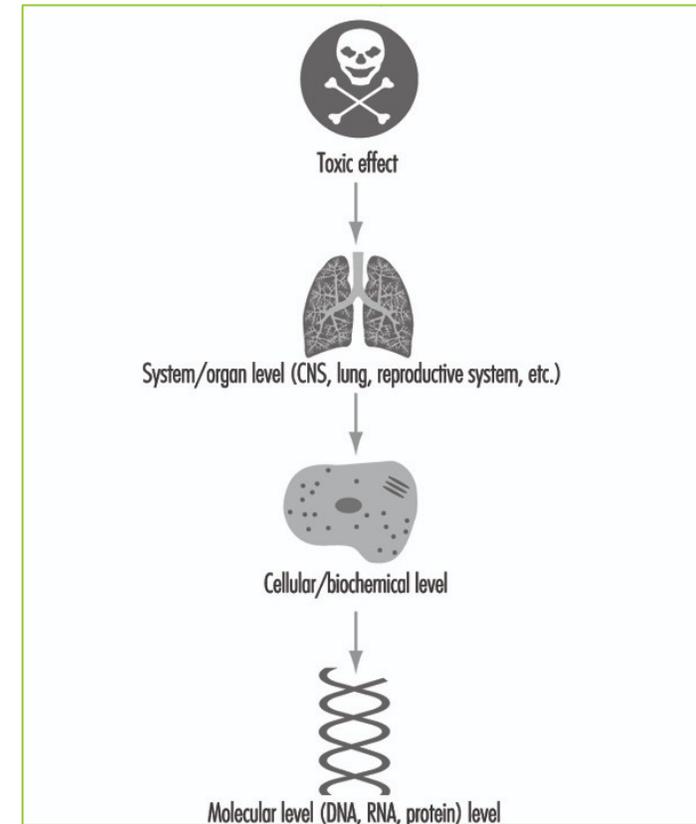
Descriptive Toxicology

- ❖ It is concerned with gathering **toxicological information** from **animal** experimentation.
- ❖ These types of experiments are used to establish **how much** of a chemical would cause **illness or death**.
- ❖ The emphasis is on the **testing of toxicants**, typically on **animals**.
- ❖ It focuses on the **dose-response relationship** and **extrapolation to humans**.



Mechanistic Toxicology

- ❖ It is the **study of how** chemical or physical agents **interact with living organisms** to cause **toxicity**.
- ❖ Looks at **how** the agent induces its **biochemical or physiological** effect on the organism, that is **modes of action**.
- ❖ **Biochemical and Molecular Toxicology** is a synonym for this branch.



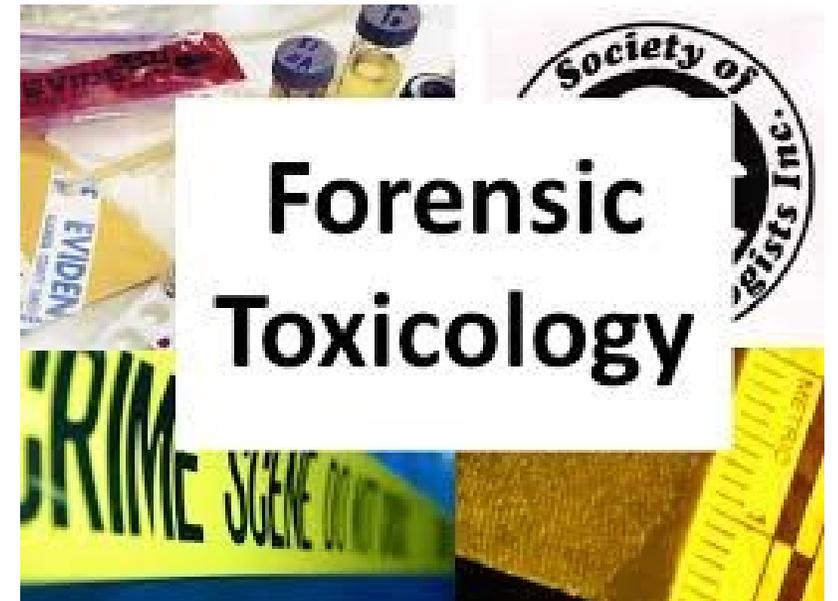
Clinical Toxicology

- ❖ This branch focuses on the **effects** of **drugs** and other **chemicals** on **humans**, particularly, but also on other animals.
- ❖ Its work is often involved with **drug overdoses** and other **poisonings** and **determining** the **substance** involved and its **amount** in the body.



Forensic Toxicology

- ❖ Concerned with the **cause of death** from toxic agents, often in instances of drug **abuse or misuse**.
- ❖ With a focus on **homicides** and **suicides**, this branch of toxicology goes hand in hand with the work of the **police and medical examiners**.



Environmental Toxicology

- ❖ **Investigates** the **effects** of toxicant exposures on the **general environment** and **living organisms** therein.
- ❖ Thus, pollution of air, water, and soil, and effects on plants and wildlife would fall within this branch.
- ❖ **Ecotoxicology**, a **more specialized** area, is devoted to the effects of toxic chemicals on
 1. Population
 2. Communities
 3. Terrestrial, freshwater, and marine ecosystems

Occupational Toxicology

- ❖ It is the application of the principles and methodology of **toxicology** toward chemical and biologic hazards encountered at **work**.
- ❖ Deals with the study of **chemicals** and other agents in the **workplace**, worker exposures, safety and health, and standard-setting.



Regulatory Toxicology

- ❖ Focuses on **ways** in which humans and the environment can be **protected from toxic effects**, through **regulations** and **standard-setting**.
- ❖ Considers **scientific decision-making** within a societal and legal framework.
- ❖ Relies heavily upon **risk assessment**.

Selective Toxicity

- ❖ Selective toxicity means that a **chemical** produces **injury** to **one kind** of living matter (such as a cell or organism) **without** harming **another** form of life even though the two may exist in **intimate** contact.
- ❖ Selective toxicity of **antibiotics** is due to interactions with **targets** being **unique** to bacteria.

Selective Toxicity

- ❖ Selective toxicity results because the chemical:
 1. Either equally toxic to both organisms but **accumulates preferentially** in the target
 2. Or alters a **unique** cellular or a biochemical **feature** that is **absent** or irrelevant in the unaffected species.

Xenobiotic

- ✓ **Xenobiotics** include a variety of **synthetic chemicals** with different intended purposes.
- ✓ **Pharmaceuticals** are xenobiotics developed to treat disease, whereas **pesticides** are used to deter pests.
- ✓ So xenobiotic is a term referring to substances, whether **toxic or not**, **foreign** to a given organism.



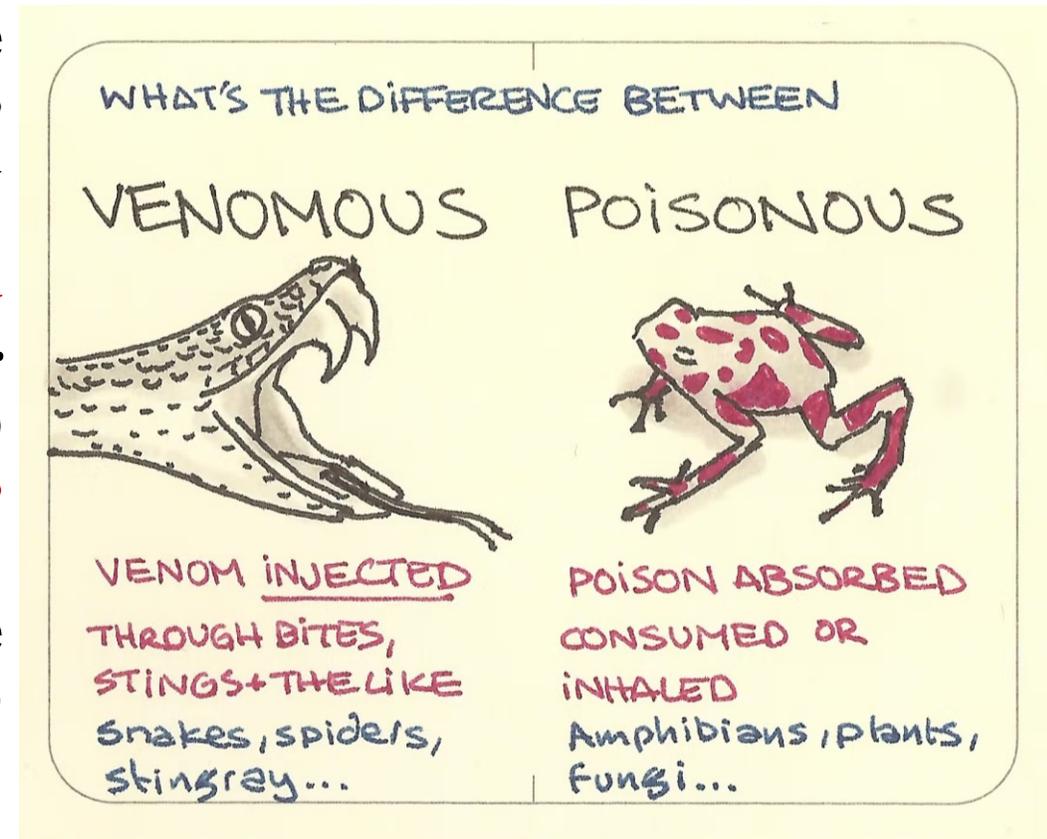
Toxin

- ✓ **Toxins** include both **poisons**, that originate from **plants and microbial organisms** and **venoms**, that are released by **animals**.
- ✓ **Aflatoxin** is an example of a toxin produced and released from the **fungus *Aspergillus*** that grows on foods such as corn and nuts.
- ✓ **Exposure** to aflatoxin is associated with an increased risk of **liver cancer**.



Poison vs Venom

- ✓ One needs to clarify the use of the words **poison** and **venom** when used as animal adjectives, though often used **interchangeably**, they are **distinct**.
- ✓ A **venom** requires a **delivery mechanism**, thus, because a **snake**, for example, **injects** its venom (or toxin) into its victim, it is considered a **venomous animal**.
- ✓ Instead, a **toxic mushroom** must be **ingested** to make its effect, thus, it is considered a **poisonous plant**.



Toxicant

- ✓ Toxin formally **should be** used to refer to toxic substances produced **biologically**.
- ✓ Thus, technically, **chemicals** such as formaldehyde or asbestos, would **not be** considered toxins.
- ✓ There are several **other terms** that could be used to delineate the broader category of substances that are **toxic, regardless of origin**.
- ✓ Examples are a **toxicant, toxic agent, and toxic substance**.

Toxicant

- ✓ For example, the chemical “**dioxin**” is generated during the **production** and/or **combustion** of certain chlorinated organic chemicals.
- ✓ A unique skin toxicity, called **chloracne**, has been observed in individuals exposed to dioxin.



Fig. 2. President Viktor Yushchenko of Ukraine before and after dioxin poisoning with 2,3,7,8-TCDD (courtesy of the Associated Press).

Toxicant



Pictures of a chlorine rash

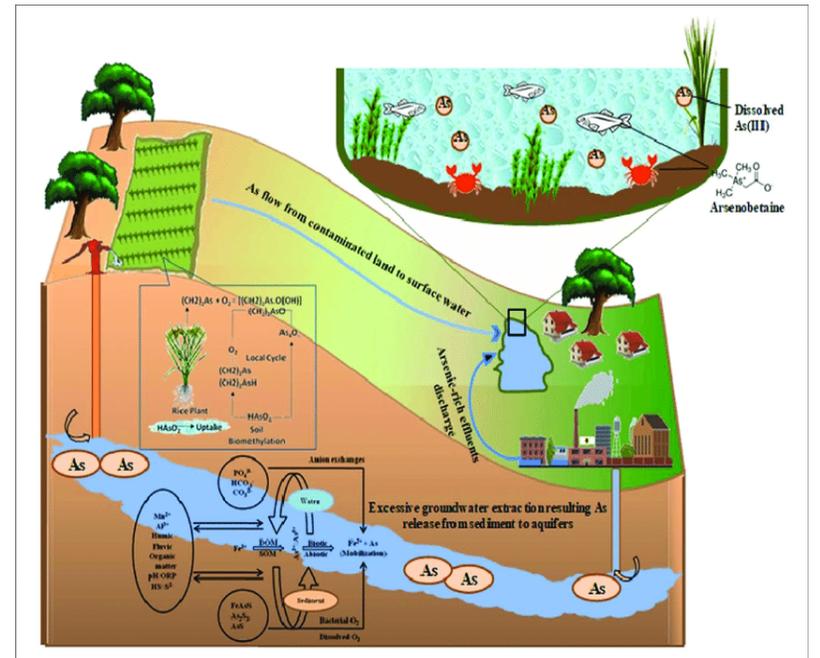
Toxicant

- ✓ Some toxic substances can be produced by both **natural** and **anthropogenic** activities.
- ✓ For example, **polyaromatic hydrocarbons** are produced by the **combustion** of organic matter through **ordinary processes** (e.g., forest fires) and **human activities** (e.g., combustion of coal for energy production and cigarette smoking).



Toxicant

- ✓ **Arsenic**, a toxic **metalloid**, largely appears in **groundwater** as a **natural** contaminant but also enters groundwater from other sources as **well**.
- ✓ Generally, such toxic chemicals are referred to as **toxicants**, rather than toxins, **because**, although they may be naturally produced, they are not produced by biological systems.



Toxicant



(g)



Different skin symptoms due to arsenic toxicity

Classification of Toxic Chemicals

✓ Toxic chemicals may also be classified in terms of:

1. **Their physical state** (gas, dust, liquid, size; e.g., nanoparticles)
2. **Their chemical stability or reactivity** (explosive, flammable, corrosive)
3. **General chemical structure** (aromatic amine, halogenated hydrocarbon, etc.)

Classification of Toxic Chemicals

4. **Ability to cause significant toxicity** (extremely toxic, very toxic, slightly toxic, etc.).
 5. Classification of toxic chemicals on the basis **of their biochemical mechanisms of action** (e.g., an alkylating agent, cholinesterase inhibitor, and endocrine disruptor).
- ✓ The **last classification** is usually more **informative** than classification by general terms such as irritants and oxidizers.

Modifying Factors of toxicity

- ✓ **Not** all humans respond to toxicants in the **same manner** and to the **same degree** as each other.
- ✓ Multiple **factors** modify one's **susceptibility** to adverse outcomes.
- ✓ **Particularly** important modifiers include genetic variation among a population, age and life stages, sex and hormonal status, microbiome, and circadian rhythm.
- ✓ **Other** influences that can impact the extent of toxicity include the concomitant use of tobacco, alcohol, nutraceutical, pharmaceutical and illicit drugs, exercise, nutrition, and co-exposures in the workplace and at home.

Modifying Factors of toxicity

1. Genetics:

- ✓ **Hereditary** differences in a single gene that occur in more than 1% of the population are referred to as **genetic polymorphisms**.
- ✓ The **metabolism** of exogenous and endogenous chemical toxins may be **modified** by **inherited** and **induced** variation in CYP (P450), acetyltransferase and glutathione S-transferase genes.

Modifying Factors of toxicity

2. Age

- ✓ Life **stage**, and in turn **age**, is an important factor that can alter **susceptibility** to toxicity.
- ✓ **Metabolic processes** that aid in xenobiotic **clearance** are often altered at **juvenile** and **advancing** ages.
- ✓ For example, newborns have relatively **low** gastric emptying, gastrointestinal motility, and expression of the metabolic enzymes including CYP2D6, CYP2E1, and CYP3A4.
- ✓ **Reduced** metabolic capacity can **decrease** the **clearance** of some chemicals and **increase** the risk of **toxicity**.

Modifying Factors of toxicity

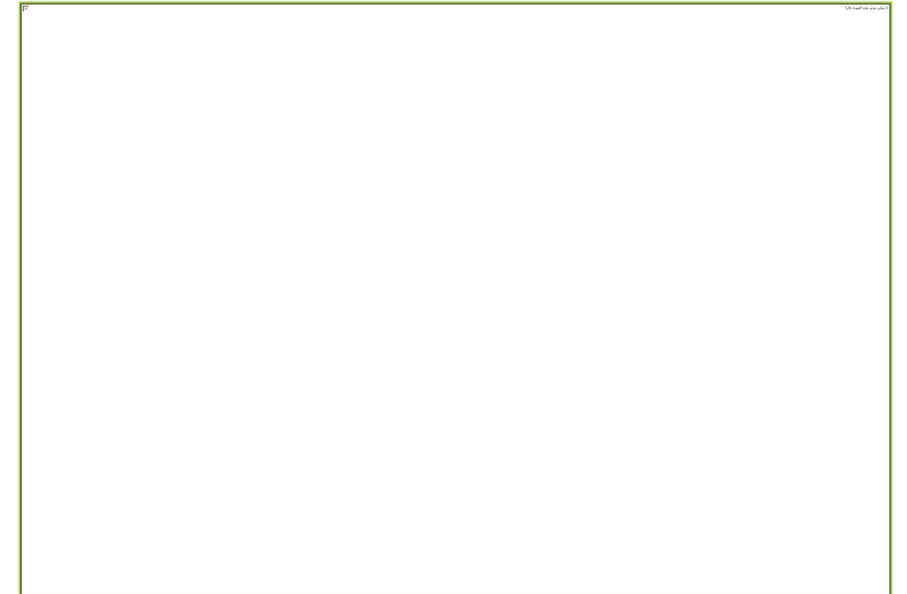
3. Sex:

- ✓ Along with genetics and age, sex can be a **determinant** of xenobiotic **disposition** and **toxicity**.
- ✓ One of the notable sex-related differences in humans is the effect of **alcohol**.
- ✓ This is in part due to the **lower extent of body water** in women compared to men of **similar weight**.
- ✓ Toxicities such as **liver disease** and **brain damage** due to alcohol consumption appear to be **more frequent and/or earlier** in females compared to males.

Modifying Factors of toxicity

4. Circadian Rhythm

- ✓ Circadian rhythm is a **24-hour cycle** that regulates a number of molecular and physiological processes.
- ✓ Within the 24-hour cycle, there are **diurnal** (light cycle), **nocturnal** (dark cycle), and **crepuscular** (transition) periods.



Modifying Factors of toxicity

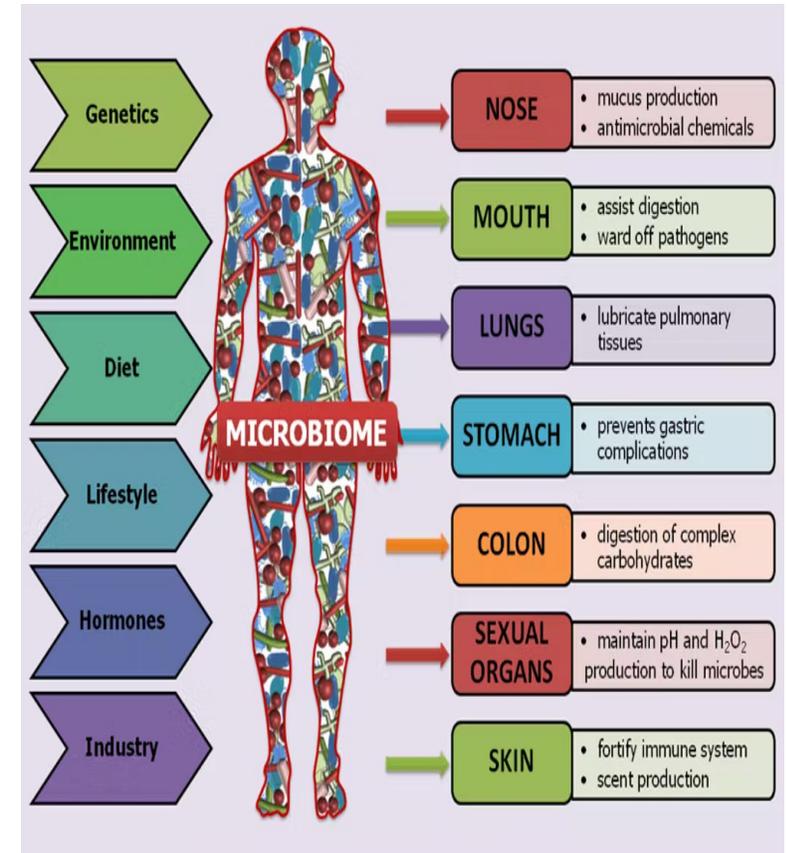
4. Circadian Rhythm

- ✓ The circadian clock consists of a **cellular clock** with specific genes that oscillate in expression.
- ✓ **Timing** in the circadian system is **affected** by a number of factors including **light, activity, food consumption, and social cues**.
- ✓ While most changes in physiological processes during the 24-hour period are **not readily apparent**, they can still impact **susceptibility** to toxicity.

Modifying Factors of toxicity

5. Microbiome

- ✓ Within the body, **bacteria** outnumber human cells by a ratio of **10:1**.
- ✓ Typically, **anaerobic and facultative** aerobic bacteria comprise the **resident** microflora of the intestinal tract.
- ✓ The influence of **commensal microbes** on human health, including toxicologic responses, is garnering greater attention with the advent of highly **sensitive methods in metagenomics**.



Chemical Toxicity & LD50

- ✓ LD stands for "**Lethal Dose**".
- ✓ LD50 is the **amount** of a material, given all at **once**, which causes the **death** of **50%** (one half) of a group of test **animals**.
- ✓ The LD50 is one way to **measure the short-term poisoning potential** (acute toxicity) of a material.
- ✓ Toxicologists can use **many kinds of animals** but most often testing is done with **rats and mice**.

Chemical Toxicity & LD50

- ✓ It is usually **expressed** as the amount of chemical administered (e.g., **milligrams**) per 100 grams (for smaller animals) or per **kilogram** (for bigger test subjects) of the bodyweight of the test animal.
- ✓ The LD50 can be found for **any route** of entry or administration but **dermal** (applied to the skin) and **oral** (given by mouth) administration methods are the most common.

Chemical Toxicity & LD50

- ✓ Chemicals **differ** in their ability to produce serious injury or death.
- ✓ Chemicals produce death in **microgram** doses and are commonly denoted as **extremely poisonous**.
- ✓ Other chemicals may be **relatively** harmless after doses in excess of **several grams**.

Approximate acute LD₅₀ of Some Chemicals

CHEMICAL	LD ₅₀ (MG/KG)*
Ethyl alcohol	10,000
Glyphosate	5,600
Sodium chloride	4,000
Ferrous sulfate	1,500
Morphine sulfate	900
Phenobarbital sodium	150
Chlorpyrifos	18
Picrotoxin	5

Strychnine sulfate	2
Nicotine	1
VX nerve gas	1
D-Tubocurarine	0.5
Hemicholinium-3	0.2
Tetrodotoxin	0.10
Dioxin (TCDD)	0.001
Botulinum toxin	0.00001

**LD₅₀ is the dose (mg/kg body weight) causing death in 50% of exposed animals.*

**Thank You For
Your Attention**