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

Introduction to General Toxicology

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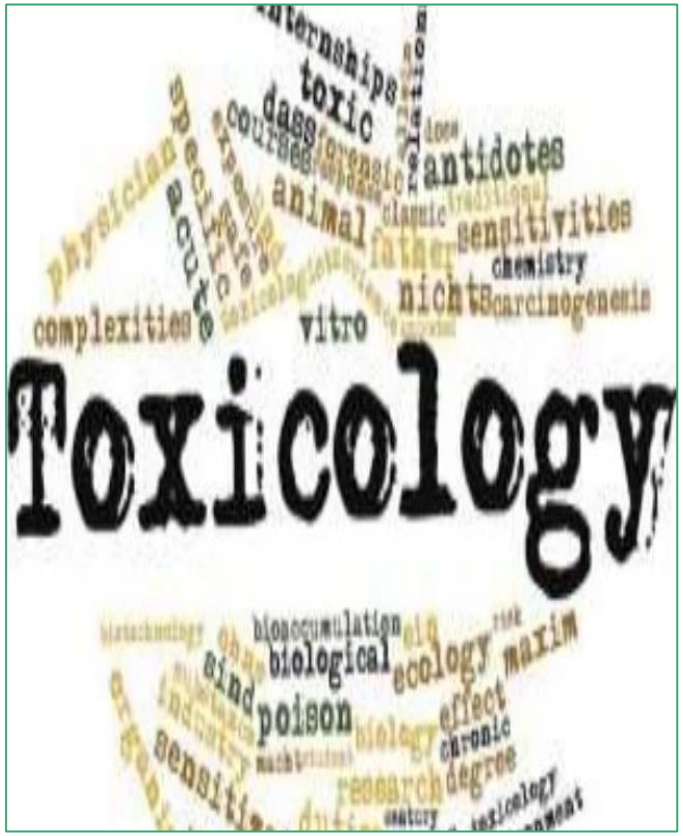
Definition

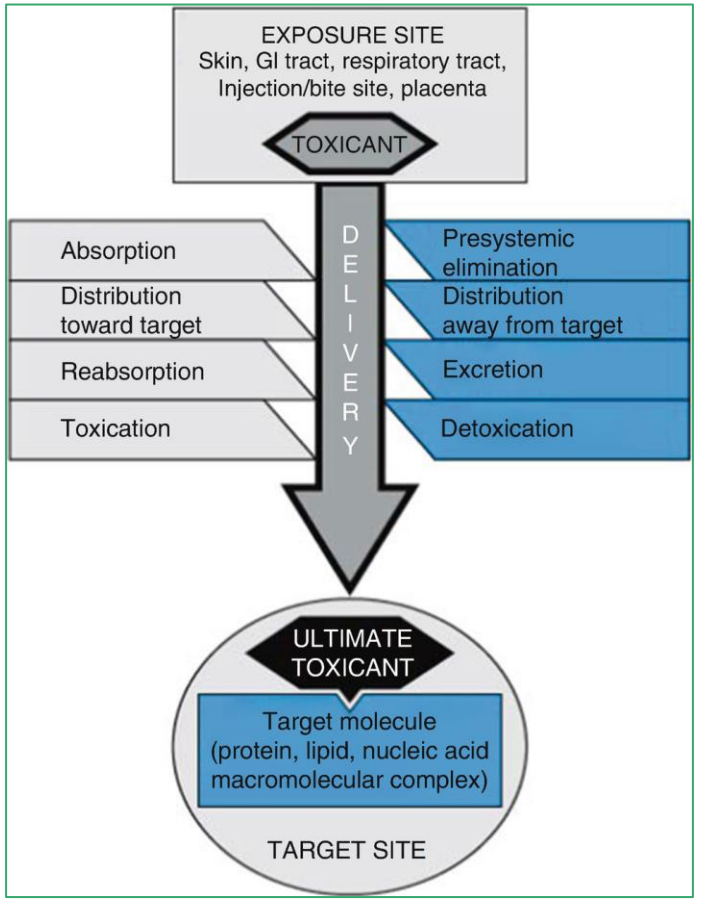
- ✓The term toxicology derives from the Greek **Toxicon**, meaning **poison**, and **logos**, meaning **science**.
- ✓Toxicology is the **study** of the **adverse effects** of chemical, physical, or biological agents on **living organisms** and the **ecosystem**, including the **prevention** and **amelioration** of such adverse effects.



Definition

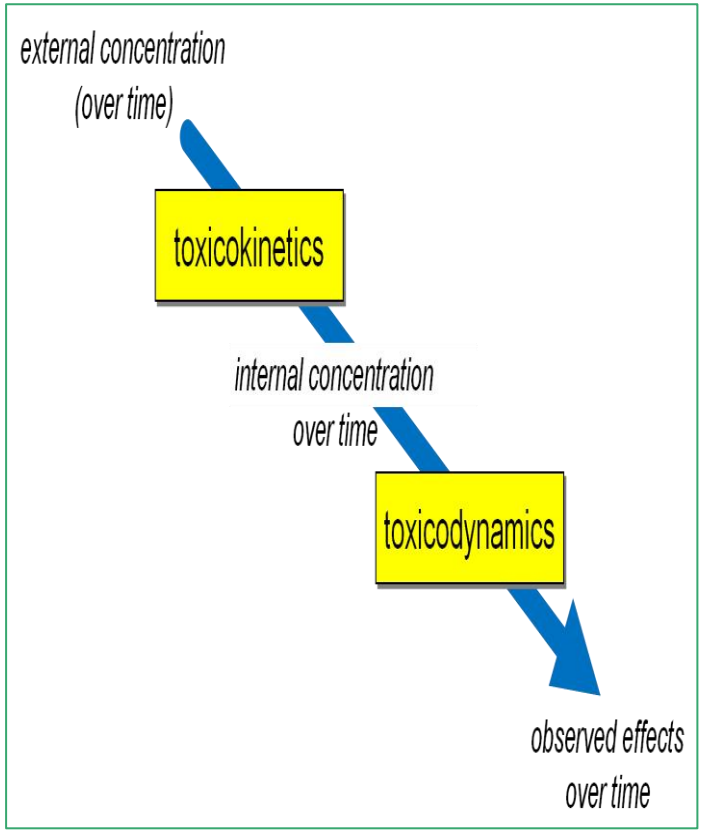
✓**Toxicology focuses on the study of:**

1. **The agents responsible for adverse effects**
2. **The mechanisms involved**
3. **The damage that may ensue**
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

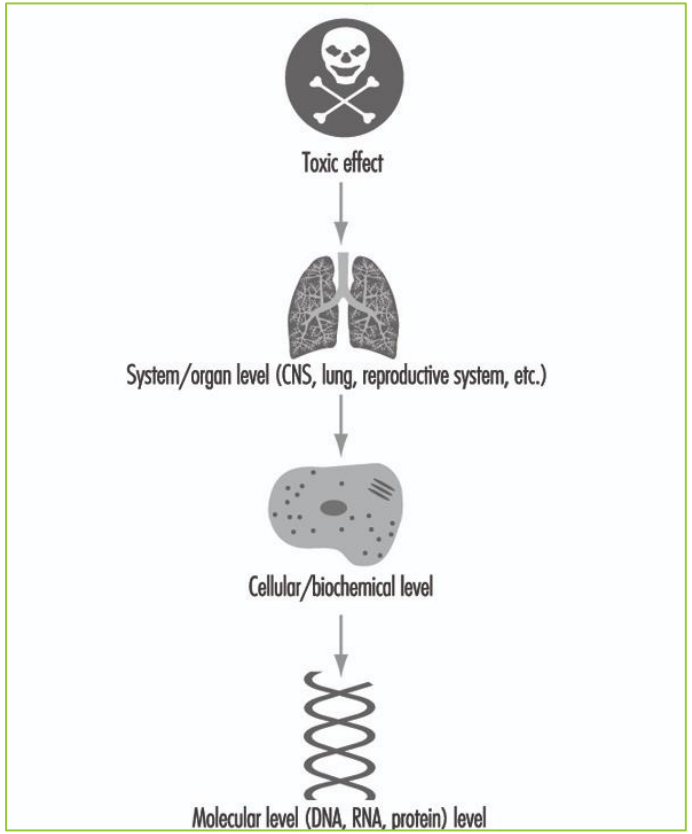
- **Descriptive Toxicology**
- **Mechanistic Toxicology**
- **Clinical Toxicology**
- **Forensic Toxicology**
- **Environmental Toxicology**
- **Occupational Toxicology**
- **Regulatory Toxicology**

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 **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

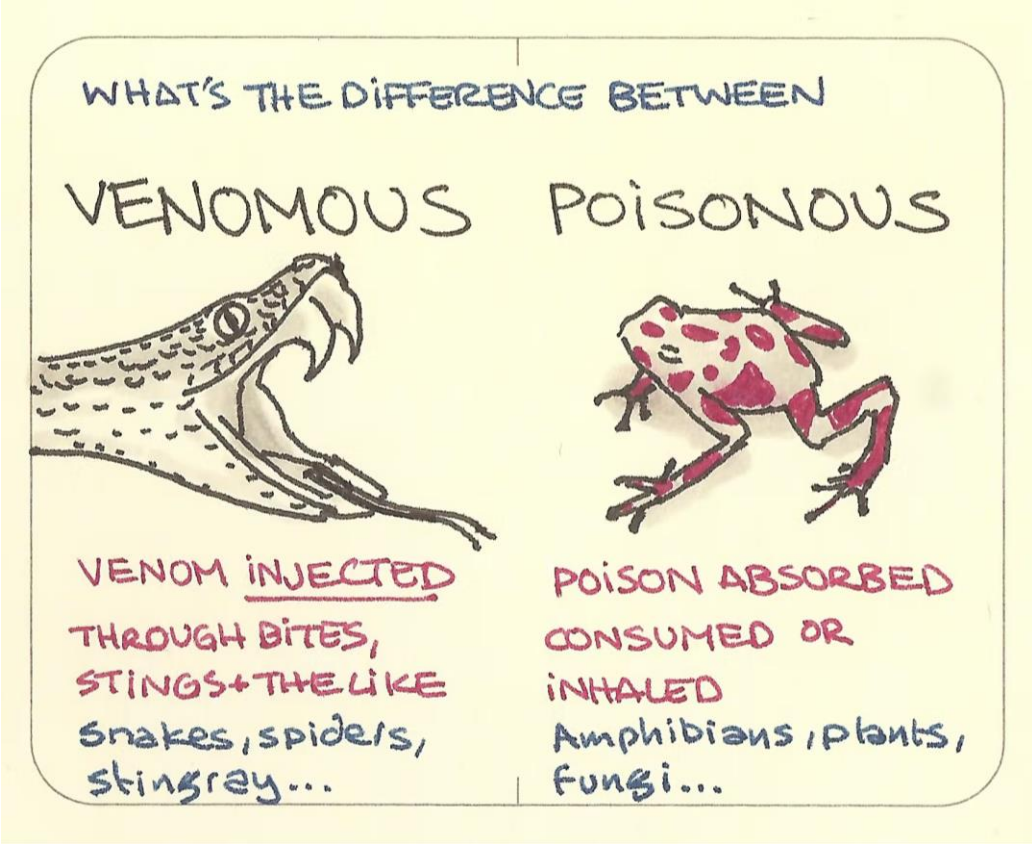
- ✓By comparison, **xenobiotics** include a variety of **synthetic chemicals** with different intended purposes.
- ✓**Pharmaceuticals** are xenobiotics developed to treat disease, whereas **pesticides** are used to deter pests.
- ✓ So xenobiotic is a term referring to substances, whether **toxic or not**,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

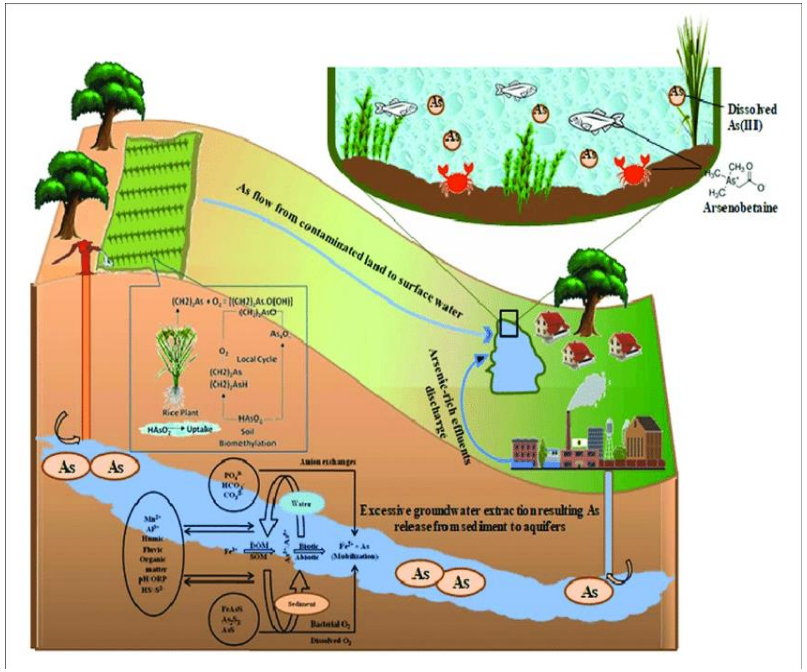
Pictures of a chlorine rash

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

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 (NAT) and glutathione S-transferase (GST) 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

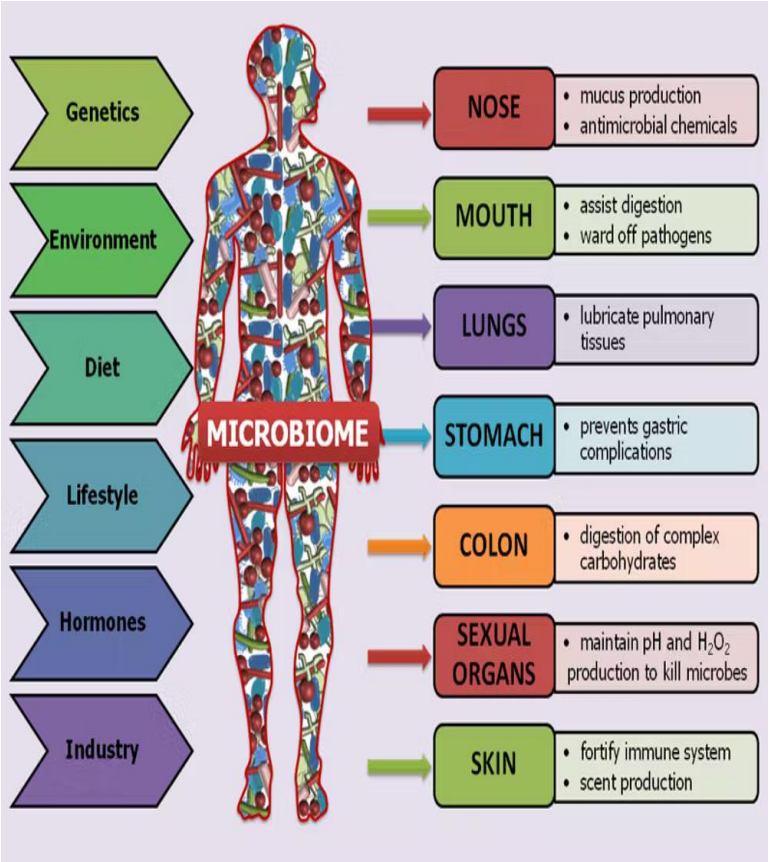
4. Circadian Rhythm

- ✓**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 LD_{50} 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

**LD_{50} is the dose (mg/kg body weight) causing death in 50% of expo animals.*

Thank Your For Your Attention