Democrtic and Popular Republic of Algeria
Ministry of Higher Education and Scientific Research
Mohamed Khider University -BISKRA
Department of Nature and Life Sciences

3LMD Courses (Licence)

Food Toxicology

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2022-2023

Objectives of course

- History of toxicology
- Examples of Toxicological Cases
- Classification (The Field of Toxicology)
- Differentiate the sub-disciplines of toxicology
- Define toxicology
- Basic Terminology
- Liste sources of toxicants.
- Discuss the principles of toxicology
- Dose response

Objectives of course

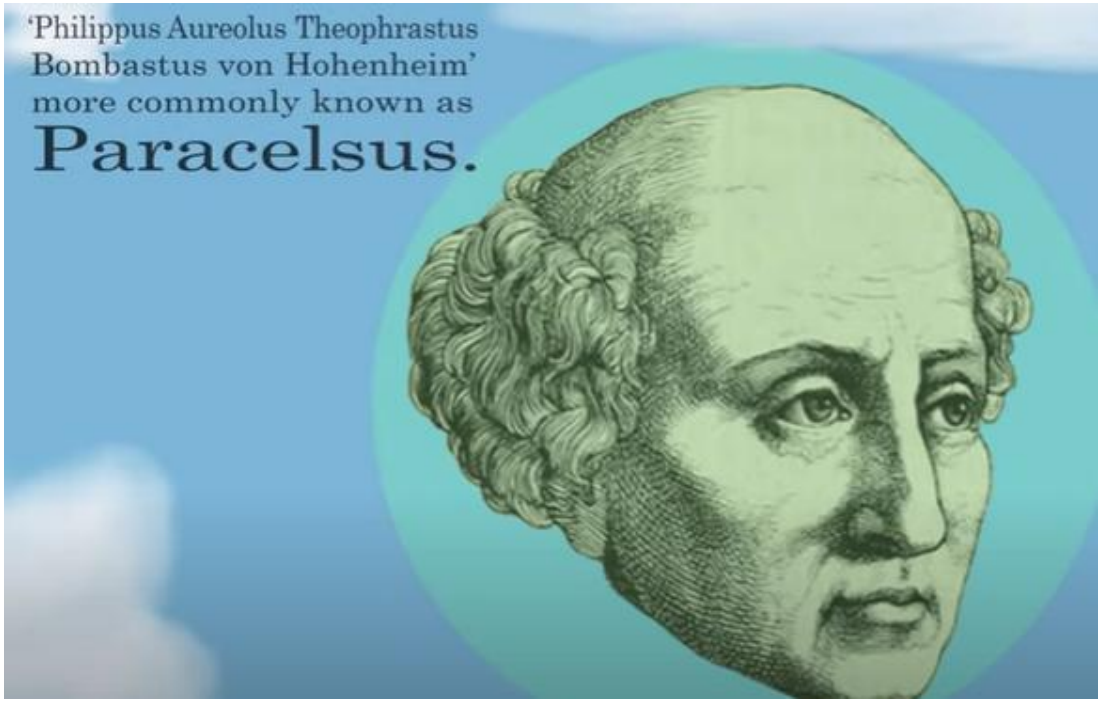
- Discuss the effects influencing toxicity.
- Discuss the nature of toxic responses, routes of poisoning.
- Toxicokinetics/toxicodynamics.
- Food Toxicology.
- Nutritional toxicology.
- Gastrointestinal (GI) tract
- Pesticide Residues in the Food Supply
- FUNGAL TOXINS

- # PART I: PRINCIPALES OF TOXICOLOGY

History of toxicology

“All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy.”

This early observation concerning the toxicity of chemicals was made by Paracelsus (1493-1541)



History of toxicology

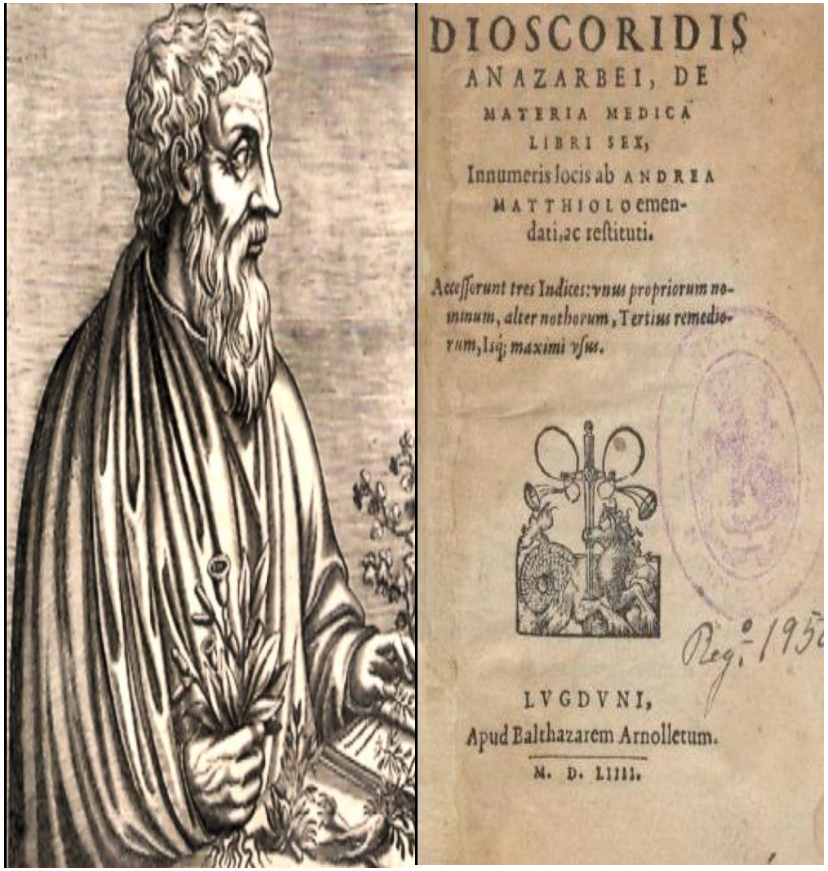
The historical development of toxicology began with early cave dwellers who recognized poisonous plants and animals and used their extracts for hunting or in warfare.

By 1500 BC, written recordings indicated that hemlock, opium, arrow poisons, and certain metals were used to poison enemies or for state executions. With time, poisons became widely used and with great sophistication.

BC: before Christ

In the past it was mainly a practical art utilized by murderers & assassins.
Notable poisoning victims include Socrates, Cleopatra, and Claudius. By the time of the Renaissance and Age of Enlightenment, certain concepts fundamental to toxicology began to take shape.

History of toxicology



- Dioscorides (50 AD) was a Greek physician, pharmacologist, botanist, and author of *De materia medica*
- Classify poisons as animal, plant or mineral & recognizing the value of emetics

AD:Anno Domini, Latin for "in the year of the Lord, years measured after Christ

History of toxicology

- Avicenna was born at Afshana near Bokhara in Persia in AD 980.
- He mastered a wide range of disciplines, including mathematics, physics, metaphysics, astrology, geology, chemistry, alchemy, anatomy, physiology, pharmacology, **toxicology** and medicine, as well as philosophy, logic, and ethics.

History of toxicology

معلومات شخصية	
الميلاد	30 مارس 1138 قرطبة
الوفاة	13 ديسمبر 1204 (66 سنة) القاهرة
مكان الدفن	طبريا
مواطنة	الأندلس[1]
الديانة	يهودية

- Maimmonides (1135-1204 AD), أَبُوعَمْرَان مُوسَى بْن مَيْمُون بْن عُبَيْد ٱلله ٱلْقُرْطُبِيّ; Musa ibn ʿUbaidallah al-Qurtubi al-Israʾili; wrote poisons and their antidote which detailed some of the treatments consideration to be effective

History of toxicology

Philippus Theophrastus Aureolus Bombastus von Hohenheim
PARACELSUS
(Einsiedeln, Zürich, 1493 - Salzburg, 1541)

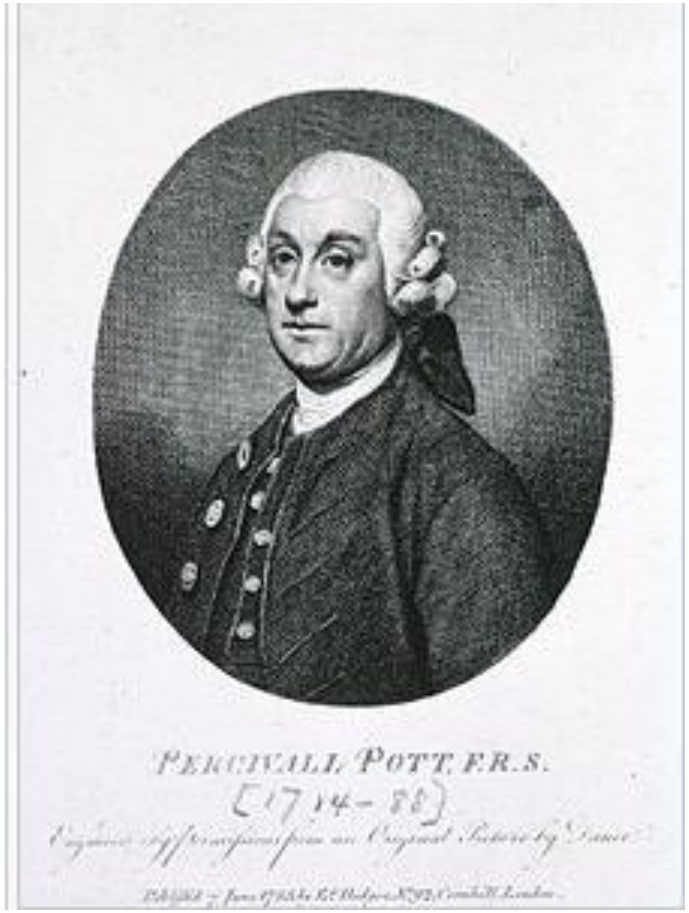
All substances are poisons; it is the dose that makes the poison

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.**

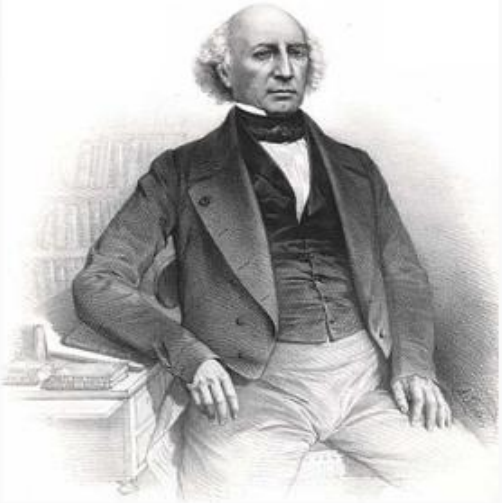
This is now known as the **dose-response** relationship, a major concept of toxicology. Paracelsus was one of the founders of modern toxicology. His best known quote: **All substances are poisons; it is the dose that makes the poison = Dose determines toxicity.**

History of toxicology



- **Percivall Pott** (6 January 1714, in London – 22 December 1788) was an English **surgeon**, one of the founders of **orthopaedics**, and the first scientist to demonstrate that a cancer may be caused by an environmental **carcinogen**.
- Is the first found that **soot** caused **scrotal cancer** in chimney sweeps. Much later the carcinogens in soot found to be **polycyclic aromatic hydrocarbons.**

History of toxicology



Alexandre Collette, *Mathieu Orfila*, lithographie.

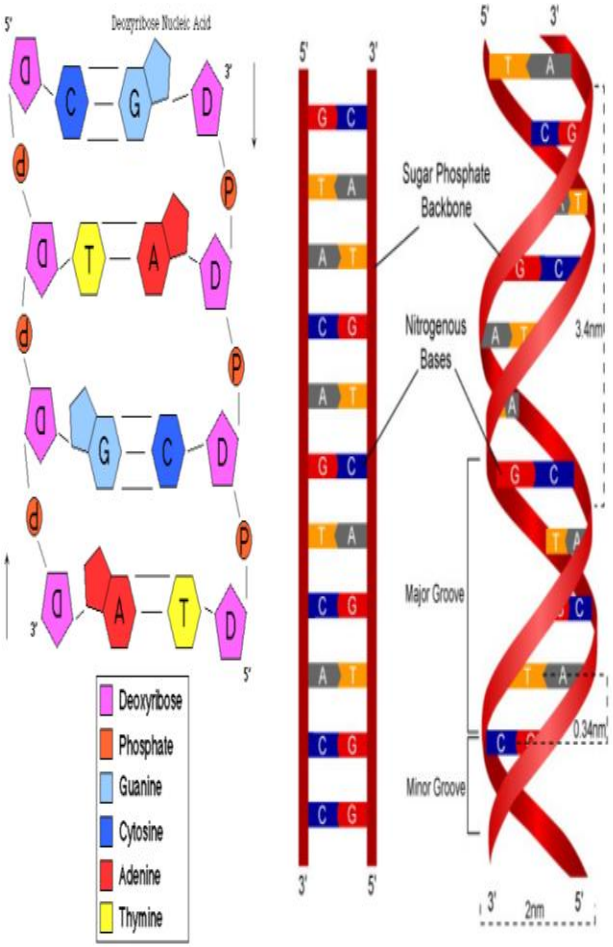
Naissance	24 avril 1787 Mahón (Espagne)
Décès	12 mars 1853 (à 65 ans) Paris (France)
Nationalité	France par naturalisation en 1818.
Résidence	Minorque, Valence, Madrid
Domaines	médecine, chimie
Institutions	Faculté de médecine de Paris
Renommé pour	toxicologie médico-légale

- **Orfila**, a Spanish physician, is often referred to as the founder of toxicology.
- It was 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.

History of toxicology

- Rachel Carson (May 27, 1907 – April 14, 1964), was an **American biologist** well known for her writings on environmental pollution and the natural history of the sea. Her book, Silent Spring (1962), became one of the most influential books in the modern environmental movement and provided the impetus for tighter control of pesticides, including DDT.
- Rachel Carson/EPA led to ban of insecticide DDT for environmental and health concerns

History of toxicology

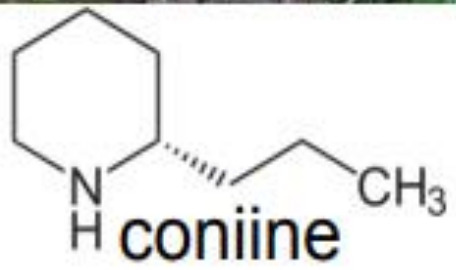


DNA

- **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 biochemicals

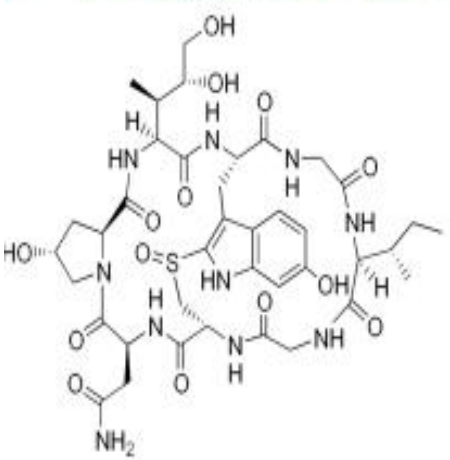
Examples of Toxicological Cases

- 399 B.C. Socrates, a Greek Philosopher died of Hemlock poisoning (according to Plato), (for teaching radical ideas to youths).
- Coniine is the active toxic ingredient
- Antagonist for the nicotinic acetylcholine receptor, leading to cessation of neurotransmission, muscular and respiratory collapse and death.



Examples of Toxicological Cases

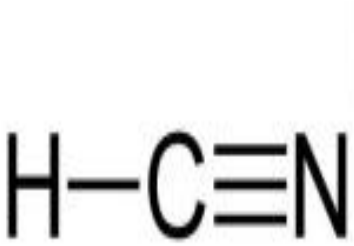
- October 20th, 1740 Charles VI, Holy Roman Emperor, King of Bohemia, Hungary, and Croatia died from eating death cap mushrooms
- Active ingredient is alpha-amanitin that inhibits RNA polymerase inhibiting protein synthesis leading to hepatocellular lysis, liver failure, kidney failure, coma, respiratory failure, and death.



Alpha-amanitin

Examples of Toxicological Cases

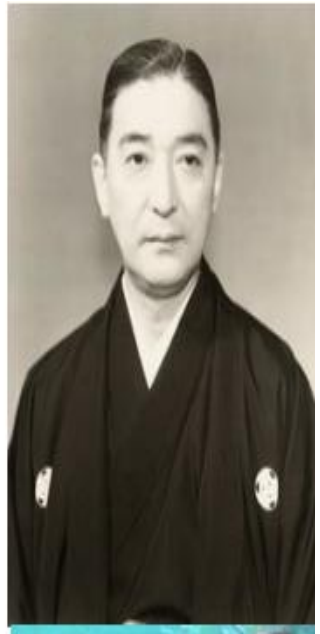
- April 30th, 1945, Eva Braun, long-time companion of Hitler committed suicide with a cyanide capsule.
- Inhibitor of cytochrome c oxidase, part of complex IV of the electron transport chain and inhibits ATP production leading to brain death and heart cessation, hypoxia, and death.

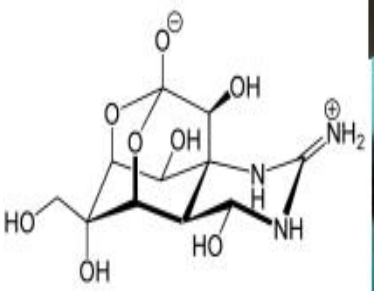


Examples of Toxicological Cases

- Jan 16th, 1975 Bando Mitsugoro VIII, a famous Japanese Kabuki

  actor died from eating 4 livers of pufferfish
- Active toxic ingredient is tetrodotoxin
- Tetrodotoxin blocks voltage-gated sodium channels leading to suppression of neurotransmission, numbness, bronchospasms, coma, respiratory failure, death





tetrodotoxin

Examples of Toxicological Cases

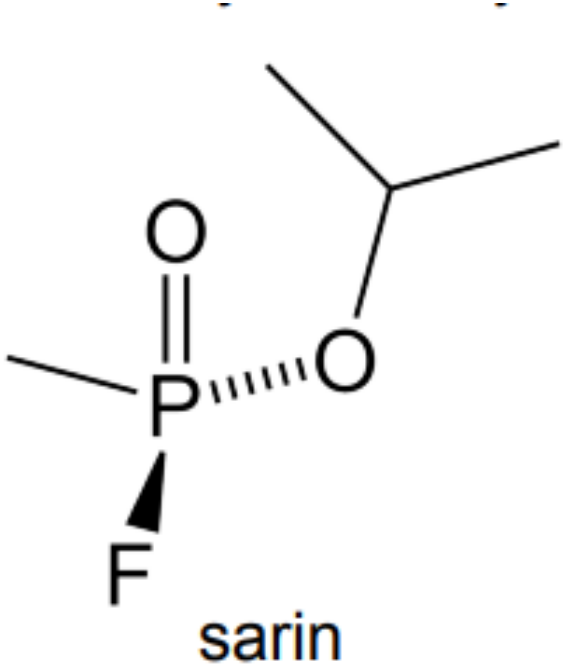
- 1932-1968: Minamata disaster—caused by methylmercury toxicity from industrial wastewater from Chisso Corporation in Minamata City in Japan
- 2265 victims
- Caused neurological syndrome associated with methyl mercury poisoning including ataxia, numbness, insanity, muscle weakness, hearing and speech loss, birth defects, paralysis, coma, death
- Alters neurochemistry and neurotransmission through multiple mechanisms

$H_3C—Hg^+ X^-$

Methyl mercury

Examples of Toxicological Cases

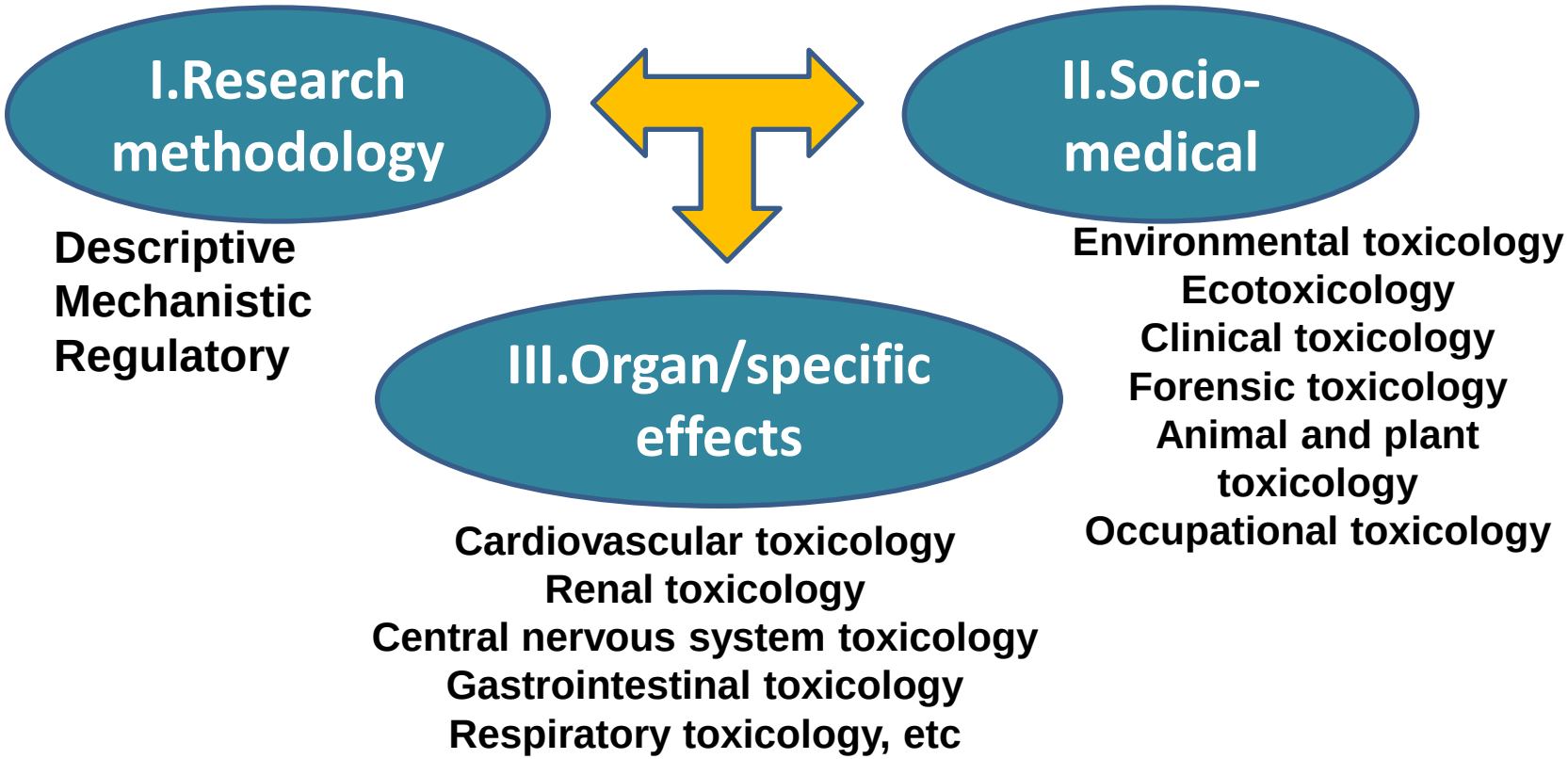
- 1995, Japanese subway sarin attack by terrorist group; 2006 day 5 of “24”—Jack Bauer saves LA from VX attack in TV show; 2013 Assad uses sarin against rebels
- Sarin and VX are an organophosphorus chemical warfare agents that inhibits acetylcholinesterase, leading to excess acetylcholine and hyperstimulation of neurons, resulting in seizures, tremoring, convulsions, excess salivation, excess tearing, urination, defecation, bronchoconstriction, respiratory failure, death



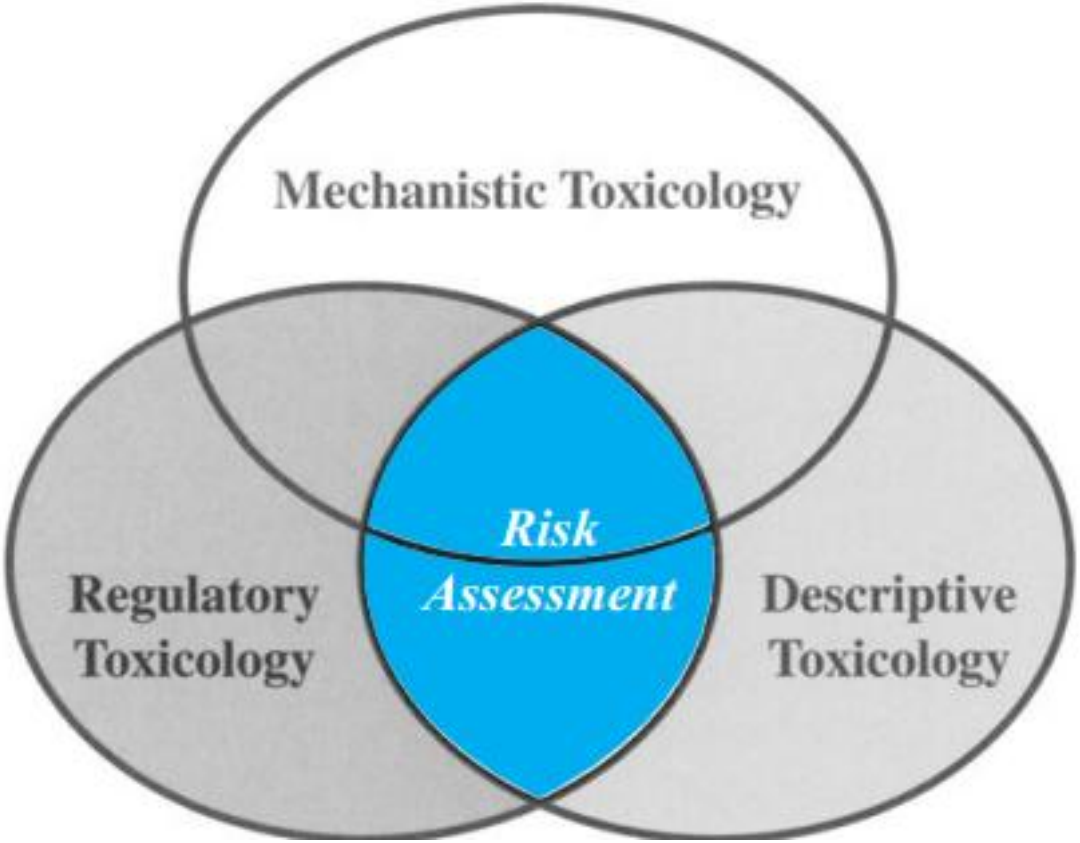
sarin

Classification=The Field of Toxicology

- Toxicology is broadly divided into different classes Depending on:



Classification=The Field of Toxicology

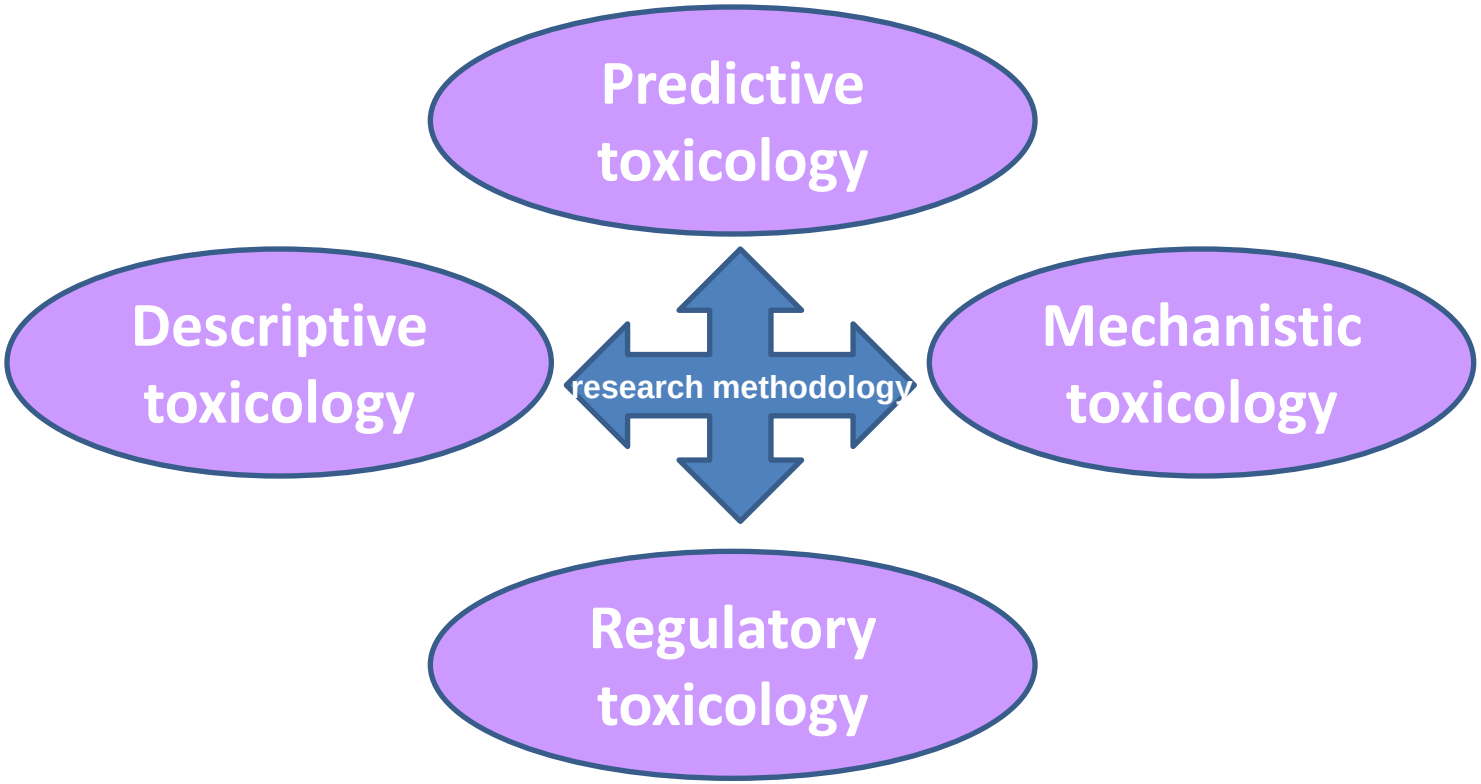


The professional activities of toxicologists fall into three main categories: descriptive, mechanistic, and regulatory (Fig. XX). Although each has distinctive characteristics, each contributes to the other, and all are vitally important to chemical risk assessment.

Figure XX. Graphical representation of the interconnections between different areas of toxicology (Reference

Classification=The Field of Toxicology

- Based on research methodology



I. Based on research methodology

Descriptive toxicology

- **Descriptive toxicology (testing)**
- Is concerned directly with toxicity testing, which provides information or safety evaluation and regulatory requirements.

- 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.

I. Based on research methodology

Descriptive toxicology

- Assesses the concentration-dependent hazard a chemical may present
  - Human health
  - Natural populations
- Results typically applied to
  - Approval of product use
  - Regulating allowable concentrations in the environment.

I. Based on research methodology

Descriptive toxicology

Types of toxicity testing

- ***In vitro*** (test tube)—useful in detecting potential biochemical and genetic effects
  - Use model systems (bacteria, cultured animal cells, DNA interactions)
- ***In vivo*** (animal)—are essential for detecting health effects
  - Acute, chronic, multi-generation
  - Experimental animals may be treated with high doses over a lifetime to evaluate potential to cause cancer
- ***In silico*** (computer-based)—biological experiments conducted by computer models; these depend on data previously collected in other experiments

Completion of all toxicity tests may take five or six years and is very costly

I. Based on research methodology

Descriptive Toxicology
Toxicity Testing

- Molecular and cellular studies in toxicology often supplement toxicity testing results to help ascertain chemical hazard. They often unravel complex processes that underlie an adverse response.
- Use of toxicants can help determine the function of proteins in complex networks.

I. Based on research methodology

Descriptive Toxicology

Private and public sectors invest in toxicity testing that aims to protect human health:

- Chemical Manufacturers
- Pharmaceutical Industry
- US Federal Agencies and Programs
  - National Toxicology Program (NTP)
  - Environmental Protection Agency (EPA)
  - National Institute of Environmental Health Sciences (NIEHS)
  - Occupational Safety and Health Administration (OSHA)
  - Food and Drug Administration (FDA)
- State and Local Governmental Bodies

I. Based on research methodology

Mechanistic Toxicology

- **Mechanistic toxicology (basic biology and chemistry)**
- makes observations on how toxic substances cause their effects
- This is important for rational treatment

Focuses on how

- Chemicals produce adverse effects
- Biological systems protect themselves against adverse effects

Involves

- Cellular and Molecular Biology
- Chemistry, often xenobiotic metabolism

I. Based on research methodology

Mechanistic Toxicology

Chemical research in toxicology usually investigates metabolic transformations of drugs or potentially hazardous chemicals

(classical toxicology)

- How persistent is a chemical in the body?
- Are metabolic products toxic?
- Do test animals exhibit the same results as humans or other species of concern?

I. Based on research methodology

Regulatory Toxicology

- Studies whether the chemical substances has low risk to be used in living systems.

- Determines from available data whether a chemical poses a sufficiently low risk to be marketed for a stated purpose and established standards for the amount of chemicals permitted in ambient air, industrial atmospheres, and drinking water.

- Determination of risk based on descriptive and mechanistic studies, and developing safety regulations

I. Based on research methodology

Regulatory Toxicology

- Setting rules and assuring compliance
  - Product registration
  - Allowable concentrations in food or environmental media
- Technical and legal issues may require negotiation and gathering of new information
  - Risk and safety are estimated by total weight of evidence
  - Toxicity evidence is the basis, but often rules are modified by political, legal considerations, as well a technical feasibility

I. Based on research methodology

Regulatory Toxicology

Involves

*encompasses the collection, processing and evaluation of epidemiological and experimental toxicology data to permit toxicologically based decisions.

*Food and drug administration regulates drugs, food, cosmetics medical devices & supplies in USA

*Environmental protection agency regulates pesticides, toxic chemicals, hazardous wastes and toxic pollutants in USA

I. Based on research methodology

Regulatory Toxicology

- Occupational safety and health administration regulates the safe conditions for employees in USA authority.

- DACA (now FMHACA)- regulates drugs, food, cosmetics and medical devices & supplies in Ethiopia

I. Based on research methodology

Predictive toxicology

- a multidisciplinary approach to chemical toxicity evaluation that uses a suite of non-animal testing methods to forecast the effects of a chemical on biological systems.

- Predictive toxicology studies about the potential and actual risks of chemicals /drugs.

- This is important for licensing a new drug/chemical for use.

Classification=The Field of Toxicology

II. Based on specific socio-medical issues

Classification=The Field of Toxicology

II. Based on specific socio-medical issues

Occupational (Industrial) toxicology

- It deals with chemical found in the workplace.
- This field grew out of a need to protect workers from toxic substances and to make their work environment safe.

E.g.

– Industrial workers may be exposed to these agents during the synthesis, manufacturing or packaging of substances.

– Agricultural workers may be exposed to harmful amounts of pesticides during the application in the field

Classification=The Field of Toxicology

II. Based on specific socio-medical issues

Environmental toxicology

• Is concerned with the study of chemicals that contaminate food, water, soil, or the atmosphere.

•This deals with the potentially deleterious impact of chemicals, present as pollutants of the environment, to living organisms.

•This sub-discipline addresses the question of how various plants, animals, and humans are affected by exposure to toxic substances.

Classification=The Field of Toxicology

II. Based on specific socio-medical issues

Ecotoxicology

• Ecotoxicology has evolved as an extension of environmental toxicology

•It is concerned with the toxic effects of chemical and physical agents on living organisms, especially in populations and communities with defined ecosystems

Classification=The Field of Toxicology

II. Based on specific socio-medical issues

Clinical toxicology

• Is concerned with diseases and illnesses associated with short term or long term exposure to toxic chemicals.

• Deals with diagnosis and treatment of the normal diseases or effects caused by toxic substances of exogenous origin.

Classification=The Field of Toxicology

II. Based on specific socio-medical issues

Forensic toxicology

•is used to help establish cause and effect relationships between exposure to a drug or chemical and the toxic or lethal effects that result from that exposure.

•It deals with the medical and legal aspects of the harmful effects of chemicals on man, often in post mortem material, for instance, where there is a suspicion of murder, attempted murder or suicide by poisoning.

Classification=The Field of Toxicology

II. Based on specific socio-medical issues

Animal and plant toxicology

• Deals with the diagnosis and treatment of harmful effects of animals and plants.

Analytical toxicology

• Identifies the toxicant through analysis of body fluids, stomach content, excrement, or skin.

Classification=The Field of Toxicology

II. Based on specific socio-medical issues

Social hygiene

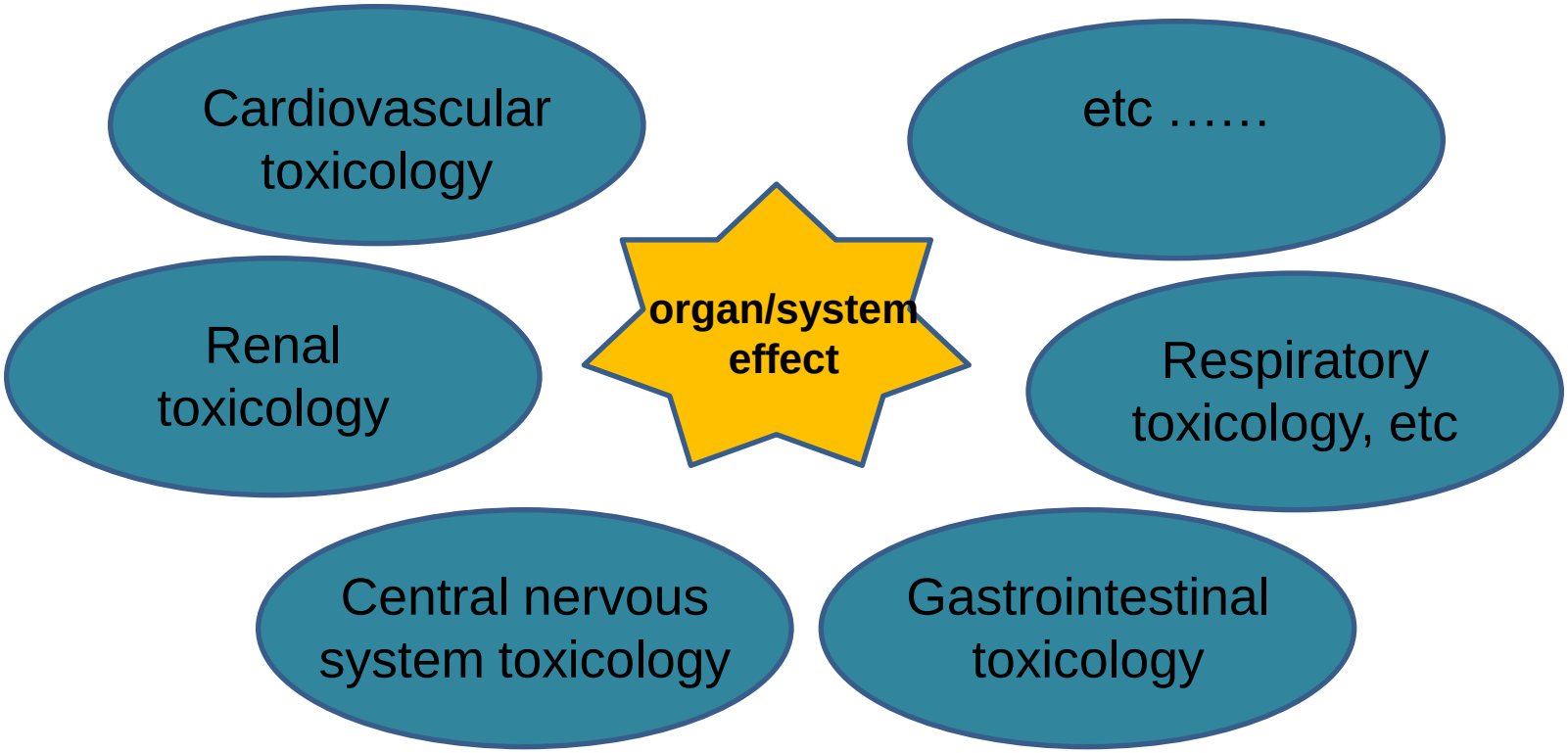
- study of drug addiction and the fight against drugs

Food Toxicology

- study of substances found in food that might be harmful to those who consume sufficient quantities of the food containing such substances.

Classification=The Field of Toxicology

III. Based on the organ/system effect



Define toxicology

- **What is Toxicology**?

- The classic connotation of toxicology was "**the science of poisons.**“
- Is the study of the **interaction** between **chemical agents** and **biological systems**
- Is the study of the **harmful effects** of chemical and physical agents on living organisms.
- Is the study of the **adverse effects** of chemical or physical agents on living systems or organisms.

Define toxicology

- **Toxicology**
- Derived from Greek word, **toxikon** and **logos**

Define toxicology

What are harmful or adverse effects?

Harmful or adverse effects are those that are damaging to either the survival or normal function of the individual.

Desired effect on human body

Side effect

Undesired effect= adverse effects on human body

Adverse effects may occur in many forms

immediate death to subtle changes not realized 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

Adverse effect

Substance → Living organisms

Substance=xenobiotic=toxic agent

Poison: the origin of the toxic substance is unknown

Toxin: are poisons produced within living cells or organs of plants, animals, and bacteria.

Toxicant : are synthetic, human-made, toxic chemicals.

Define toxicology

adverse effects are defining as

Any

- Biochemical
- Physiological
- Anatomical
- Pathological
- and/or behavioral change

That results in functional impairment

that may affect the performance of the whole organism or reduce the ability of the organism to respond to an additional challenge

➢ The term "**toxin**" usually is used when talking about toxic substances produced naturally. A toxin is any poisonous substance of microbial (bacteria or other tiny plants or animals). a poison of natural (biological) origin

➢A toxicant is any chemical that can injure or kill humans, animals, or plants.

The term "toxicant" is used when talking about toxic substances that are produced by or are a by-product of human-made activities. For example, dioxin (2,3-7,8-tetrachlorodibenzop-dioxin {TCDD}), produced as a by-product of certain chlorinated chemicals, is a toxicant.

On the other hand, arsenic, a toxic metal, may occur as a natural contaminant of groundwater or may contaminate groundwater as a by-product of industrial activities.

Basic Terminology

- **A toxicologist**

- is a scientist that determines the harmful effects of agents and the cellular, biochemical, and molecular mechanisms responsible for the effects.

- **Toxicosis.**

- A disease state that results from exposure to a poison.

Basic Terminology

•What is Xenobiotic?

is the general term that is used for a foreign substance taken into the body.

It is derived from the Greek term **xeno** which means "**foreigner**."

Xenobiotics may produce beneficial effects (such as a pharmaceuticals) or they may be toxic (such as lead).

As Paracelsus proposed centuries ago, dose differentiates whether a substance will be a remedy or a poison

A xenobiotic in small amounts may be non-toxic and even beneficial but when the dose is increased, toxic and lethal effects may result

Basic Terminology

- **What is Toxic?**

- This term relates to poisonous or deadly effects on the body by inhalation (breathing), ingestion (eating), or absorption, or by direct contact with a chemical.

Having the characteristic of producing an undesirable or adverse health effect

- **Toxic Symptom?**

- This term includes any feeling or sign indicating the presence of a poison in the system.

Basic Terminology

- **What are Toxic Effects?**

- This term refers to the health effects that occur due to exposure to a toxic substance; also known as a poisonous effect on the body.

- **What is Toxicity?**

- any toxic (adverse) effect that a chemical or physical agent might produce within a living organism.
- can be defined as the **relative ability** of a substance to cause adverse effects in living organisms

Basic Terminology

- **What is Selective Toxicity?**

- "Selective toxicity" means that a chemical will produce injury to one kind of living matter without harming another form of life, even though the two may exist close together

Basic Terminology

- **What is a dose?**

- The dose is the actual amount of a chemical that enters the body.
- The dose received may be due to either acute (short) or chronic (long-term) exposure.

- **What is a Dosage**

- The amount of toxicant per unit of animal mass or weight e.g: 2.5 mg/kg/day for 2 years

Basic Terminology

- **Acute poisoning**

- is caused by an excessive single dose, or several dose of a poison taken over a short interval of time. e.g. Strychnine, potassium cyanide.

- **Chronic Poisoning**

- is caused by smaller doses over a period of time, resulting in gradual worsening e.g. arsenic, phosphorus, antimony and opium

Basic Terminology

- **What is Hazard?**

- something that could potentially cause harm.
- is any source of **potential** damage, harm or adverse health effects on something or someone e.g knife, Benzene, electricity…….

- **What is Risk?**

- the degree of likelihood that harm will be caused.
- is the chance, high or low, that any hazard will actually cause somebody harm.
- For exemple "cigarette smokers are 12 times (for example) more likely to die of lung cancer than non-smokers"

RISK= HAZARD + EXPOSURE

Basic Terminology

- **Sub acute poisoning**

- Shows features of both acute and chronic poisoning.

- **Fulminant poisoning**

- Is produced by a massive dose.
- in this death occur rapidly, sometimes without preceding symptoms

Basic Terminology

- **Threshold dose**

- The highest dose of a toxicant at which toxic effects are not observed.

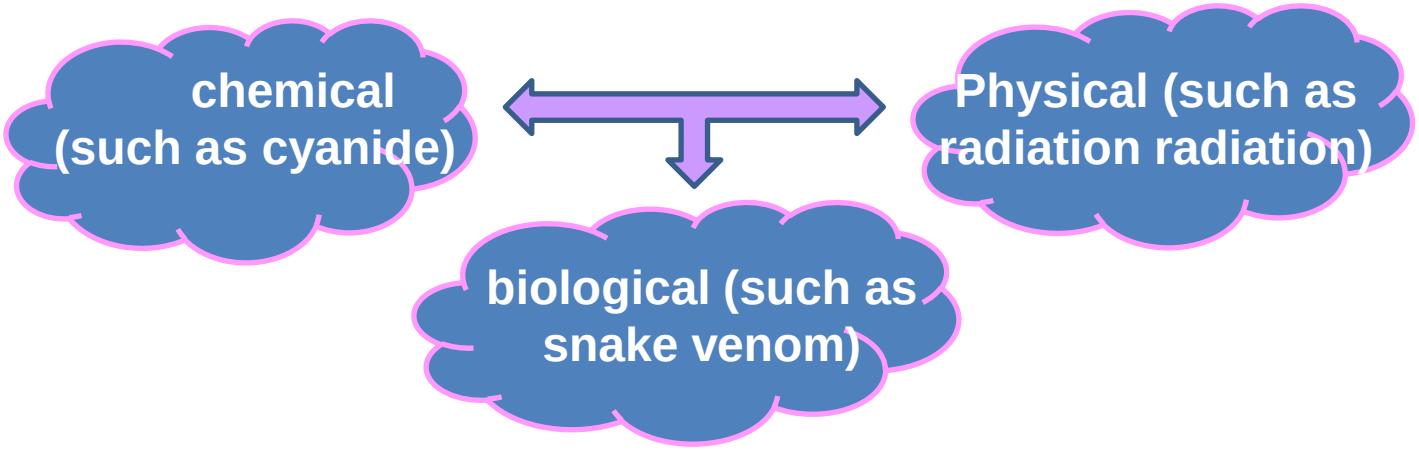
- **Lethal concentration (LC)**

- is the lowest concentration of a chemical or drug in a matrix (usually feed or water) that causes death.

Basic Terminology

- **Toxic agent**

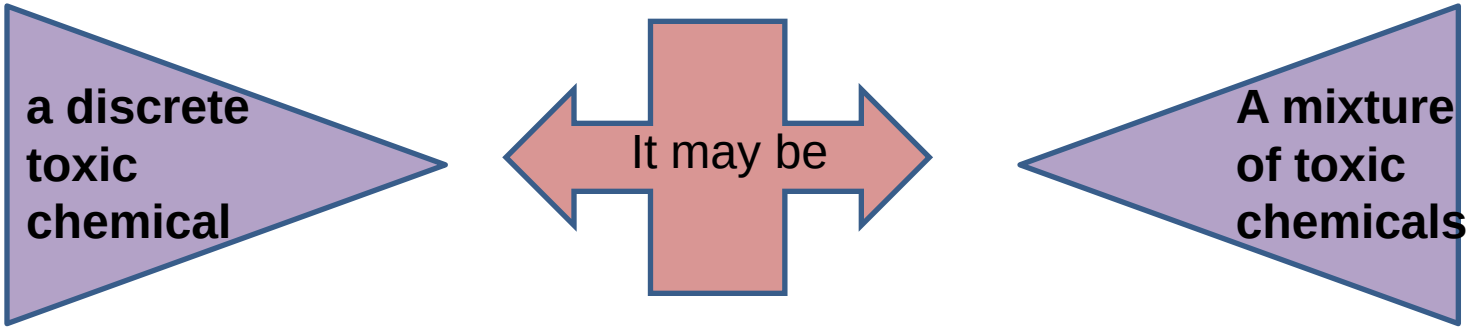
- is anything that can produce an adverse biological effect.
  - Toxic agents may be



Basic Terminology

- **Toxic substance**

- is simply a material which has toxic properties



For example, lead chromate, asbestos, and gasoline are all toxic substances.

*__Lead chromate__ is a discrete __toxic chemical__.

*__Asbestos__ is a __toxic material__ that does not consist of an exact chemical composition but a variety of __fibers and minerals__.

*__Gasoline__ is also a __toxic substance__ rather than a toxic chemical in that it contains a mixture of many chemicals.

Toxic substances may not always have a constant composition. For example, the composition of gasoline varies with octane level, manufacturer, time of season, etc.

Basic Terminology

- **Toxic substances** may be

organic or **inorganic in composition**

Substances that were originally derived from living organisms.
Contain carbon and often are large molecules can be synthesized as well as be obtained from natural sources

Specific chemicals that are not derived from living organisms.
Generally small molecules consisting of only a few atoms (such as nitrogen dioxide

Basic Terminology

- **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.
Examples: 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.

A organ toxin is one that affects only specific tissues or organs.
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).

Sources of Poison

- **Domestic or household sources**: detergents, disinfectants, cleaning agents, antiseptics, insecticides, rodenticides etc.
- **Agricultural and horticultural sources**: different insecticides, pesticides, fungicides and weedicide
- **Industrial sources :** In factories, where poisons are manufactured or poisons are produced as by products
- **Commercial sources:** From store-houses, distribution centres and selling shops
- **From uses as drugs and medicines :** Due to wrong medication, overmedication and abuse of drugs

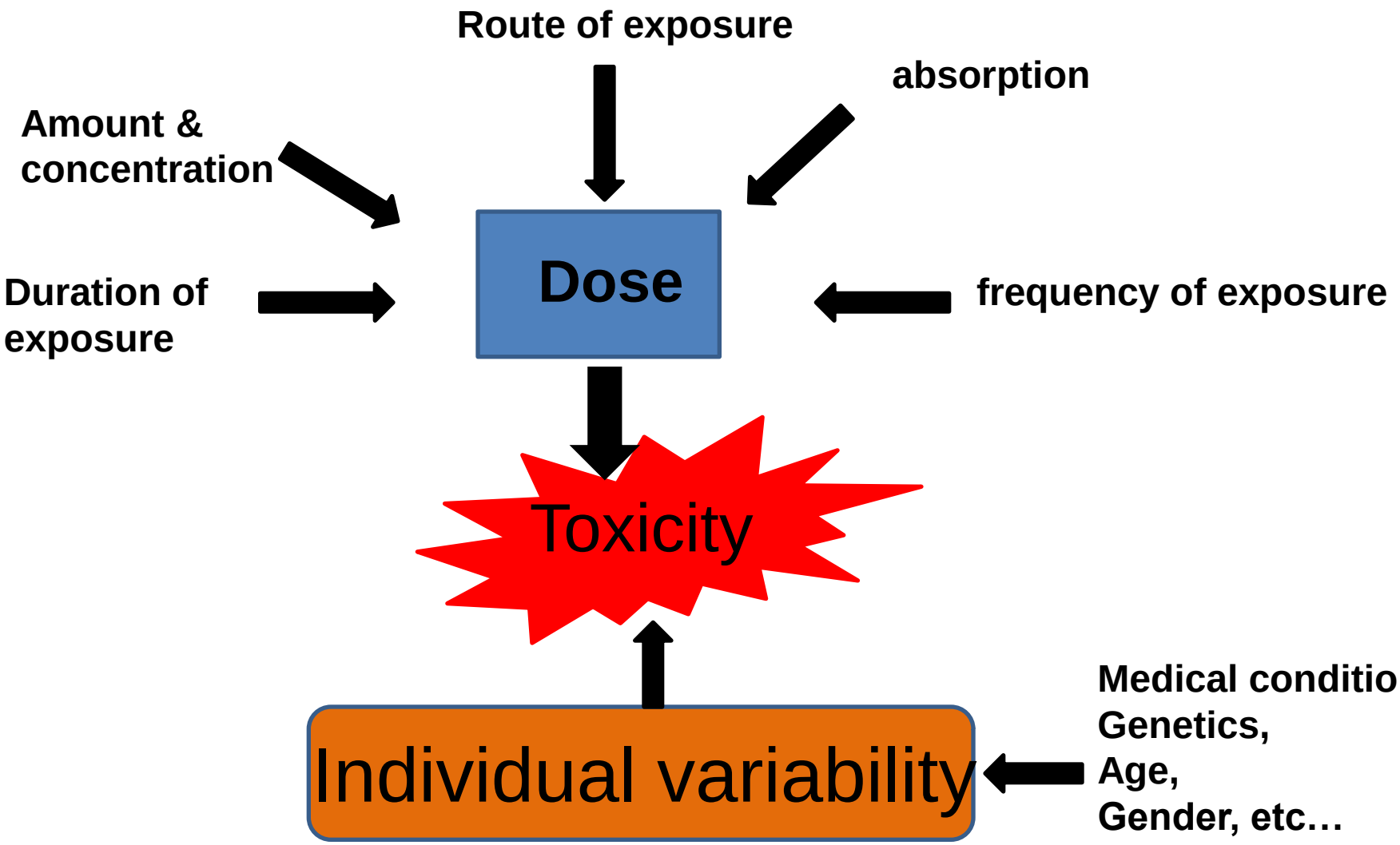
Sources of Poison

- **Food and drink :**contamination in way of use of preservatives of food grains or other food material, additives like colouring and odouring agents or other ways of accidental contamination of food and drink
- **Miscellaneous sources** :snakes bite poisoning, city smoke, sewer gas poisoning etc.

Effects influencing Toxicity

- Toxicity is deponds on
- Factors related to the substance (**Relative ability of the toxic substance).**
- Factors related to person exposed (**Individual sensitivity)**
- Factors related to exposure

Effects influencing Toxicity



Effects influencing Toxicity

Factors Related to the Substance

- This **“relative ability”** is dependent upon several conditions:
  - Intrinsic toxicity of the substance
  - Dose

Effects influencing Toxicity

Factors Related to the toxic Substance

Intrinsic toxicity

- **Chemical properties**
  - moleculare structure & functional groups
  - solubility - insolubility
  - volatility
  - stability (light, water, acids, enzymes,
  - reactivity
- **Physical properties**
  - gas (density, …)
  - liquid (vapour pressure, …)
  - solid (crystal structure, size, shape, …

Effects influencing Toxicity

Factors Related to the Substance

Intrinsic toxicity: Chemical properties

- **Moleculare structure (forme):** 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. Cr3+ is relatively nontoxic whereas Cr6+ causes skin or nasal corrosion and lung cancer.
- **Functional groups:** The nature of chemical reaction is determined by the functional groups of the chemical and toxicity is a response of organisms consequent upon reaction between chemical and certain part of the organism.

Effects influencing Toxicity

Factors Related to the Substance

Intrinsic toxicity: Chemical properties

- **Solubility – insolubility:** The polar (hydrophilic) chemicals are not easily soluble in lipids. Therefore, they cannot easily cross the membranous barriers and thus cannot easily reach the target sites for appropriate action. However, non-polar or lipophilic substances are highly soluble in lipids and other organic solvents. They can readily penetrate the lipoprotein layers of membranes
- **Stability** :means that some compounds might change under influence of light, water, acids or other external factors.

Effects influencing Toxicity

Factors Related to the Substance

Intrinsic toxicity: physical properties

- **Gaseous** or **volatile** poisons are very quickly absorbed and are thus most rapidly effective
- **Liquid** poisons are more rapid than solid poisons
- Some poisonous vegetable seeds may pass through the intestinal canal ineffective when taken intact due to their impermeable pericarp

Effects influencing Toxicity

Factors Related to the Substance

- **Dose**

- is the amount of a substance administered at one time.
- is the amount, usually per unit body mass, of a toxicant to which an organism is exposed
- There are numerous types of doses:

Exposure dose	Absorbed dose	administered dose	Total dose
The amount of xenobiotic encountered in the environment	The actual amount of the exposed dose that entres the body, can also be called **internal dose**	The quantity administrated usually orally or by injection, an administered dose taken orally may not necessarily be absorbed	The sum of all individual doses.

Effects influencing Toxicity

Factors Related to the Substance

Dose

- Not all substances that enter the body are necessarily absorbed by it. This concept applies to water intake. When a person drinks a large quantity of water at one time, some of it is absorbed while the rest of the water is eliminated.

Effects influencing Toxicity

Factors Related to the Substance

Dose-response

Dose-response relationship: is a fundamental and essential concept in toxicology. It correlates exposures and the spectrum of induced effects.

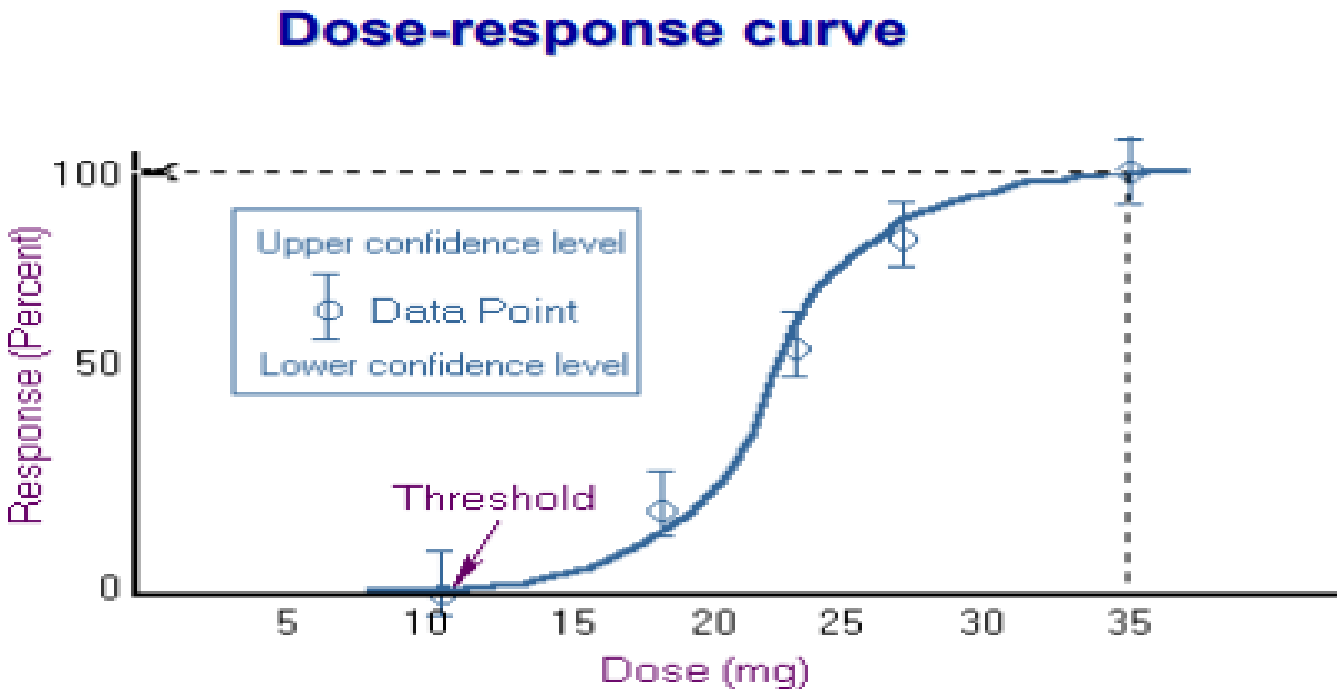
The dose-response relationship is based on **observed data from experimental** animal, human clinical, or cell studies.

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 (below which there is no response).
- determines the rate at which injury builds up - the slope for the dose response

Effects influencing Toxicity

Factors Related to the Substance

Dose-response



- **The dose-response curve** normally takes the form of a **sigmoid curve**.
- For most effects, small doses are not toxic.
- The point at which toxicity first appears is known as the t**hreshold** dose level. From that point, the curve increases with higher dose levels. In the hypothetical curve above, no toxicity occurs at 10 mg whereas at 35 mg 100% of the individuals experience toxic effects.

Effects influencing Toxicity

Factors Related to the Substance

Dose-response

- the greater the amount of a substance that enters your body, the greater is the effect on your body. This connection between amount and effect is called the “dose-response relationship.
- 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 subtoxic 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

Effects influencing Toxicity

Factors Related to the Substance

Dose-response

Estimating doses for toxic effects

- **Lethal Doses/Concentrations,:** such as LD0, LD10, and LC50, which denote doses or concentrations that are expected to lead to death in specific percentages of a population.
  - **LD0** is just below the threshold for lethality;
  - **Lethal Dose 10% (LD10)** :refers to the dose at which 10% of the individuals will die.
  - **Lethal dose 50% (LD50):** A calculated dose of a substance which is expected to cause the death of 50 percent of an entire defined experimental animal population. It is determined from the exposure to the substance by any route other than inhalation.
  - **Lethal Concentration 50% (LC50)** : for inhalation toxicity, air concentrations are used for exposure values.
  - The LC50 refers to the calculated concentration of a gas lethal to 50% of a group. Occasionally LC0 and LC10 are also used.

Effects influencing Toxicity

Factors Related to the Substance

Dose-response

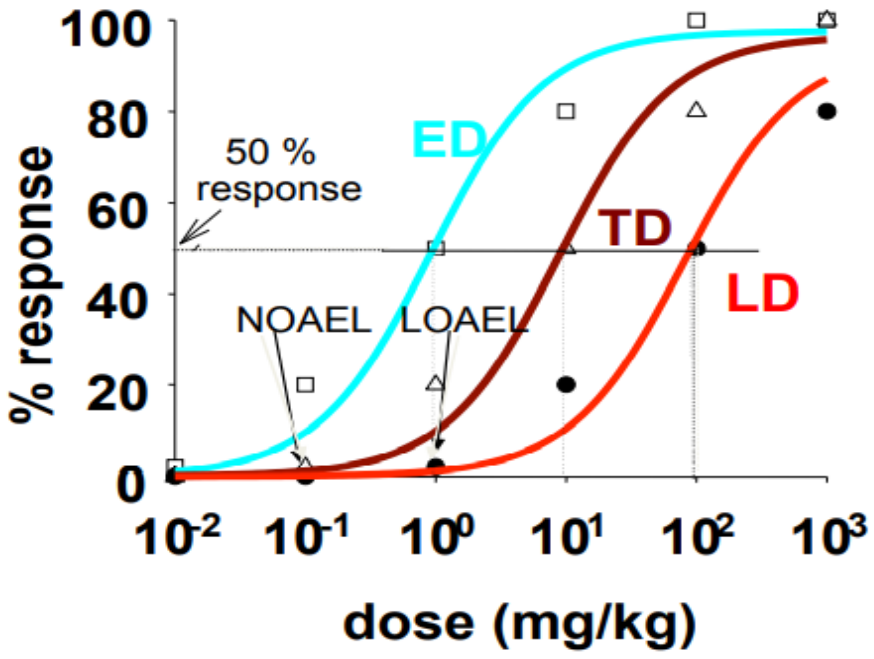
- **Effective Doses**: such as ED50 and ED90, which denote doses that are effective in achieving a desired endpoint in specific percentages of a population.
- **Toxic Doses**, such as TD0 and TD50, which denote doses that cause adverse toxic effects in specific percentages of a population.
- **The Therapeutic Index (TI):** compares the effective dose to the toxic dose of a drug.
- **The Margin of Safety (MOS)** compares the toxic dose to 1% of the population to the effective dose to 99% of the population.
- NOAEL is the highest dose at which there is no observed toxic effect.
- LOAEL is the lowest dose at which there is an observed toxic effect.

Effects influencing Toxicity

Factors Related to the Substance

Dose-response

Evaluating Dose-Response Relationships



ED: Effective dose
(therapeutic dose of a drug)

TD: Toxic dose
(dose at which toxicity occurs)

LD: Lethal dose
(dose at which death occurs)

NOAEL: no observed adverse effect level

LOAEL: lowest observed adverse effect level

ED_{50}: dose at which 50% of population therapeutically responds.

(In this example, ED_{50}=1 mg/kg)

TD_{50}: dose at which 50% of population experiences toxicity **(TD_{50}=10 mg/kg).**

LD_{50}: dose at which 50% of population dies **(LD_{50}=100 mg/kg).**

Effects influencing Toxicity

Factors Related to the Substance

Dose-response

Comparing Toxicity of Compounds

Therapeutic Index (TI)

$$TI = LD_{50}/ED_{50}$$

$$\text{or} \quad TI = TD_{50}/ED_{50}$$

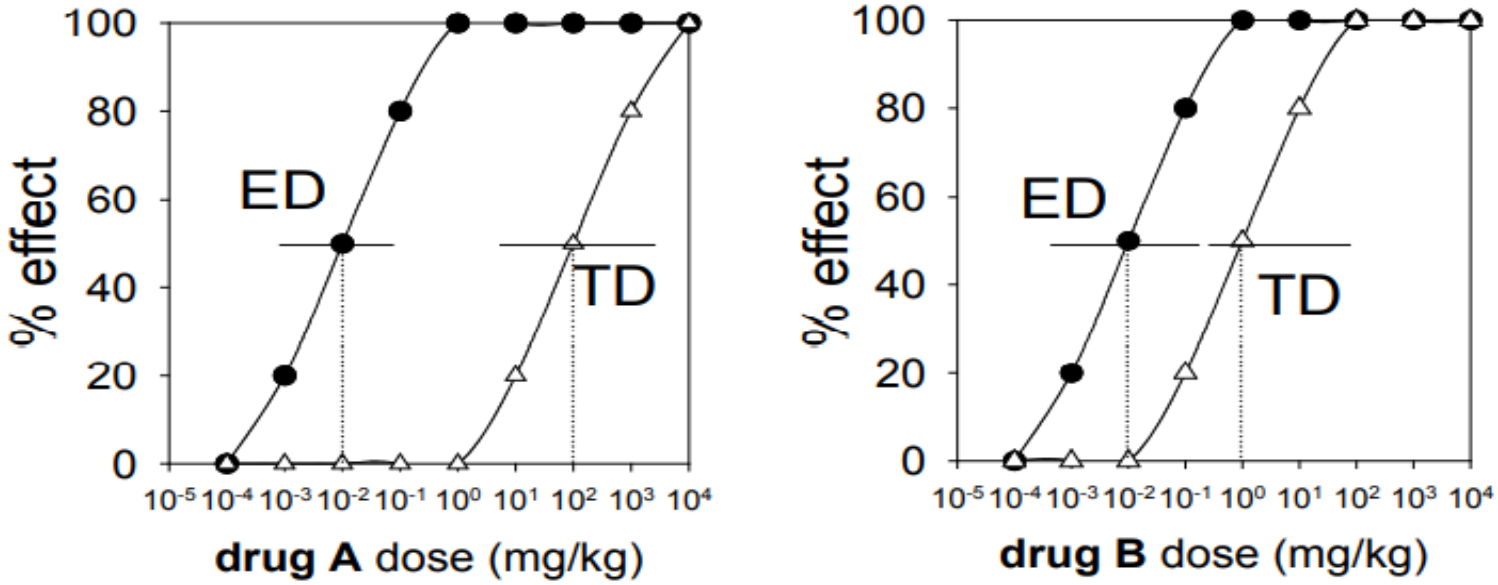
- TI is the ratio of the doses of the toxic and the desired responses.
- TI is used as an index of comparative toxicity of two different materials; approximate statement of the relative safety of a drug.
- The larger the ratio, the greater the relative safety.

Effects influencing Toxicity

Factors Related to the Substance

Dose-response

Example of using TI to compare relative safety of 2 drugs.



Drug A: $TI = TD_{50}/ED_{50} = 100/0.01 = 10000$

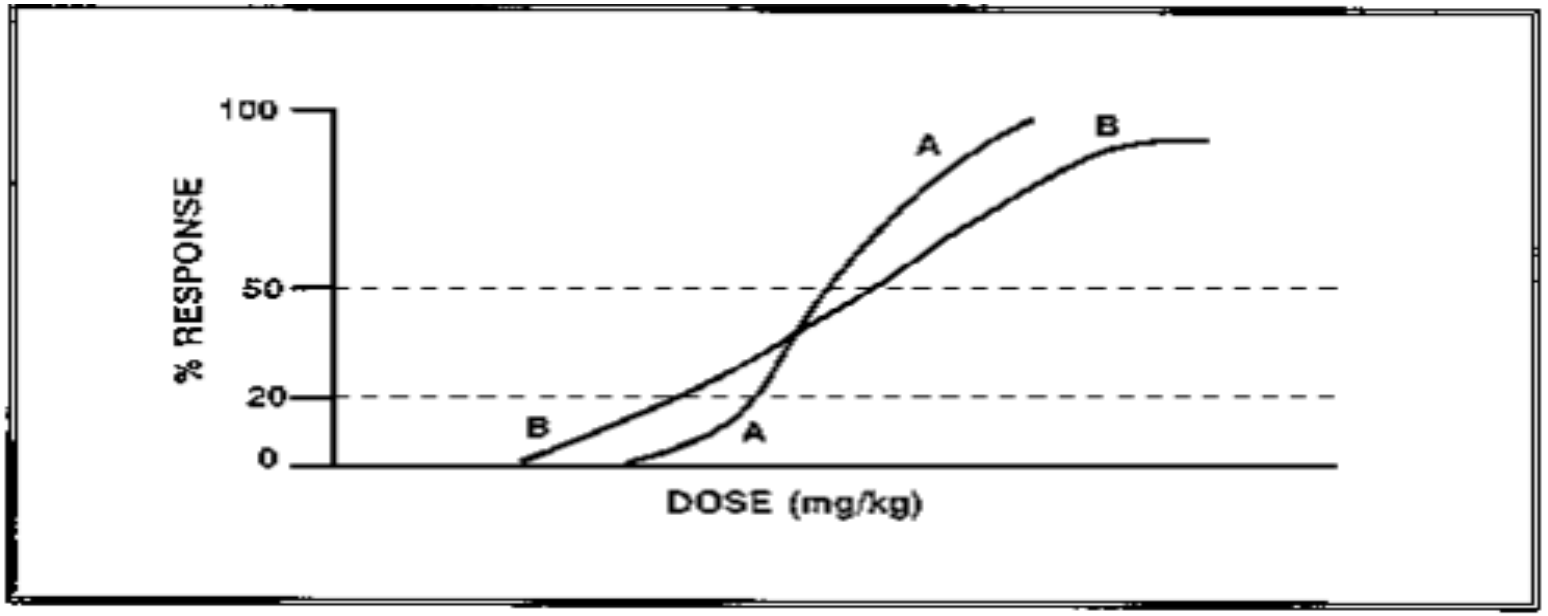
Drug B: $TI = TD_{50}/ED_{50} = 1/0.01 = 100$

Which drug is safer?

Effects influencing Toxicity

Factors Related to the Substance

Dose-response



Graph 2
Comparison of Dose-Response Curves for Two Substances

Comparison of Dose-Response Curves for Two Substances

Chemical A is assumed to be more toxic than Chemical B based on LD50, but at lower doses the situation is reversed. At LD20, Chemical B is more toxic than Chemical A.

Effects influencing Toxicity

Factors Related to the Substance

Dose-response

NOAEL and LOAEL

- **No Observed Adverse Effect Level (NOAEL)**
- **Lowest Observed Adverse Effect Level (LOAEL**).

- These terms refer to the **actual doses used** in human **clinica**l or **experimental animal** studies.

- They are defined as follows:
  - **NOAEL** : Highest dose at which there was not an observed toxic or adverse effect.
  - **LOAEL** : Lowest dose at which there was an observed toxic or adverse effect.

Sometimes the terms No Observed Effect Level **(NOEL)** and Lowest Observed Effect Level **(LOEL)** are also used.

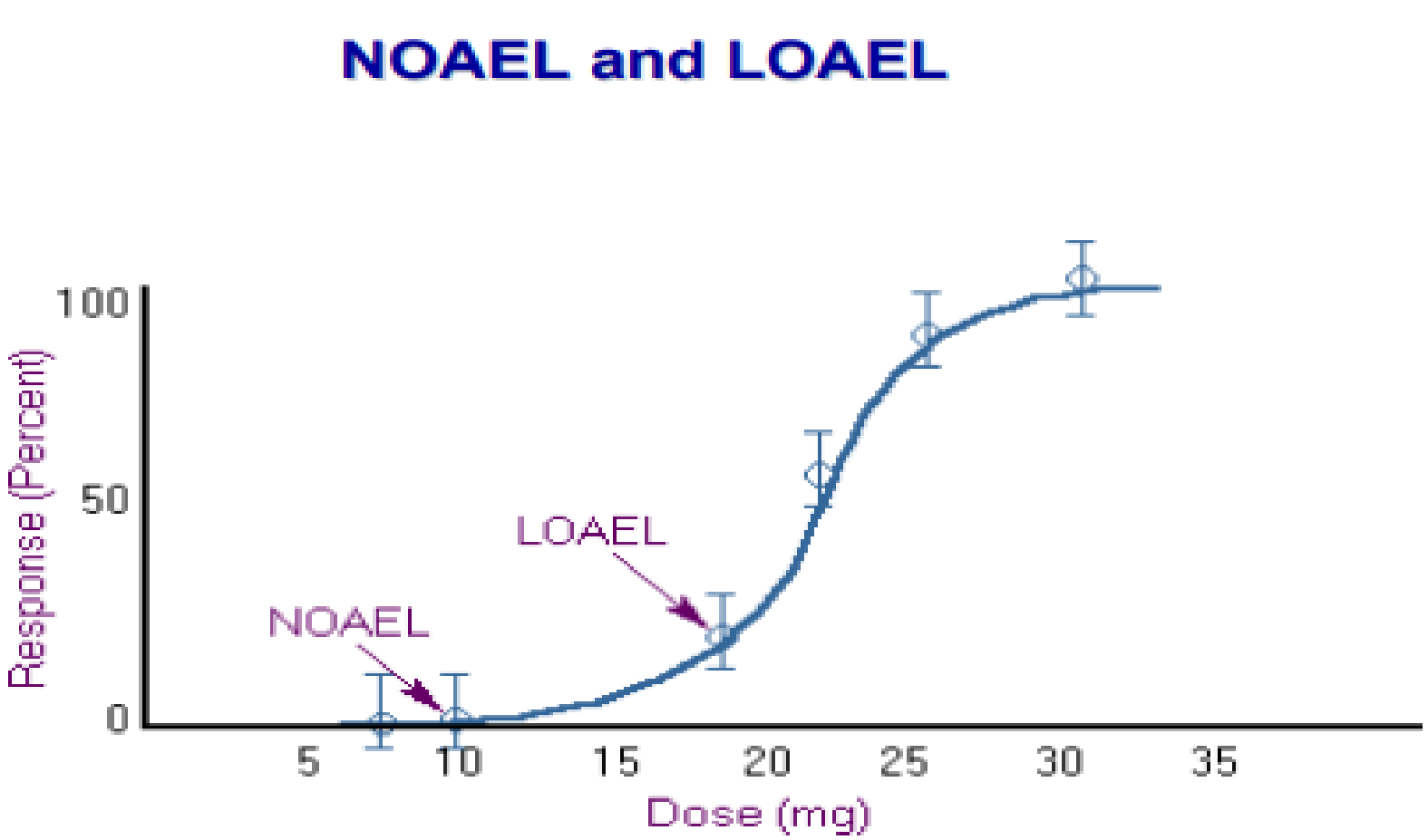
NOELs and LOELs do not necessarily imply toxic or harmful effects and can be used to describe beneficial effects of substances.

Effects influencing Toxicity

Factors Related to the Substance

Dose-response

NOAEL and LOAEL



Effects influencing Toxicity

Factors Related to the Substance

- **Dose Terms:**
- In toxicology, studies of the dose given to test organisms is expressed in terms of the quantity administered:
- • **Quantity per unit mass** (**or weight**):Usually expressed as milligram per kilogram of body weight (mg/kg).
- • **Quantity per unit area of skin surface**: Usually expressed as milligram per square centimeter (mg/cm2).
- • **Volume of substance in air per unit volume of air**: Usually given as microliters of vapor or gas per liter of air by volume (ppm). Particulates and gases are also given as milligrams of material per cubic meter of air (mg/m3).

Effects influencing Toxicity

Factors Related to the Organism

- **Individual sensitivity** to a hazardous agent depends on:

  - Age,

  -Genetics [Variations between different species (interspecies)
  Variations among members of the same species (intraspecies)

  -Gender (sex),

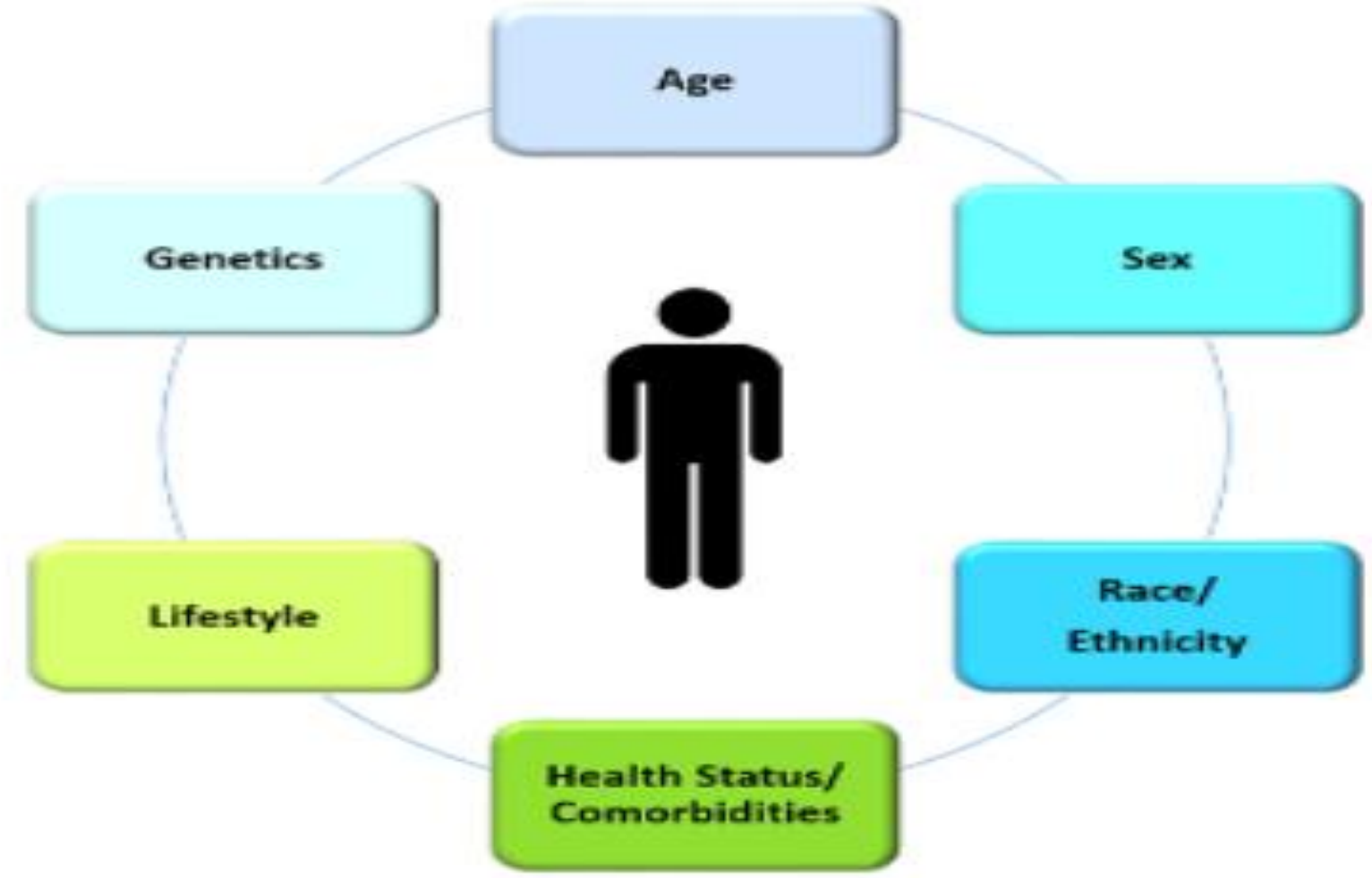
  -Personal health:current or prior illness (preexisting diseases).

  -Nutrition,

  -Current or history of exposure to chemical agents (acclimatation).

Effects influencing Toxicity

Factors Related to the Organism



Effects influencing Toxicity

Factors Related to the Organism

- **Age** :generally, the young animals are more susceptible to xenobiotics.

  For a majority of chemicals, the youngs are 1.5 to 10 times more susceptible than the adults.

  It has already been reported that the newly born individuals do not posses the enzyme systems catalyzing the biotransformation reactions.

  – For example:

  - Parathion is more toxic to young animals - nitrosamines are more carcinogenic to newborn or young animals

  - Opium and its alkaloids are tolerated better by elderly subjects but badly by children and infants. Belladonna group of drugs are better tolerated by children than by adults

Effects influencing Toxicity

Factors Related to the Organism

- **Genetics** :defective or missing enzymes which are not involved in the degradation of a substance; A dose which is lethal for one species may have no effect on another.
- e.g. genetically related alteration of cholin-esterase activity which results in a prolonged stimulation by neurotransmitters or may even provoke a permanent activation of the synapse (depolarization cannot be performed due to the absence of the down-breaking enzyme ACh-ase).
- e.g. Some can tolerate caffeine before bed, while for others such exposure would result in a restless night.

  Most species differences are attributable to differences in metabolism. Others may be due to anatomical or physiological differences.

For example, rats cannot vomit and expel toxicants before they are absorbed or cause severe irritation, whereas humans and dogs are capable of vomiting.

Effects influencing Toxicity

Factors Related to the Organism

- **Selective toxicity :** refers to species differences in toxicity between two species simultaneously exposed. This is the basis for the effectiveness of pesticides and drugs.
- Examples are: - an insecticide is lethal to insects but relatively nontoxic to animals
  - antibiotics are selectively toxic to microorganisms while virtually nontoxic to humans.

- **Gender (sex)** :The toxicity of chemicals differs with respect to sexes, because the males and females differ in their responses due to hormonal and metabolic differences. Males in some species biotransform compounds more rapidly than females.f.g.
  - Examples are: - male rats are 10 times more sensitive than females to liver damage from DDT - female rats are twice as sensitive to parathion as male rats .

- **Personal health**: generally, the healthy individuals are more tolerant to toxicants than diseased ones. The diseased and parasitized individuals have been reported to be mo.re sensitive to various toxicants than the normal ones.
- an individual who suffers from asthma may find exposure to wood smoke extremely harmful, whereas many people can tolerate short exposures to it fairly well. (Wood smoke is nevertheless toxic in either case, and chronic exposure can lead to health problems.

Effects influencing Toxicity

Factors Related to the Organism

- **Size**: The toxicity of chemicals is also affected by the size of the organisms. Often larger sized individuals are more resistant to toxicants and this has been found true in case of certain fishes. some pesticides are tested on three species of stonefly naiads and have concluded smaller species to be more susceptible to pesticides than the larger species.

  various pesticides has also tested against a freshwater prawn and experienced smaller individuals to be more susceptible to those pesticides in comparison to larger individuals of the same species.

- **Nutrition:** Diet particularly affects the susceptibility of organisms to pesticides. Supply of proteinrich diet to rainbow trout improves its tolerance to lethal levels of an organochlorine pesticide, chlordane, by six folds.

- **Acclimatation** The animals acclimated to sub lethal levels of a toxicant may become more tolerant or more weakened, depending upon the mode of action of toxicant and the types of detoxifying mechanism of the animals. For instance, acclimation of trout to sub lethal (0.22 mg/1) level of arsenic for three weeks, increased the threshold of LC50 by a factor of 1.5.

Effects influencing Toxicity

Factors Related to exposure

- Route of entry (route exposure)
- Duration
- Frequency of exposure.

Effects influencing Toxicity

Factors Related to exposure

- The major routes (pathways) by which toxic agents can enter to the body are:

Primary routes

***Gastrointestinal (GI) tract (Orale, ingestion)**
***Respiratory tract (inhalation), lung exposure.**
***Skin (dermal exposure, topical or percutaneos**

Other exposure routes

***Injections Implants**
***Conjunctival instillations (eye drops)**
***Suppositories**

The exposure routes in descending order of toxicity are: inhalation> intraperitoneal>subcutaneous>intramuscular>oral>topical.

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

Effects influencing Toxicity

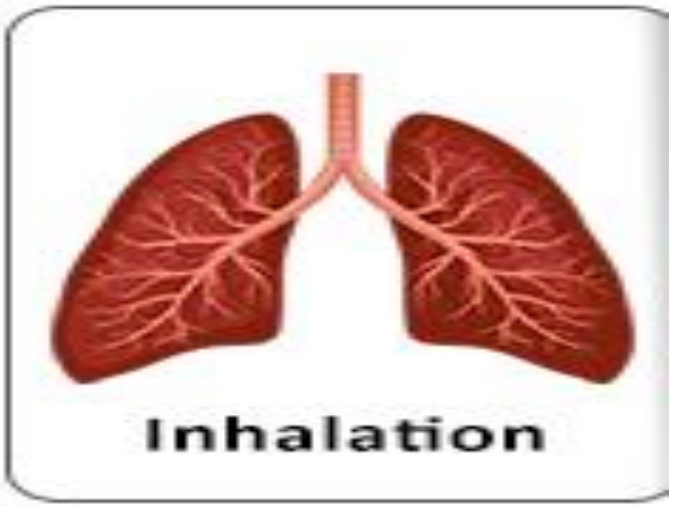
Factors Related to exposure

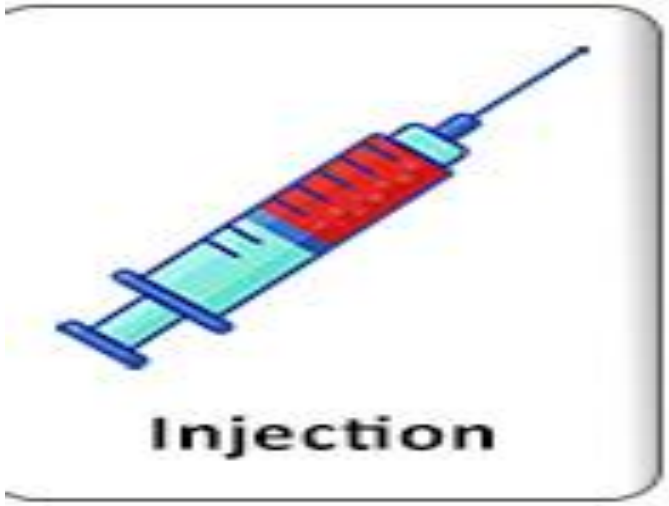
Primary routes

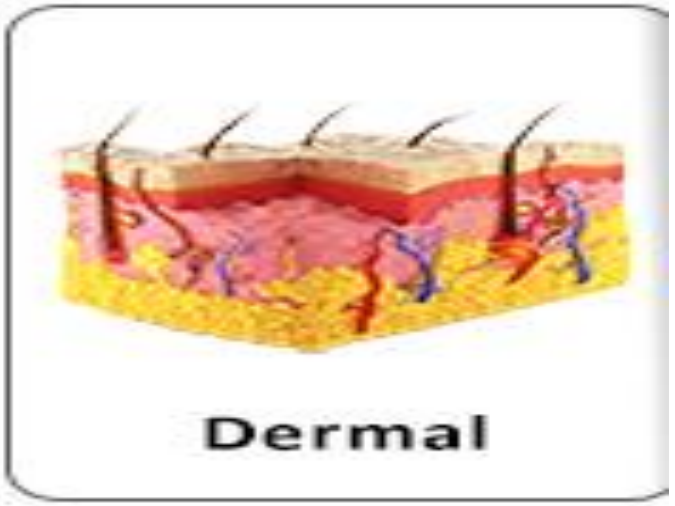
- **Gastrointestinal (GI) tract** — important for environmental exposure to contaminants from food and water; the main route for many pharmaceuticals.
- **Respiratory tract —** important for environmental and occupational exposure to air contaminants; some pharmaceuticals (such as nasal or oral aerosol inhalers) use this route, smoking.
- **Skin —** important environmental and occupational exposure route; many consumer and pharmaceutical products are applied directly to the skin, cosmetics.

Effects influencing Toxicity

Factors Related to exposure







Effects influencing Toxicity

Factors Related to exposure

Other exposure routes

used primarily for specific medical purposes:

- **Injections** : primarily used for pharmaceuticals.
  - **Intramuscular Injection**: Injection of the substance into muscular tissue;
  - **Intraperitoneal Injection**: Injection into the abdominal cavity; used for rapid resorption especially in experimental toxicology;
  - **Intravenous Injection**: Injection of the substance into a vein
- **Implants** : pharmaceuticals may be implanted to permit slow, time-release (for example, hormones). Many medical devices are implanted for which minimal absorption is desired (such as artificial lens or tendons). Some materials enter the body via skin penetration as the result of accidents or weapons.

Effects influencing Toxicity

Factors Related to exposure

Other exposure routes

- **Conjunctival instillations** (eye drops) : primarily for treating ocular conditions; however, in some cases, considerable absorption can occur and cause systemic toxicity.
- **Suppositories** :used for medicines that may not be adequately absorbed after oral administration or that are intended for local therapy; usual locations for suppositories are the rectum and vagina. Cell Membrane

Effects influencing Toxicity

Factors Related to exposure

- **Duration** is the length of time a person is exposed.
- **Frequency** is how many times a person is exposed.
- **Frequency** and **duration** both influence whether an exposure is acute or chronic.

Effects influencing Toxicity

Factors Related to exposure

- **Duration**: The longer you are exposed to a chemical, the more likely you are to be affected by it.

  Chemical exposure which continues over a long period of time is often particularly hazardous because some chemicals can accumulate in the body or because the damage does not have a chance to be repaired. The combination of dose and duration is called the **rate of exposure.**

  If a dose is administered slowly so that the rate of elimination or the rate of detoxification keeps pace with intake, it is possible that no toxic response will occur. The same dose could produce an effect with rapid administration.

  For example, if you work with a chemical for eight hours each day, you have the rest of the day (16 hours) to eliminate it from your body before you are exposed again the next day. If your body can't eliminate all the chemical in 16 hours and you continue to be exposed, the amount in the body will accumulate each day you are exposed.

Effects influencing Toxicity

Factors Related to exposure

- **Acute exposure** is exposure for a short period of time, occurs almost immediately (hours/days), often measured in minutes to hours.
- An **acute exposure** is usually a single dose or a series of doses received within a 24 hour period. Death is a major concern in cases of acute exposures.
- An example of acute exposure is an agricultural worker who is exposed once to high concentrations of toxic vapors and passes out within a few minutes.
- Frequency: once
- Duration: three minutes

Effects influencing Toxicity

Factors Related to exposure

- **Subchronic Toxicity** results from repeated exposure for several weeks or months. This is a common human exposure pattern for some pharmaceuticals and environmental agents.
- Examples are:

  - Ingestion of coumadin tablets (blood thinners) for several weeks as a treatment for venous thrombosis can cause internal bleeding.

  - Workplace exposure to lead over a period of several weeks can result in anemia

Effects influencing Toxicity

Factors Related to exposure

- **Chronic exposure** involves repeated or continuous exposure for an extended period of time.
- **Chronic toxicity** represents cumulative damage to specific organ systems and takes many months or years to become a recognizable clinical disease
- An example of chronic exposure is an agricultural worker who is exposed every day to low concentrations of toxic vapors for one month and who complains of worsening headaches.

  - Frequency: every day
  - Duration: one month

- Examples of chronic toxic affects are:
  - cirrhosis in alcoholics who have ingested ethanol for several years;
  - chronic kidney disease in workmen with several years exposure to lead;
  - chronic bronchitis in long-term cigarette smokers;
  - pulmonary fibrosis in coal miners (black lung disease).

Effects influencing Toxicity

Factors Related to exposure

Acute	Chronic
Occurs immediately or soon after exposure (short latency).	Occurs over time or long after exposure (long latency)
Often involves a high exposure (large dose) over a short period.	Often involves low exposures (small doses) over a long period.
Often reversible after exposure stops.	Many effects are not reversible.
Can be minor or severe. For example, a small amount of ammonia can cause throat or eye irritation; larger amounts can be serious or even fatal.	Chronic effects are still unknown for many chemicals. For example, most chemicals have not been tested for cancer or reproductive effects.
Relationship between chemical exposure and symptoms is generally, although not always, obvious.	It may be difficult to establish the relationship between chemical exposure and illness because of the long time delay or latency period.
Knowledge often based on human exposure.	Knowledge often based on animal studies.

Effects influencing Toxicity

Chemical Combinations (chemical interaction)

- As noted in "Factors Influencing Toxicity," the presence of other chemicals, at the same time, earlier, or later may:
- Decrease toxicity (antagonism).
- Add to toxicity (additivity).
- Increase toxicity (synergism or potentiation) of some chemicals.

Effects influencing Toxicity

Chemical Combinations (chemical interaction)

- A reaction occurs when chemicals **combine with each other** to produce a **new substance**. The new substance may have properties different from those of the original substances, and it could be more hazardous.
- Combinations of chemicals produce different effects from those attributed to each **individually.**

Effects influencing Toxicity

Chemical Combinations (chemical interaction)

- **Synergism** when the effect of two chemicals is greater than the effect of individual chemicals
- 1) Example: 2 + 2 = 20 e .g carbon tetrachloride + alcohol= more toxic to the liver than the sum of the individual drugs.
- 2) Example of synergism is the increased risk of developing lung cancer caused by exposures to both cigarette smoking and asbestos.

  By either smoking one pack of cigarettes per day or being heavily exposed to asbestos, you may increase your risk of lung cancer to six times higher than someone who does neither. But if you smoke a pack a day and are heavily exposed to asbestos, your risk may be 90 times higher than someone who does neither.

Effects influencing Toxicity

Chemical Combinations (chemical interaction)

- **Additive effect:** An additive effect occurs when the combined effect of two chemicals corresponds to the sum of the effects of each chemical given alone
- Example: 2 + 3 = 5

Effects influencing Toxicity

Chemical Combinations (chemical interaction)

- **Potentiation**: Potentiation occurs when the toxicity of a chemical on a certain tissue or organ system is enhanced when given together with another chemical that alone does not have toxic effects on the same tissue or organ system

  Example : 0 + 2 = 10 .
- e.g. Carbontetrachloride (CCl4) toxicity to the liver is enhanced with isopropanol (Isopropanol is not hepatoxic).

Effects influencing Toxicity

Chemical Combinations (chemical interaction)

- **Antagonism**: An antagonistic effect occurs when the combined effect of two chemicals is less than the sum of the effects of each chemical given alone (this phenomenon is well known for substances competing for the same hormonal or enzymatic receptor sites). Example: 4 + 0 = 1; 4+6=10.
- Example: Dimercaprol chalets with metal ions, As, Pb…

Effects influencing Toxicity

Chemical Combinations (chemical interaction)

- There are four types of antagonists

Chemical

Dispositional

Fonctional

Receptor

Effects influencing Toxicity

Chemical Combinations (chemical interaction)

Antagonists

Fonctional

- Produces opposite effects on the same physiologic function. For example, phosphate reduces lead absorption in the gastrointestinal tract by forming insoluble lead phosphate.

Chemical

- Reacts with the toxic compound to form a less toxic product. For example, chelating agents bind up metals such as lead, arsenic, and mercury.

Effects influencing Toxicity

Chemical Combinations (chemical interaction)

Antagonists

Receptor

Occurs when a second chemical either binds to the same tissue receptor as the toxic chemical or blocks the action of receptor and thereby reduces the toxic effect. For example, atropine interferes with the receptor responsible for the toxic effects of organophosphate pesticides.

Effects influencing Toxicity

Chemical Combinations (chemical interaction)

Antagonists

Dispositional

Alters absorption, metabolism, distribution, or excretion. For example, some alcohols use the same enzymes in their metabolism:

* ethanol--------> acetaldehyde-------> acetic acid

*methanol------> formaldehyde------> formic acid

The aldehydes cause toxic effects (hangover, blindness). Ethanol is more readily metabolized than methanol, so when both are present, methanol is not metabolized and can be excreted before forming formaldehyde. Another dispositional antagonist is Antabuse which, when administered to alcoholics, inhibits the metabolism of acetaldehyde, giving the patient a more severe prolonged hangover

Nature of toxic responses

- **a) Reversibility Vs. Irreversible**
  - Sub lethal doses of most toxic substances are eventually eliminated from an organ system. If there is no lasting effect from the exposure, it is said to be **reversible**
  - However, if the effect is permanent, it is termed **irreversible**
  - Irreversible effects of exposure remain after the toxic substance is eliminated from the organism
  - For various chemicals and different subjects, toxic effects may range from the totally reversible to the totally irreversible .

Nature of toxic responses

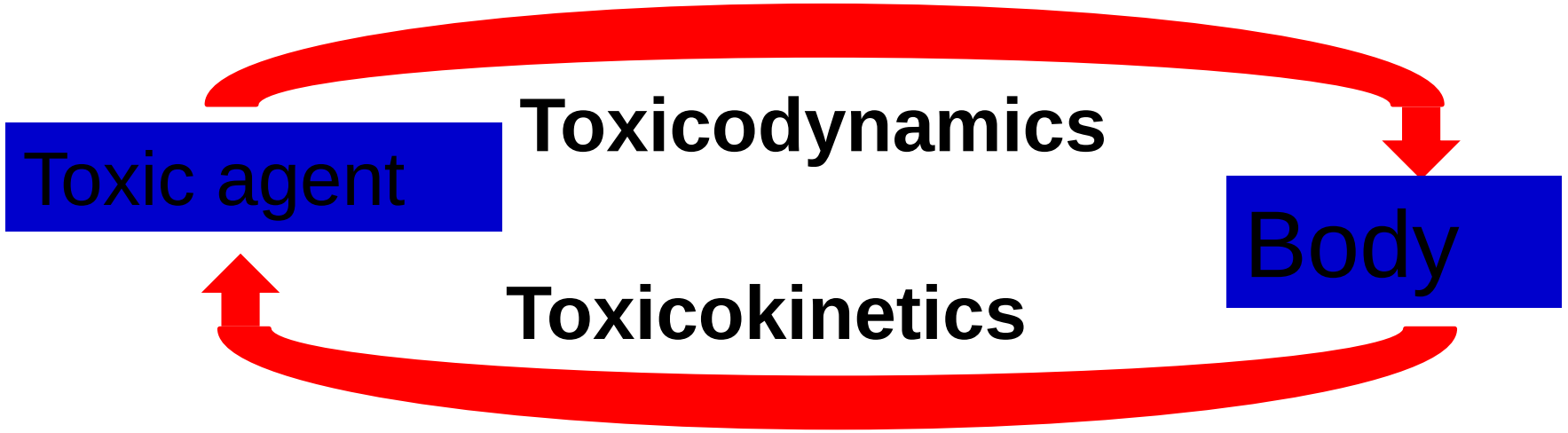
- **b)Hypersensitivity vs. Hyposensitivity**
- In some cases **hypersensitivity** is induced
- After one or more doses of a chemical, a subject may develop an extreme reaction to it.
- This occurs with penicillin, for example, in cases where people develop such a severe allergic response to the antibiotic that exposure results in death if countermeasures are not taken

Nature of toxic responses

- **Hyposensitivity** is induced by repeated exposures to a toxic substance leading to tolerance and reduced toxicities from later exposures
- Tolerance can be due to a less toxic substance reaching a receptor or to tissue building up a resistance to the effects of the toxic substance example, with repeated doses of toxic heavy metal cadmium

Toxicokinetics/toxicodynamics

- What the toxic agent does to the body

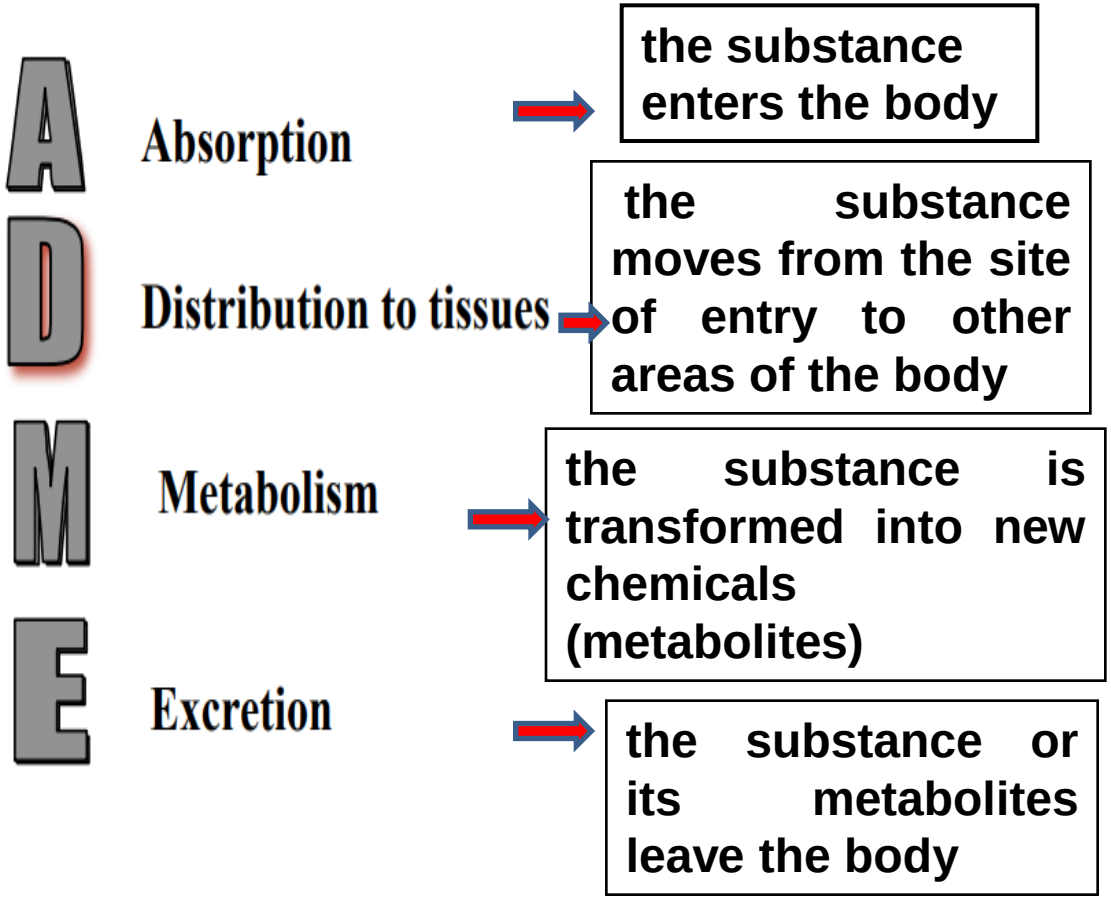


What the toxic agent does to the body

Toxicokinetics

Toxicology

is essentially the study of how a substance enters the body and what happens to it inside the body.



Toxicokinetics (ADME): 1-Absorption

Absorption

is the transfer of a chemical from the site of exposure, usually an external or internal body surface (e.g., skin, mucosa of the alimentary and respiratory tracts), into the systemic circulation.

The rate of absorption is related

- concentration of the chemical at the absorbing surface

- Lipid solubility is usually the most important property influencing absorption. In general, lipid-soluble chemicals are absorbed more readily than are water-soluble substances.

Toxicokinetics (ADME): 1-Absorption

Absorption of a Xenobiotic from the site of exposure is regulated by biological membranes lining tissues

Xenobiotics can pass through **body membranes** by

Passive transport or **Active transport.**

Passive transport moves molecules from an area of high concentration to an area of low concentration without any expenditure of cellular energy

Active transport requires specialized carrier proteins and the expenditure of cellular energy.

Food disasters Goldfrank's Toxicologic Emergencie

Toxicokinetics (ADME): 1-Absorption

Xenobiotics can pass through **body membranes** by

Passive transport

Requires no energy

a nonsaturable process

driven by concentration gradients

Most chemicals pass through biological membranes via this mechanism

Active transport.

require an energy expenditure on the body

a saturable process at high substrate concentrations

not driven by concentration gradients

moves xenobiotics against concentration gradients.

competitive inhibition by chemical cogeners or compounds that are carried by the same transporter

Toxicokinetics (ADME): 1-Absorption

Xenobiotics can pass through **body membranes** by

- **Passive transport**
- **Active transport.**

Simple diffusion depends

- the lipid solubility
- the size of the molecule.

In biological matrices, most xenobiotics exist in a solution as either an **ionized** or **un-ionized** form.

- **Un-ionized** (uncharged) molecules have **greater lipid solubility** than the ionized forms and can thus traverse the phospholipid bilayers with much greater ease than charged (ionized) molecules.

Toxicokinetics (ADME): 1-Absorption

Special transport processes

Filtration

Filtration is an important function for urinary excretion; renal glomeruli possess rather large pores (w70 nm) that allow passage of various solutes (e.g., glucose, small cations and anions) contained in blood into the urine and prevent the loss of larger molecules such as proteins and blood cells

Endocytosis

Endocytosis is a specialized form of transport by which very large molecules and insoluble materials are engulfed by invagination of the cell membrane, forming intracellular vesicle

Toxicokinetics (ADME): 1-Absorption

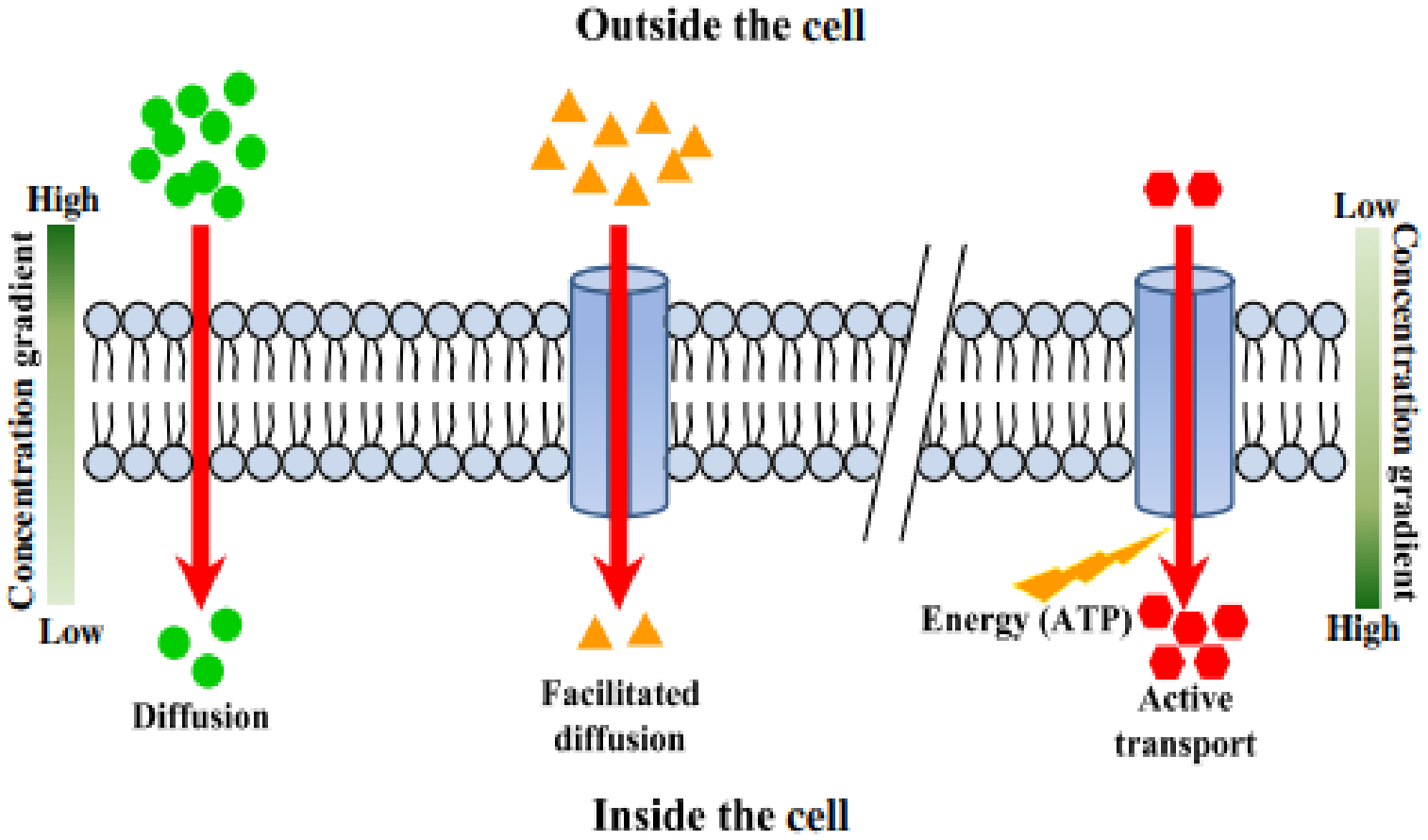


Figure 01 . Depiction of simple and facilitated diffusion and active transport of chemicals into the cell through the phospholipid bilayer membrane

Toxicokinetics (ADME): 2-Distribution

DISTRIBUTION Once absorbed across one of the body's barriers, the chemical enters the blood so that it can be distributed to the body's organs and tissues.

The chemical leaves the blood and enters the tissues at varying rates, depending on a number of factors:

(1) rate of blood flow (generally, the higher the blood flow, the more potential distribution to the organ),

(2) the ability of the chemical to traverse the capillary endothelial wall,

Toxicokinetics (ADME): 2-Distribution

(3) the physiochemical properties of the chemical, such as lipid solubility. For example, lindane is a lipid-soluble chemical that easily enters adipose tissue and remains sequestered there for an extended length of time. Conversely, ethanol is water soluble and remains in tissues that have significant amounts of water rather than distributing into the fat.

Toxicokinetics (ADME): 2-Distribution

- **Factors affected distribution**:
  - **Barrieres**:
    - Access to the brain is restricted by the presence of two barriers:
    - **the blood–brain barrier (BBB**) and the **blood–cerebral spinal fluid barrier (BCSFB)**.
    - Although neither represents an absolute barrier to the passage of toxic chemicals into the CNS,
    - The capillary endothelial cells are tightly joined, leaving few or no pores between these cells.
    - many toxicants do not enter the brain in appreciable quantities because of these barriers.

Toxicokinetics (ADME): 2-Distribution

- **Factors affected distribution**:
  - **Barrieres**:
    - the **placental barrier** does impede transfer of toxicants to the fetus against the passage of noxious substances from the mother.
    - which is therefore protected to some extent. However, the concentration of a toxicant such as methylmercury may be higher in certain fetal organs, such as the brain, because of the less-effective fetal blood–brain barrier.

Toxicokinetics (ADME): 2-Distribution

- **Factors affected distribution**:

  -**Binding and storage**

  Binding of a chemical in a tissue results in a higher concentration in that tissue.

  There are two major types of binding:

The covalent type of binding

is **irreversible** and is, in general, associated with significant toxic effects

The noncovalent binding

is **reversible.** this process plays an important role in the distribution of toxicants in various organs and tissues

Toxicokinetics (ADME): 2-Distribution

- **Factors affected distribution:**

  -Binding and storage

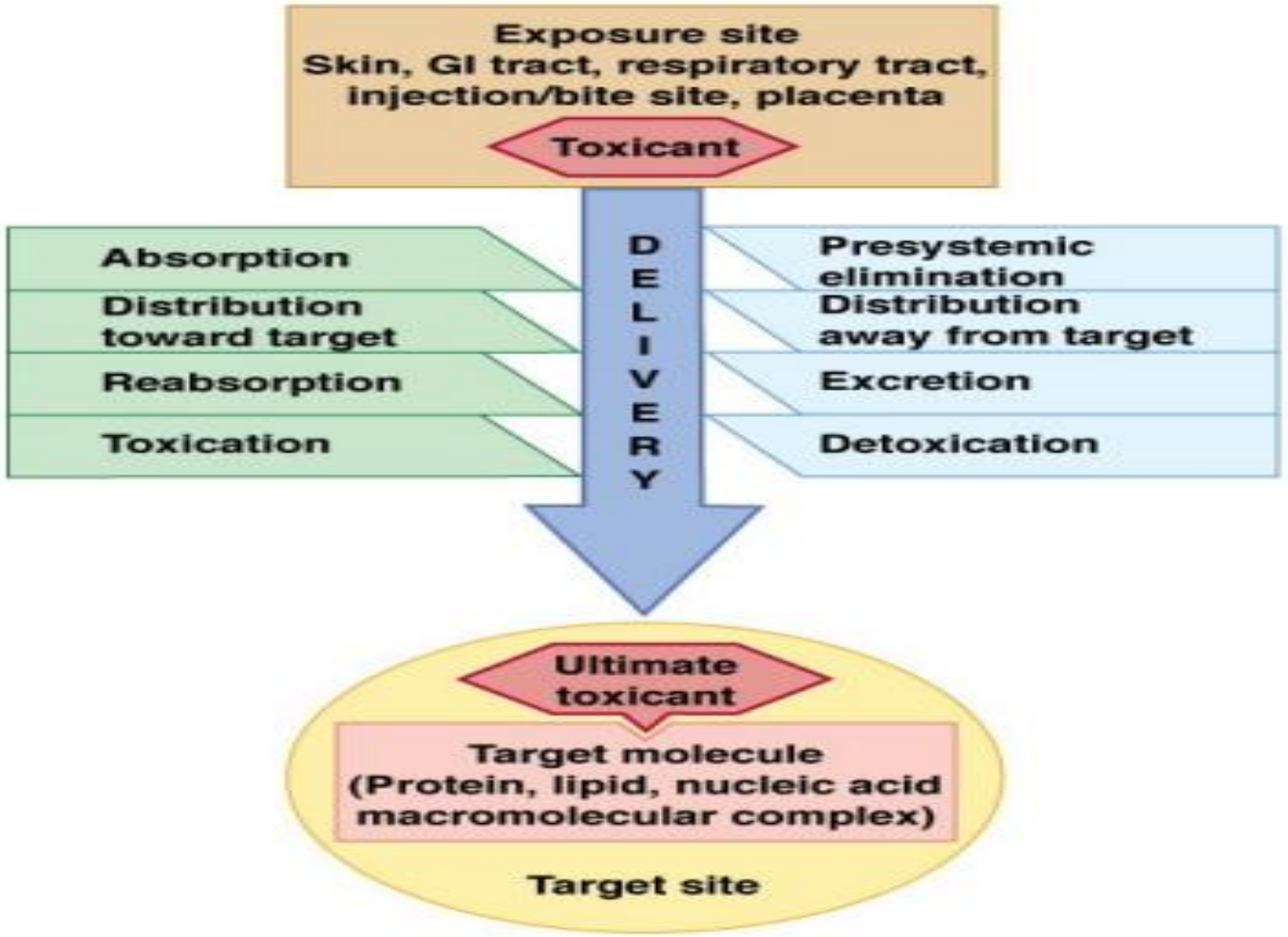
  Storage of toxicants in nontarget organs may be considered as the first step to protect our body, but their chronic release from nontarget organs into the body may produce chronic intoxication later

The **liver** **and** **kidney** have a higher capacity for binding chemicals. This characteristic may be related to their metabolic and excretory function.

Adipose tissue is an important storage depot for **lipid-soluble substances such** as dichlorodiphenyltrichloroethane (DDT), dieldrin, and polychlorinated biphenyls (PCBs). These chemicals appear to be stored in the adipose tissue by simple dissolution in the neutral fats.

Bone is a major site for **storage** of such toxicants as fluoride, lead, and strontium. By virtue of **similarities in size and charge**, F^- may readily replace OH^- , and calcium may be replaced by lead or strontium

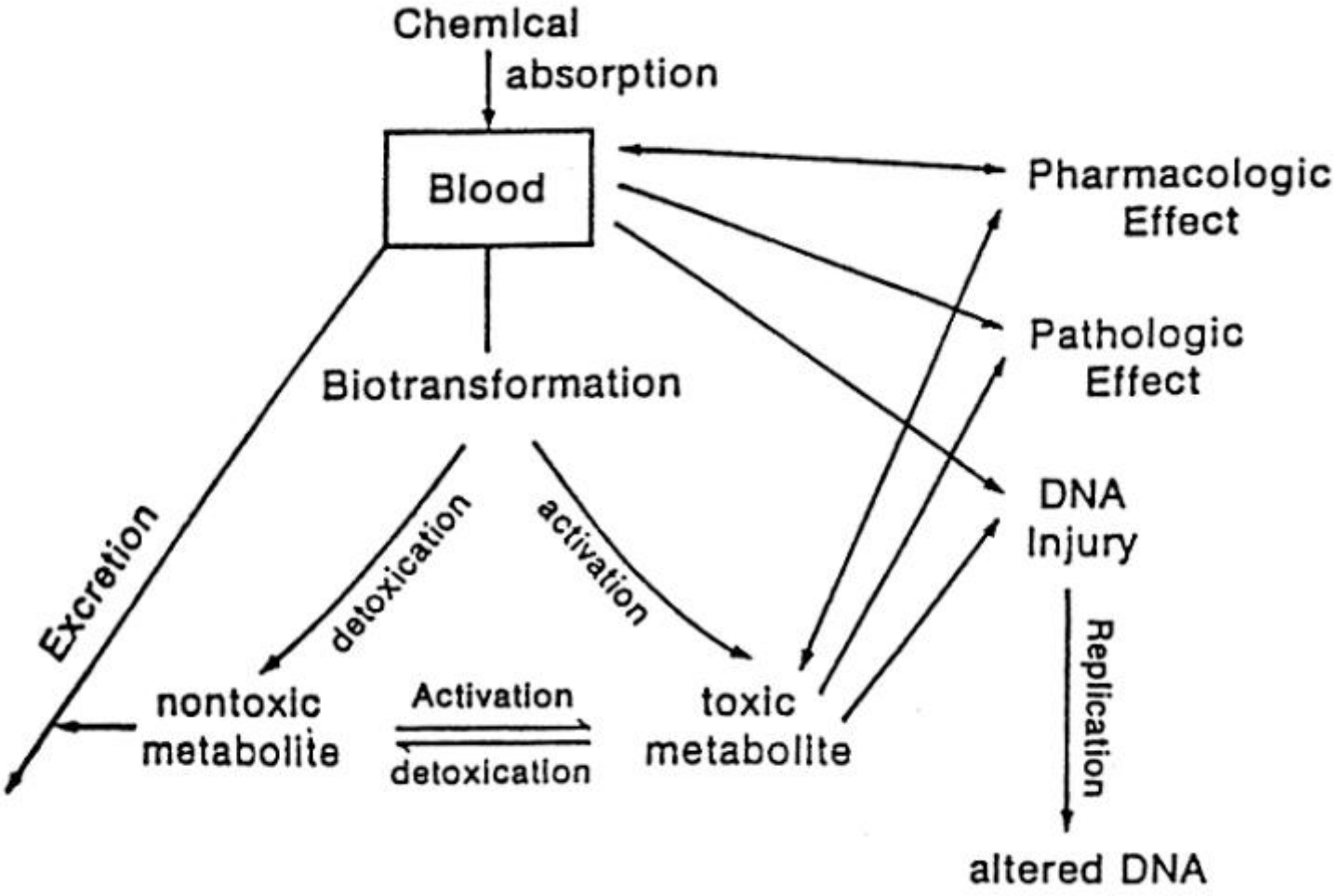
Toxicokinetics (ADME): 2-Distribution



Toxicokinetics (ADME): 3- Biotransformation

- **Biotransformation** (metabolisme)
  - a process that, in general, converts the parent compounds into metabolites and then forms conjugates.
  - it is defined also, as a converting process of **lipophilicity** to **hydrophilicity**, or a process of an **absorbable** to an **excretal** form.
  - refers to chemical alteration of a substance within the body, as by the action of enzymes.
  - is the sum of all chemical reactions that occur within a living cell.
  - Biotransformation may occur in any of several body tissues and organs, including skin, lung, intestine, liver, and kidney.
  - The liver car□ries out the majority of the chemical reactions because it contains a large number of nonspecific enzymes capable of biotransformation of xenobiotics.
  - The metabolism of foreign chemicals renders them more water soluble and better substrates for excretory transporters in the kidney or liver, thereby hastening their bodily elimination.
  - The importance of **metabolism** in clearing lipophilic molecules from the body is seen in the case of lipophilic molecules that are resistant to metabolism on chemical grounds.

Toxicokinetics (ADME): 3- Biotransformation

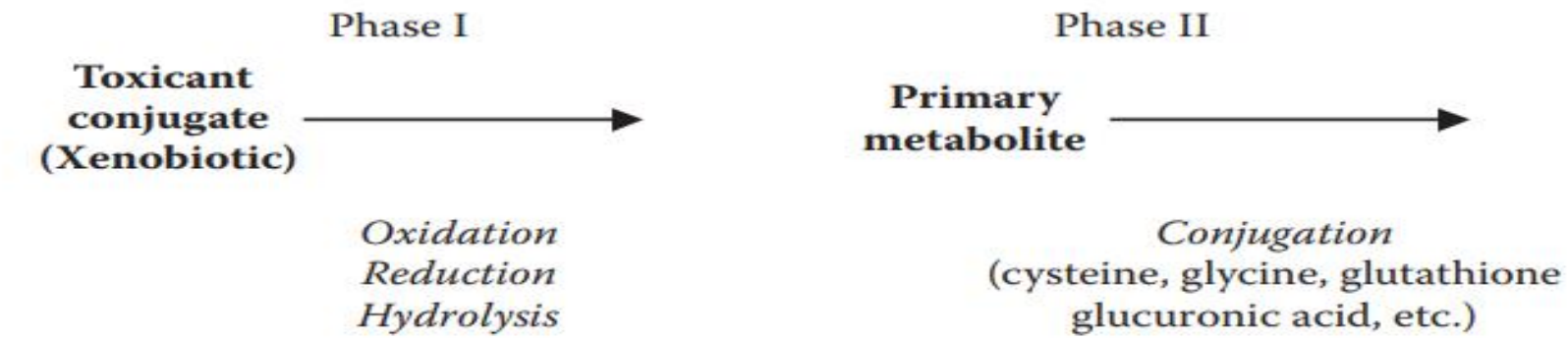


Toxicokinetics (ADME): 3- Biotransformation

- **TYPES OF BIOTRANSFORMATION:**

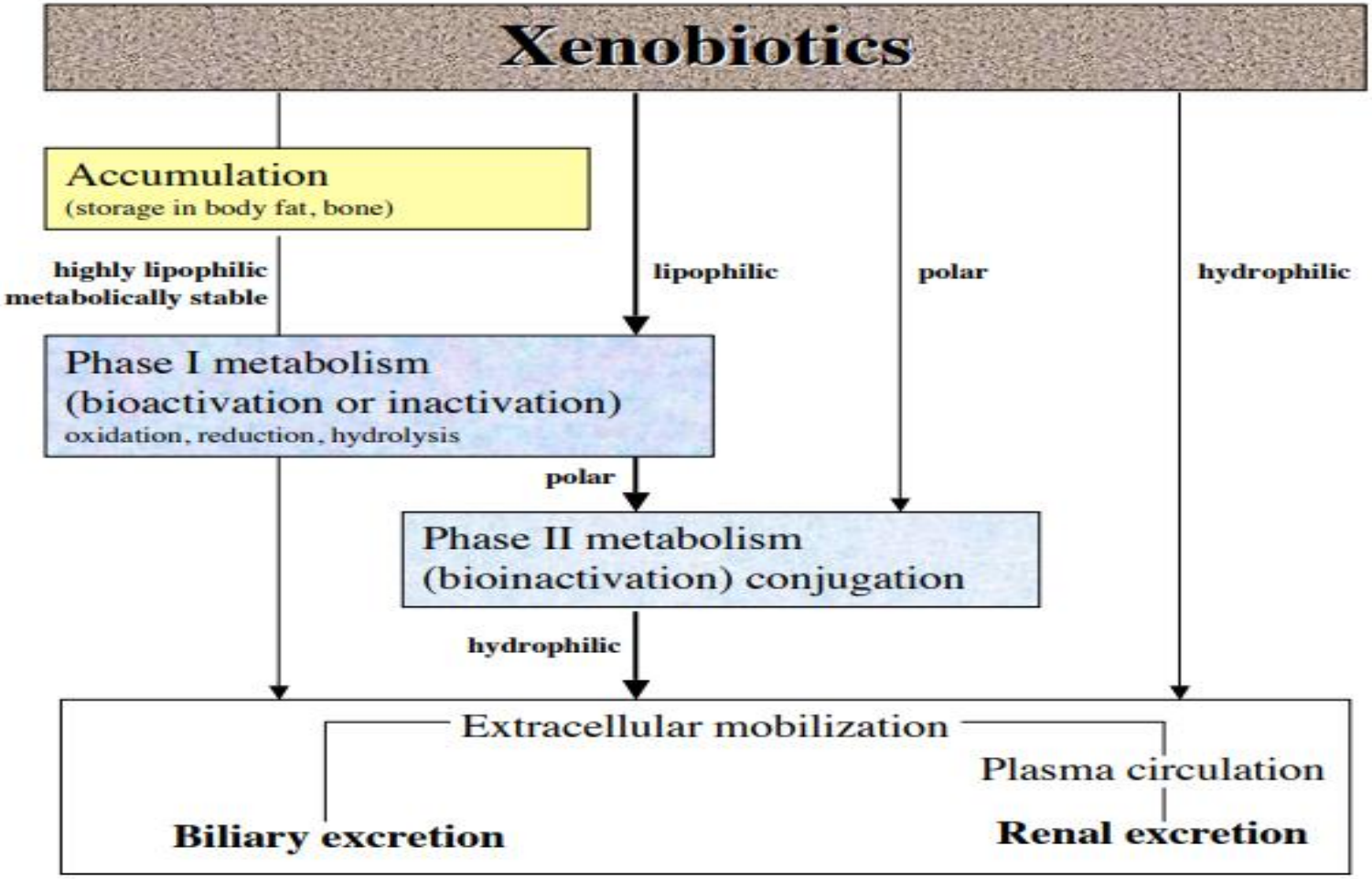
Phase I, involving oxidation, reduction, and hydrolysis may be considered degradation reactions.

Phase II, involving the production of a compound (a conjugate) that is biosynthesized from the toxicant, or its metabolite,



The two phases of biotransformation

Toxicokinetics



Toxicokinetics (ADME): 3- Biotransformation

- **Phase I reactions**:
  - Usually introduce a reactive oxygen or nitrogen atom into the xenobiotic that can serve as the site of a subsequent phase II conjugation reaction.
  - There are three types of phase I reactions:

There are three types of phase I reactions

- **Oxidation** → a great variety of chemicals involves oxidative processes.
- **Reduction** → through the function of reductases.
- **Hydrolysis** → Many toxicants contain ester-type bonds and are subject to hydrolysis

Toxicokinetics (ADME): 3- Biotransformation

Phase I

Oxidation

Microsomal monooxygenation reactions, called **mixed-function oxidations MFO** system cytochrome P450

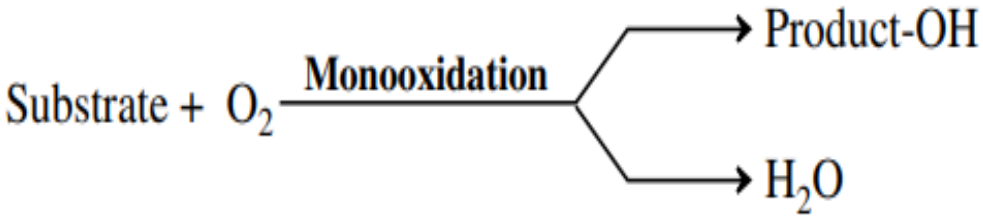
↓

located in the endoplasmic reticulum

Non-microsomal oxidoreductases

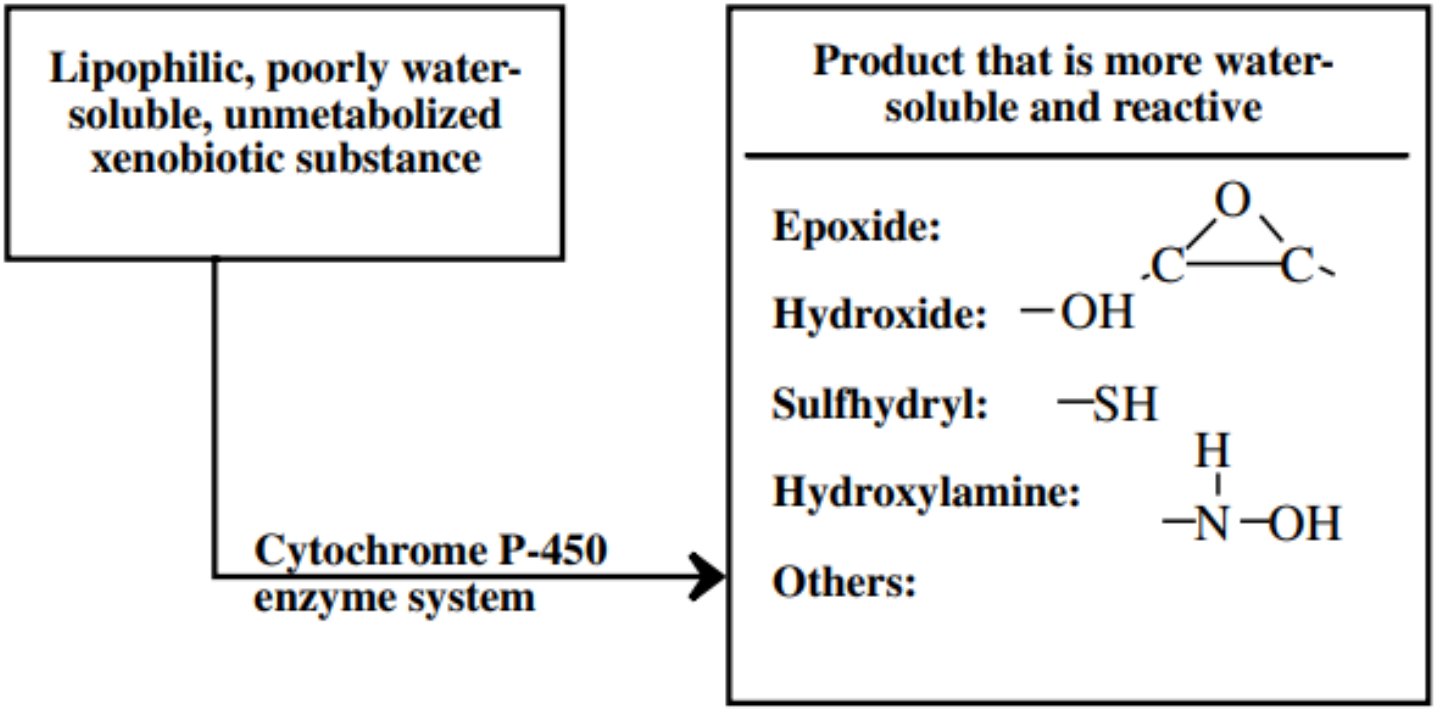
↓

located in the mitochondrial



Toxicokinetics (ADME): 3- Biotransformation

Phase I



FigureXX. Overall process of phase I reactions (Lee & Kacew, 2012)

Toxicokinetics (ADME): 3- Biotransformation

Phase I: Cyt P450

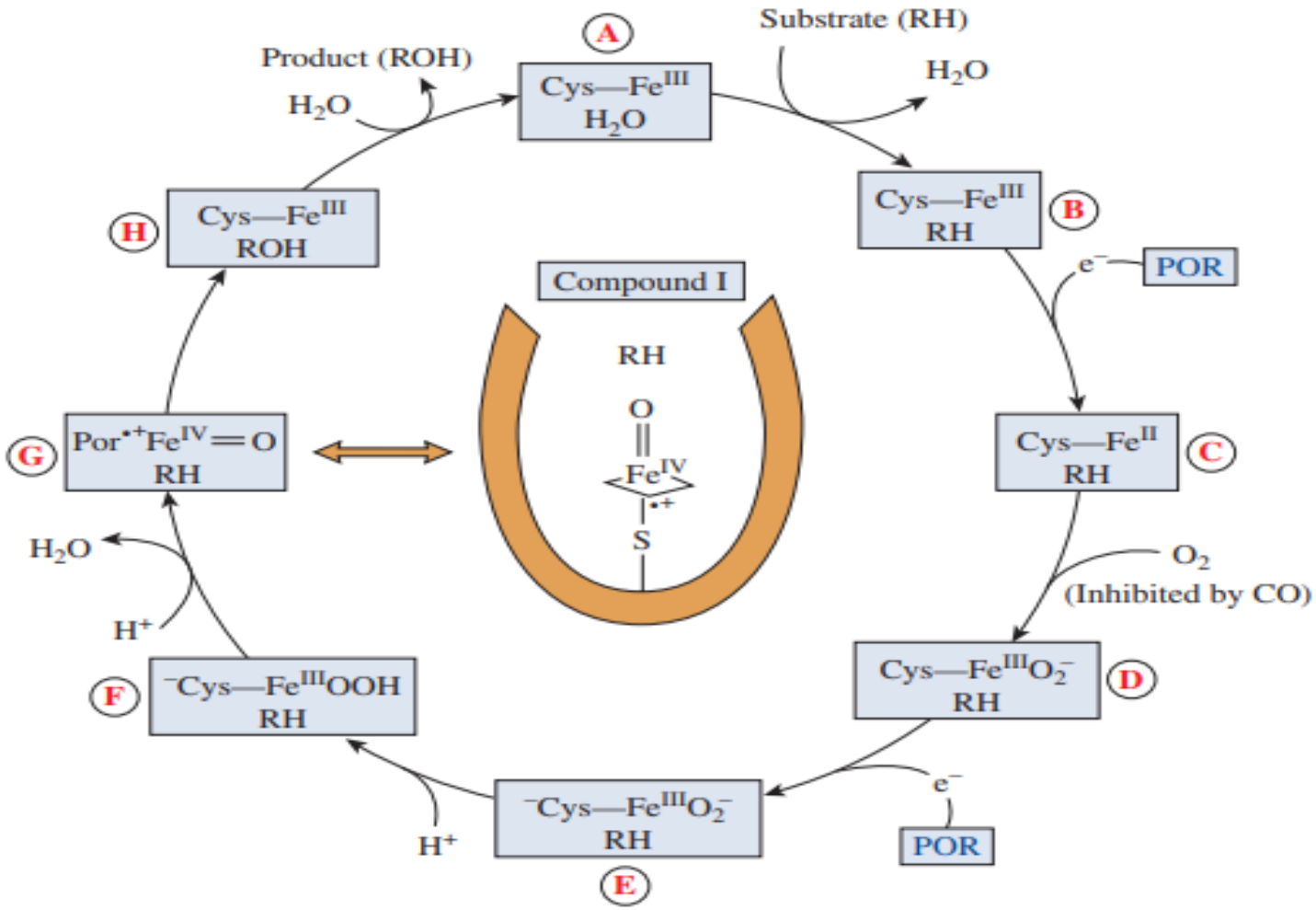


Figure 02. Catalytic cycle of cytochrome P450

Toxicokinetics (ADME): 3- Biotransformation

Phase I: Cyt P450

- Cytochrome P450 is represented as Cys-FeIII, where Cys represents the fifth ligand (a cysteine thiolate) to the ferric heme iron. RH and ROH represent the substrate and product (hydroxylated metabolite), respectively.
- The intermediates in the catalytic cycle are as follows:
  - A, ferric resting state;
  - B, substrate bound;
  - C, ferrous intermediate;
  - D, ferrisuperoxo anion intermediate;
  - E, ferriperoxo intermediate with an electron delocalized over the Cys thiolate bond;
  - F, ferrihydroperoxy intermediate (with a negative charge on the Cys thiolate bond);
  - G, compound I, an ironIV-oxo porphyrin cation, which is responsible for most substrate oxidation reactions;
  - H, enzyme in its resting state prior to the release of product formed by hydrogen abstraction followed by oxygen rebound.

FeII, FeIII, FeIV, and FeV refer to iron in the ferrous, ferric, ferryl, and perferryl state, respec□tively. It should be noted that although it is written as por•+FeIV=O, compound I is in the highly oxidized perferryl (FeV) state when the oxidation state of the porphyrin ring is also taken into account.

Toxicokinetics (ADME): 3- Biotransformation

Phase I: Cyt P450

- CYP catalyzes several types of oxidation reactions, including the following:
  - 1. Hydroxylation of an aliphatic or aromatic carbon
  - 2. Epoxidation of a double bond
  - 3. Heteroatom (S-, N-, and I-) oxygenation and N-hydroxylation
  - 4. Heteroatom (O-, S-, and N-) dealkylation
  - 5. Oxidative group transfer
  - 6. Cleavage of esters and carbamates
  - 7. Dehydrogenation

Toxicokinetics (ADME): 3- Biotransformation

Phase I

Reduction

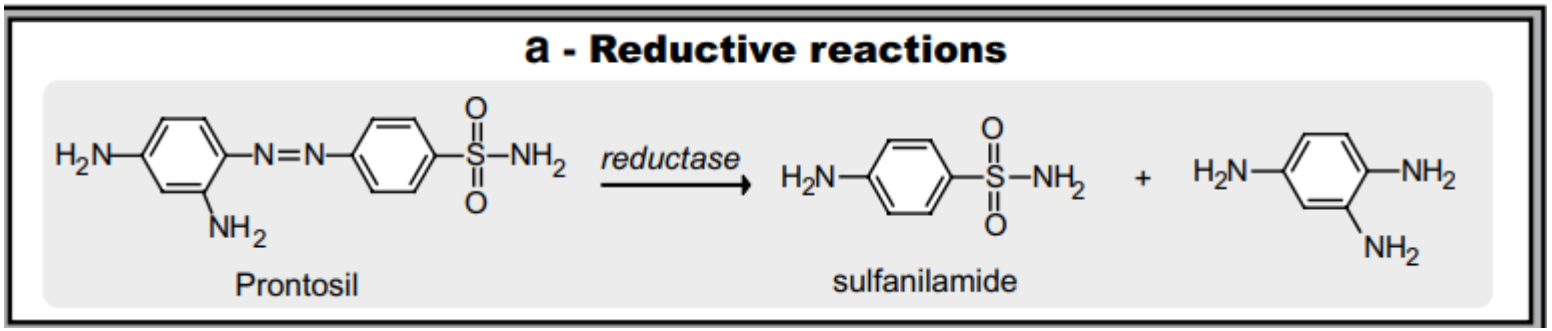
Microsomal reduction

1.Nitro reduction: for example, nitrobenzene → nitrosobenzene → phenyl hydroxylamine → aniline.

2. Azo reduction: for example, azobenzene → aniline.

Non-microsomal reduction

via the reverse reaction of **alcohol dehydrogenases**



Toxicokinetics (ADME): 3- Biotransformation

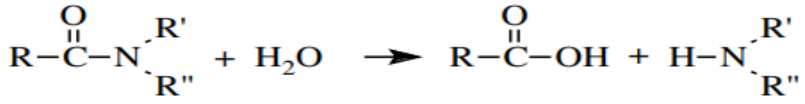
Phase I

Hydrolysis

Hydrolysis involves the addition **of H_2O** to a molecule accompanied by cleavage of the molecule into two species.

The two most common types of compounds that undergo hydrolysis are

Esters and **Amides**



By esterases enzyme,

By amidase enzyme,

Biotransformation (metabolisation)

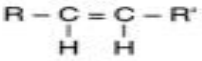
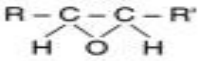
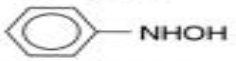
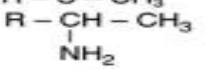
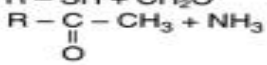
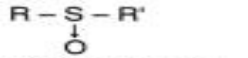
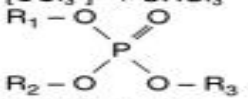
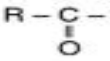
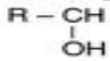
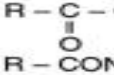
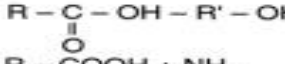
Phase I

Oxidation reactions:
Loss of electrons, often addition of **O** to replace **H**

Reduction reactions:
Gain of electrons, often addition of **H** to replace **O**

Hydrolysis reactions:
Water interacts with substrate such that O_2 makes bond

Overview of possible types of phase I biotransformation reactions

Type of reaction	*Substrate*	*Metabolite(s)*
A. oxidations		
I mixed-function oxidase-dependent reactions		
aromatic hydroxylation		
aliphatic hydroxylation	$R-CH_3$	$R-CH_2OH$
epoxidation		
N-hydroxylation		
O-dealkylation	$R-O-CH_3$	$ROH + CH_2O$
N-dealkylation	$R-NHCH_3$	$R-NH_2 + CH_2O$
S-dealkylation	$R-S-CH_3$	$R-SH + CH_2O$
deamination		
S-oxidation	$R-S-R'$	
dechlorination	CCl_4	$[CCl_3^{\bullet}] \rightarrow CHCl_3$
oxidative desulfuration		
II amine oxidation	$R-CH_2-NH_2$	$R-CHO + NH_3$
III dehydrogenation	CH_3-CH_2-OH	CH_3CHO CH_3COOH
B. reductions		
azoreduction	$R-N=N-R'$	$R-NH_2 + R'-NH_2$
nitroreduction	$R-NO_2$	$R-NH_2$
carbonyl reduction		
C. hydrolyses		
esters		
amides	$R-CONH_2$	$R-COOH + NH_3$

Toxicokinetics (ADME): 3- Biotransformation

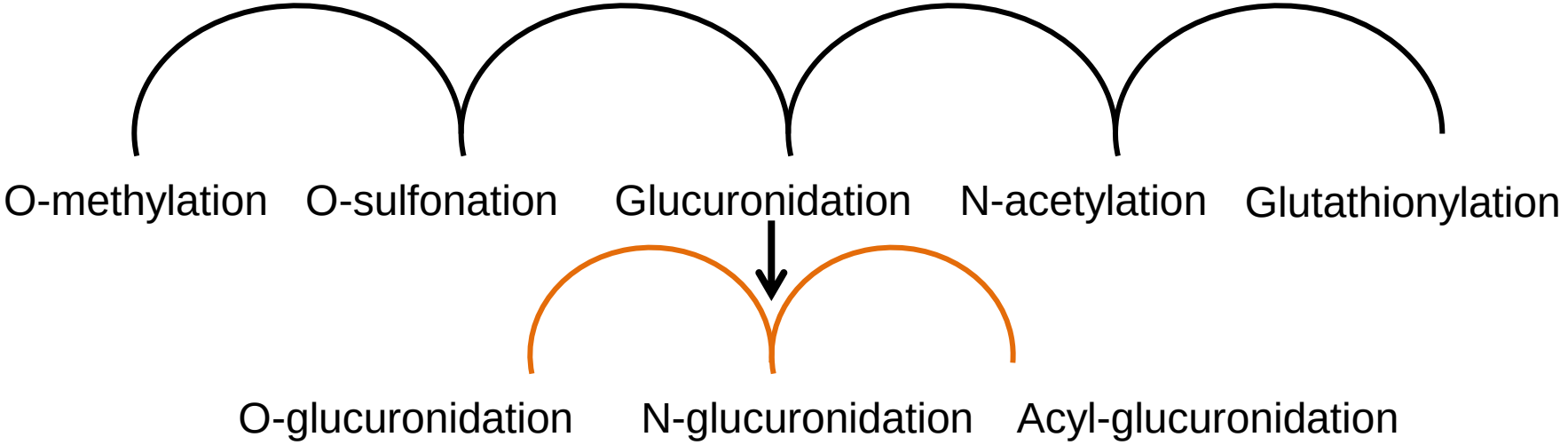
Phase 2

- **Phase 2 biotransformation** facilitates the elimination of xenobiotics by adding an ionizable group.
- formation of chemical bonds between foreign chemicals and hydrophilic substances already present in the liver.
- Phase II conjugates either the xenobiotic itself or its metabolite formed during phase I metabolism with a functional group that results in a multifold increase in water solubility.
- A xenobiotic may undergo **phase I only**, **phase II only**, or **both phase I and II**, depending on the xenobiotic.
- The conjugative pathways are not exclusively involved in the metabolism of **foreign substances**, since they also metabolise many **endobiotics.**

Toxicokinetics (ADME): 3- Biotransformation

Phase I

Conjugative Metabolism = Phase II



Other important pathways exist, including conjugation with amino acids such as **glycine** or **glutamine**

Toxicokinetics (ADME): 3- Biotransformation

Table 01. Effects of Common Phase 1 and Phase 2 Biotransformation Reactions of Xenobiotics (Klaassen & Amdur, 2013).

REACTION	EXAMPLE
Hydroxylation—aliphatic	$R–CH_3 \rightarrow R–CH_2OH$
Hydroxylation—aromatic	Benzene (Ø) → phenol (Ø-OH)
Alcohol dehydrogenation	$R–CH_2OH \rightarrow R–CHO$
Aldehyde oxidation	$R–CHO \rightarrow R–COOH$
Epoxidation	$R–HC{=}CH_2 \rightarrow R–HC(O)–CH_2$
O-demethylation	$R–CH_2O–CH_3 \rightarrow R–CH_2OH$
N-demethylation	$R–CH_2NH–CH_3 \rightarrow R–CH_2NH_2$
N-oxygenation	$R_1,R_2,R_3N \rightarrow R_1,R_2,R_3N–O$
N-hydroxylation	$R_1,R_2NH \rightarrow R_1,R_2N–OH$
Hydrolysis	$R_1CO–OR_2 \rightarrow R_1COOH + R_2OH$
O-methylation	Catechol → *O*-methylcatechol
N-acetylation	$R–NH_2 \rightarrow R–NH–COCH_3$
O-sulfonation	Phenol → phenol sulfate
O-glucuronidation	R–OH → R–O–glucuronide
N-glucuronidation	$R–NH_2 \rightarrow$ R–NH–glucuronide
Acyl-glucuronidation	R–COOH → R–COO–glucuronide
Glutathionylation (addition of glutathione)	Diethyl maleate → DEA-glutathione
Glycine conjugation	Benzoic acid → hippuric acid
	Cholic acid → glycocholic acid
Taurine conjugation	Cholic acid → taurocholic acid

Biotransformation (metabolisation)

Phase II Conjugation Reactions

Some important phase II reactions, with their intracellular location and endogenous substrates

Phase II reaction	*Location*	*Endogenous substrate*
glucuronidation	endoplasmic reticulum	steroids thyroxine catecholamines bilirubin
sulfation	cytosol	steroids carbohydrates
acetylation	cytosol	serotonin
methylation	cytosol and endoplasmic reticulum	biogenic amines
glutathione conjugation	cytosol and endoplasmic reticulum	metabolites of arachidonic acid

General Pathways of Xenobiotic Biotransformation and Their Major Subcellular Location		
REACTION	ENZYME OR SPECIFIC REACTION	LOCALIZATION
Hydrolysis	Carboxylesterase	Microsomes, cytosol, lysosomes, blood
	Butyrylcholinesterase	Plasma, most tissues
	Acetylcholinesterase	Erythrocytes, most tissues
	Paraoxonases	Plasma, microsomes, inner mitochondrial membrane
	Alkaline phosphatase	Plasma membrane
	Peptidase	Blood, lysosomes
	β-Glucuronidase	Microsomes, lysosomes, microflora
	Epoxide hydrolase	Microsomes, plasma membrane, cytosol
Reduction	Azo- and nitro-reduction	Microflora
	Carbonyl (aldo-keto) reduction	Cytosol, microsomes, blood
	Disulfide reduction	Cytosol
	Sulfoxide reduction	Cytosol
	Quinone reduction	Cytosol, microsomes
	Dihydropyrimidine dehydrogenase	Cytosol
	Reductive dehalogenation	Microsomes
	Dehydroxylation (mARC)	Mitochondria
	Dehydroxylation (aldehyde oxidase)	Cytosol
Oxidation	Alcohol dehydrogenase	Cytosol
	Aldehyde dehydrogenase	Mitochondria, cytosol
	Aldehyde oxidase	Cytosol
	Xanthine oxidoreductase	Cytosol
	Class I Amine Oxidases	
	MAO-A and B	Outer mitochondrial membrane, platelets
	PAO	Cytosol, peroxisomes, plasma
	SMOX	Cytosol, nucleus
	Class II Amine Oxidases (CuAOs)	
	SSAOs (e.g., AOC3)	Cytosolic, membrane-associated forms
	DAOs	Microsomes, extracellular matrix
	LOs	Extracellular matrix
	Peroxidases	Microsomes, lysosomes, saliva
	Flavin-monooxygenases	Microsomes
	Cytochrome P450	Microsomes, mitochondria

(Klaassen & Amdur, 2013).

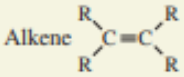
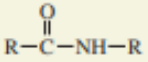
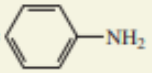
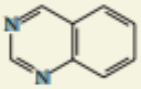
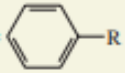
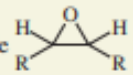
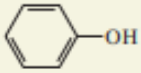
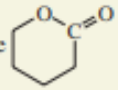
General Pathways of Xenobiotic Biotransformation and Their Major Subcellular Location

REACTION	ENZYME OR SPECIFIC REACTION	LOCALIZATION
Conjugation	UDP-glucuronosyltransferase	Microsomes
	Acyl-CoA synthetase	Mitochondria
	Sulfotransferase	Cytosol
	Glutathione transferase	Cytosol, microsomes, mitochondria
	Amino acid transferase	Mitochondria, microsomes
	N-acetyltransferase	Mitochondria, cytosol
	Methyltransferase	Cytosol, microsomes, blood

Abbreviation: mARC, mitochondrial amidoxime-reducing complex.

(Klaassen & Amdur, 2013).

Common Chemical Groups and Enzymes Possibly Involved in Their Metabolism

CHEMICAL GROUP	ENZYME(S)	REACTION(S)	CHEMICAL GROUP	ENZYME(S)	REACTION(S)
Alkane R–CH_2–R	CYP	Hydroxylation, dehydrogenation	Aldehyde 	CYP, ALDH, aldehyde oxidase	Oxidative de-formylation, oxidation to carboxylic acid
Alkene 	CYP, GST	Epoxidation, glutathionylation	Aliphatic amide 	Amidase (esterase)	Hydrolysis
Alkyne R–C≡C–R	CYP	Oxidation to ketocarbenes and carboxylic acid	Aniline 	CYP, NAT, UGT, peroxidase, SULT	*N*-hydroxylation, *N*-acetylation, *N*-glucuronidation, *N*-oxidation, *N*-sulfonation
Aliphatic alcohol R–CH_2–OH	**CYP, ADH, catalase, UGT, SULT**	**Oxidation, glucuronidation and sulfonation**	**Aromatic azaheterocycles** 	**UGT, CYP, aldehyde oxidase**	***N*-glucuronidation, hydroxylation,** *N*-oxidation, ring cleavage, oxidation
Aliphatic amine R–NH_2	CYP, FMO, MAO, UGT, SULT, MT, NAT, peroxidase	*N*-dealkylation, *N*-oxidation, deamination, *N*-glucuronidation, *N*-carbamoyl glucuronidation, *N*-sulfonation, *N*-methylation, *N*-acetylation	Carbamate R-NH-C(=O)-O-R	CYP, esterase	Oxidative cleavage, hydrolysis
Amidine HN=CR–NH_2	CYP	*N*-oxidation	Ester R–CH_2–O–C(=O)–R	CYP, esterase	Oxidative cleavage, hydrolysis
Arene 	CYP	Hydroxylation and epoxidation	Ether R–CH_2–O–CH_2–R	CYP	*O*-dealkylation
Carboxylic acid R–COOH	UGT, amino acid transferases, acyl-CoA synthetase	Glucuronidation, amino acylation, Coenzyme A thioesterification	Ketone R–CH_2–C(=O)–R	CYP, FMO, SDR, AKR	Baeyer–Villiger oxidation, reduction
Epoxide 	Epoxide hydrolase, GST	Hydrolysis, glutathionylation	Phenol 	CYP, UGT, SULT, MT	Ipso-substitution, glucuronidation, sulfonation, methylation
Lactone 	Lactonase (paraoxonase)	Hydrolysis (ring opening)	Thioether R–CH_2–S–CH_2–R	CYP, FMO	*S*-dealkylation, *S*-oxidation

Abbreviations: ADH, alcohol dehydrogenase; AKR, aldo-keto reductases; ALDH, aldehyde dehydrogenase; FMO, flavin monooxygenase; GST, glutathione S-transferase; MT, methyltransferase; SDR, short-chain dehydrogenases/reductases; SULT, sulfotransferase; UGT, UDP-glucuronosyltransferase.

SOURCE: Data from Williams et al. (2003a).

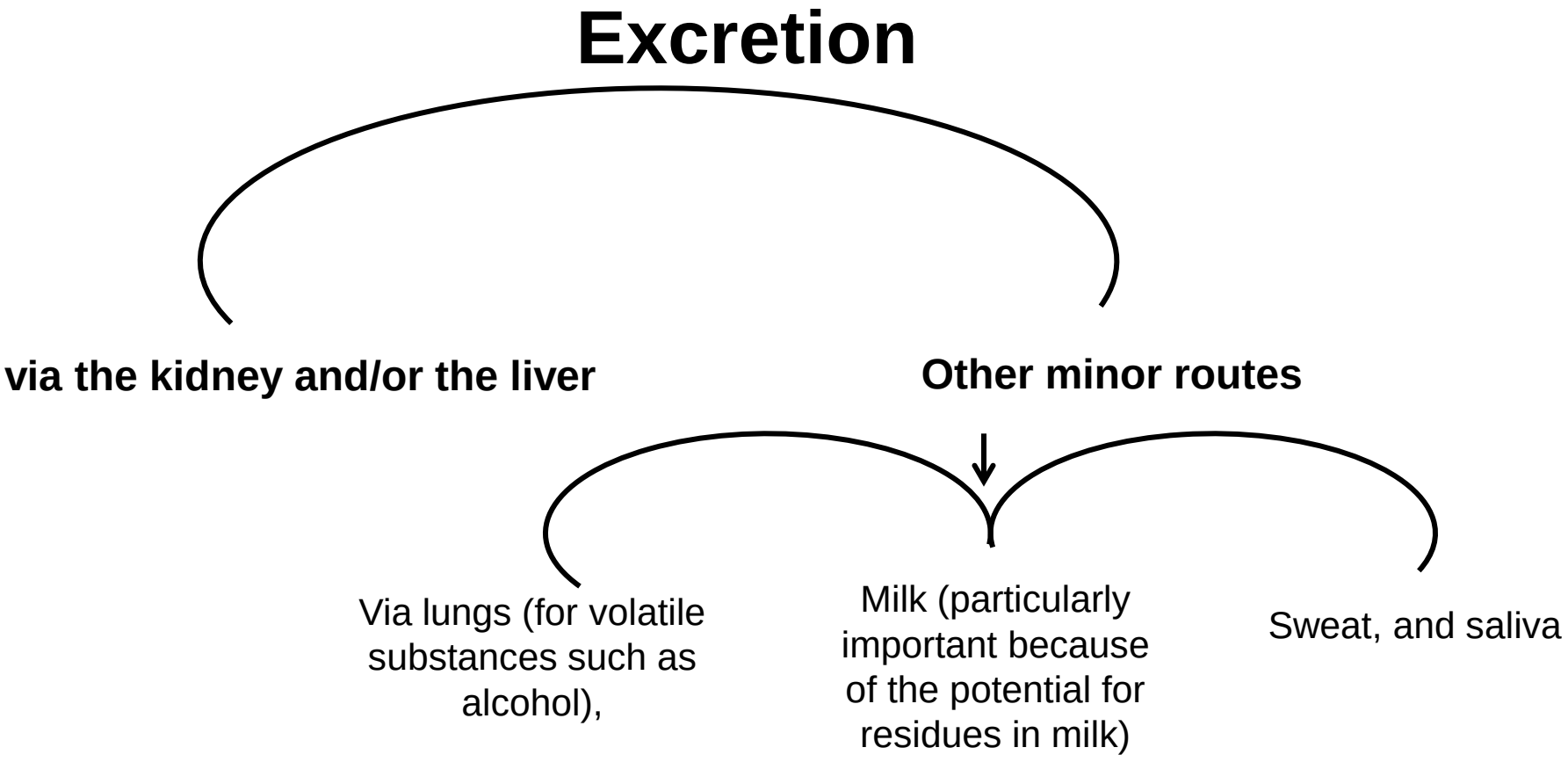
(Klaassen & Amdur, 2013).

Toxicokinetics (ADME): 4- Excretion

Definition: Excretion is the last toxicokinetic step for a xenobiotic and involves removing the xenobiotic out of the body by a number of passages.

Removing the xenobiotic via the **urine** is the most common route of excretion; however, other pathways do exist and are important alternates for some chemicals.

Toxicokinetics (ADME): 4- Excretion



Democrtic and Popular Republic of Algeria
Ministry of Higher Education and Scientific Research
Mohamed Khider University -BISKRA
Department of Nature and Life Sciences

LMD Courses

Food Toxicology

Presented by **Dr. REDOUANE-SALAH Sara**

2022-2023

Food Toxicology

Food safety Does not refer to the food it self, but also to the people consuming it

Food toxicology ≠ Nutritional toxicology

Study of toxicants found in foods

mecanisme

Study of the nutritional aspects of toxicology

- Targets the interrelations that toxicants or toxins have with nutrients in the diet, which affect nutritional status.
- Deals with the effects of diet on the expression of toxicity and the mechanisms for these effects.

Food Toxicology

Nutritional toxicology

- can refer to the means by which the diet or components of the diet prevent against the adverse effects of toxicants or toxins.

Part II:Food Toxicology

- The main site of entry of toxicants (xenobiotics) by food is the **gastrointestinal (GI) tract:** consisting of mouth, pharynx, esophagus, stomach, small intestine (duodenum, jejunum, ileum), and large intestine.

The barrier between the contents of the GI tract (especially in small intestine, where most of the absorption occurs) and the blood vessels consists of epithelium essentially only one cell thick and is easily crossed. The anatomy of the GI tract is illustrated in Figure XX

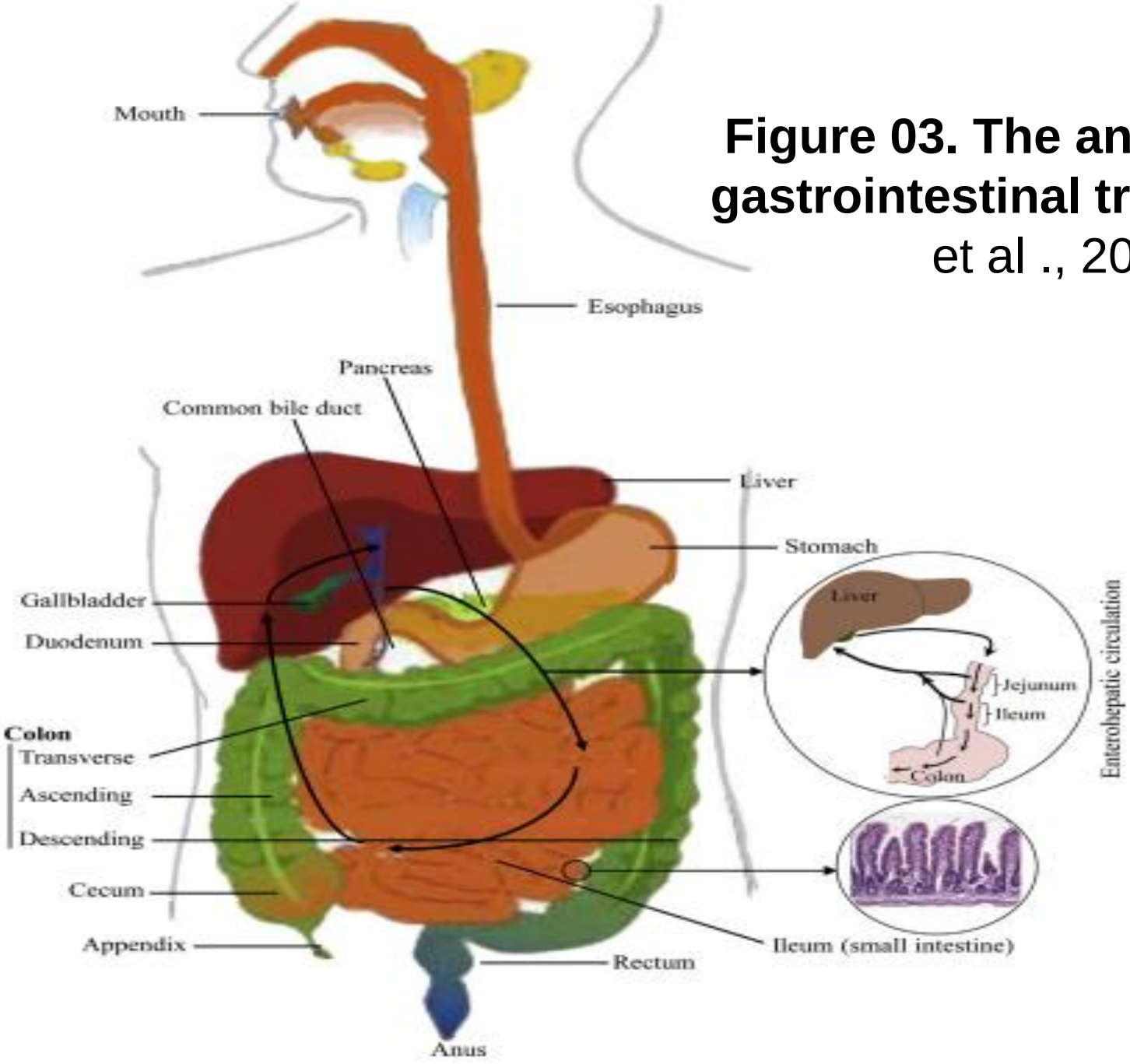


Figure 03. The anatomy of the gastrointestinal tract (WEXLER et al ., 2014)**.**

Gastrointestinal (GI) tract

Absorption occurs mostly by **passive diffusion of lipidsoluble nonionized** molecules.

The degree of ionization is directly dependent on the pH of the GI content influencing absorption of chemicals, with most of the absorption occurring at sites where the chemicals are present in nonionized form.

At the low acidic pH of the stomach (1–3), most weak organic acids such as acetylsalicylic acid (aspirin) remain nonionized and diffuse passively across the gastric mucosa at a rate proportional to the concentration gradient of the nonionized form.

On the other hand, **weak organic** bases will diffuse more **easily through** the mucosa of the small **intestine** in which pH is higher (5–8)

Gastrointestinal (GI) tract

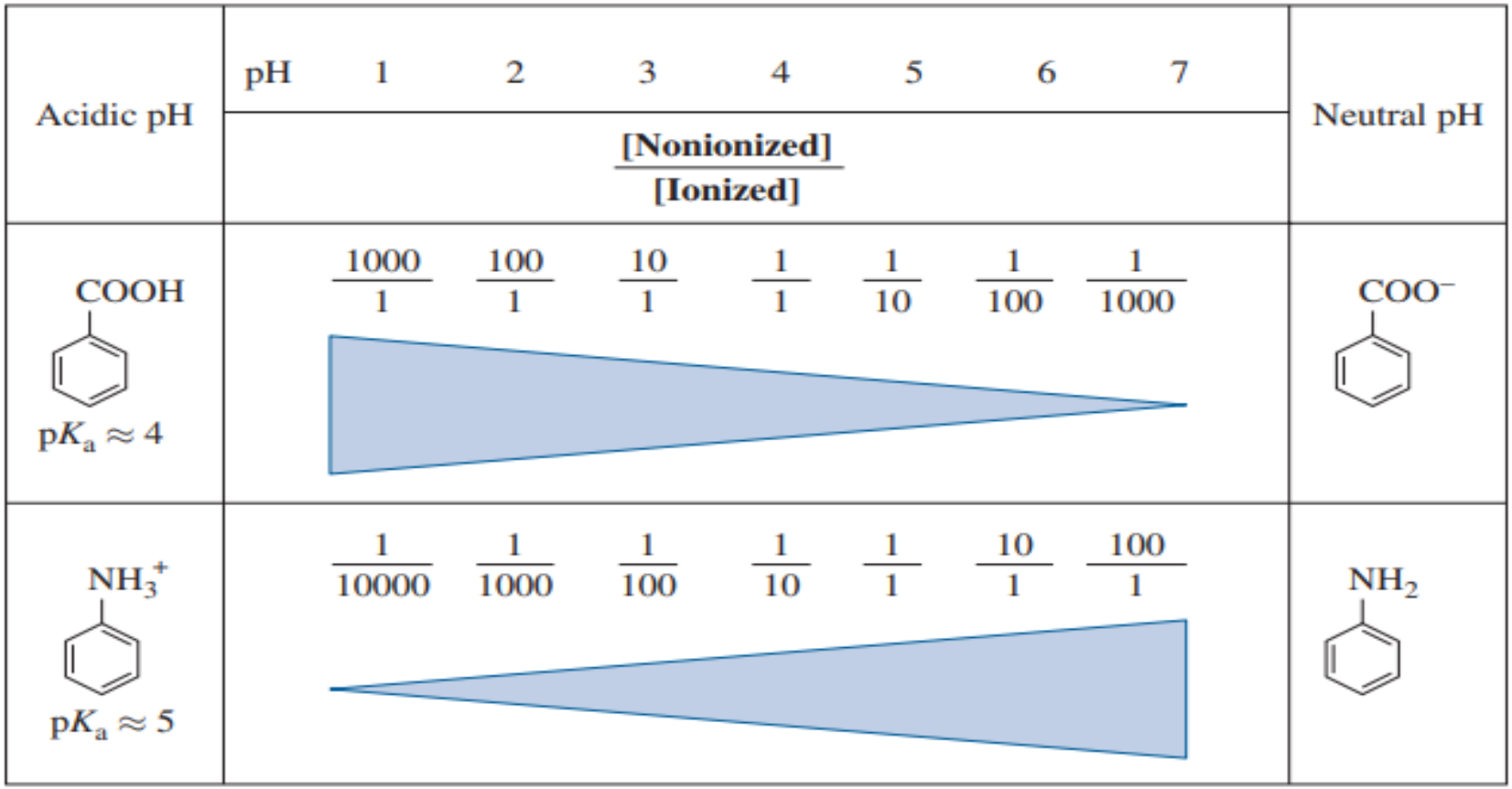


Figure 04. Effect of pH on the ionization of benzoic acid (pKa = 4) and aniline (pKa = 5), (Klaassen et al ., 2013)

Gastrointestinal (GI) tract

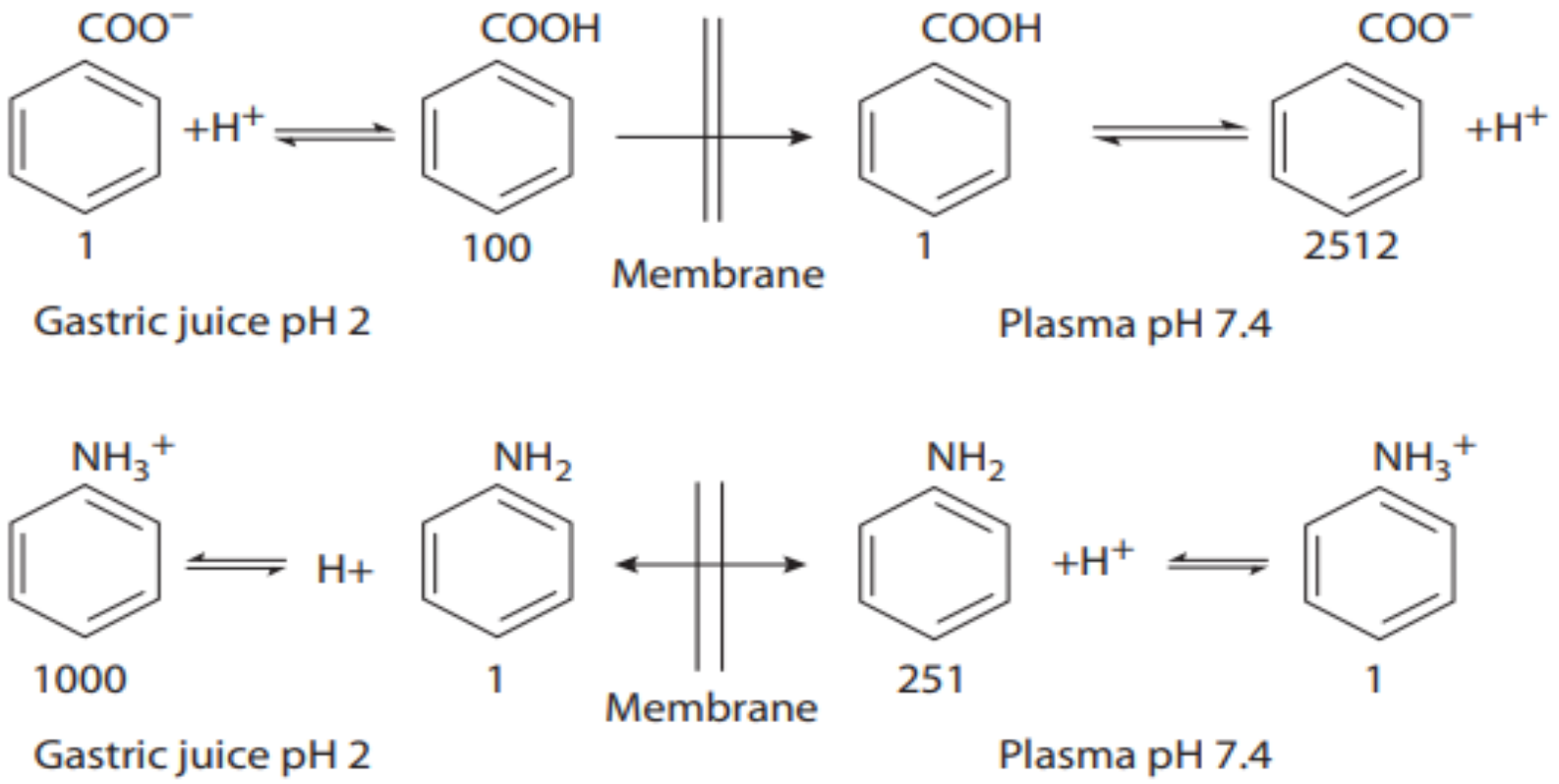


Figure 05. Disposition of benzoic acid and aniline in gastric juice and plasma. Figures immediately below the structural formulas represent proportions of ionized and nonionized forms (Lee & Kacew, 2012).

Gastrointestinal (GI) tract

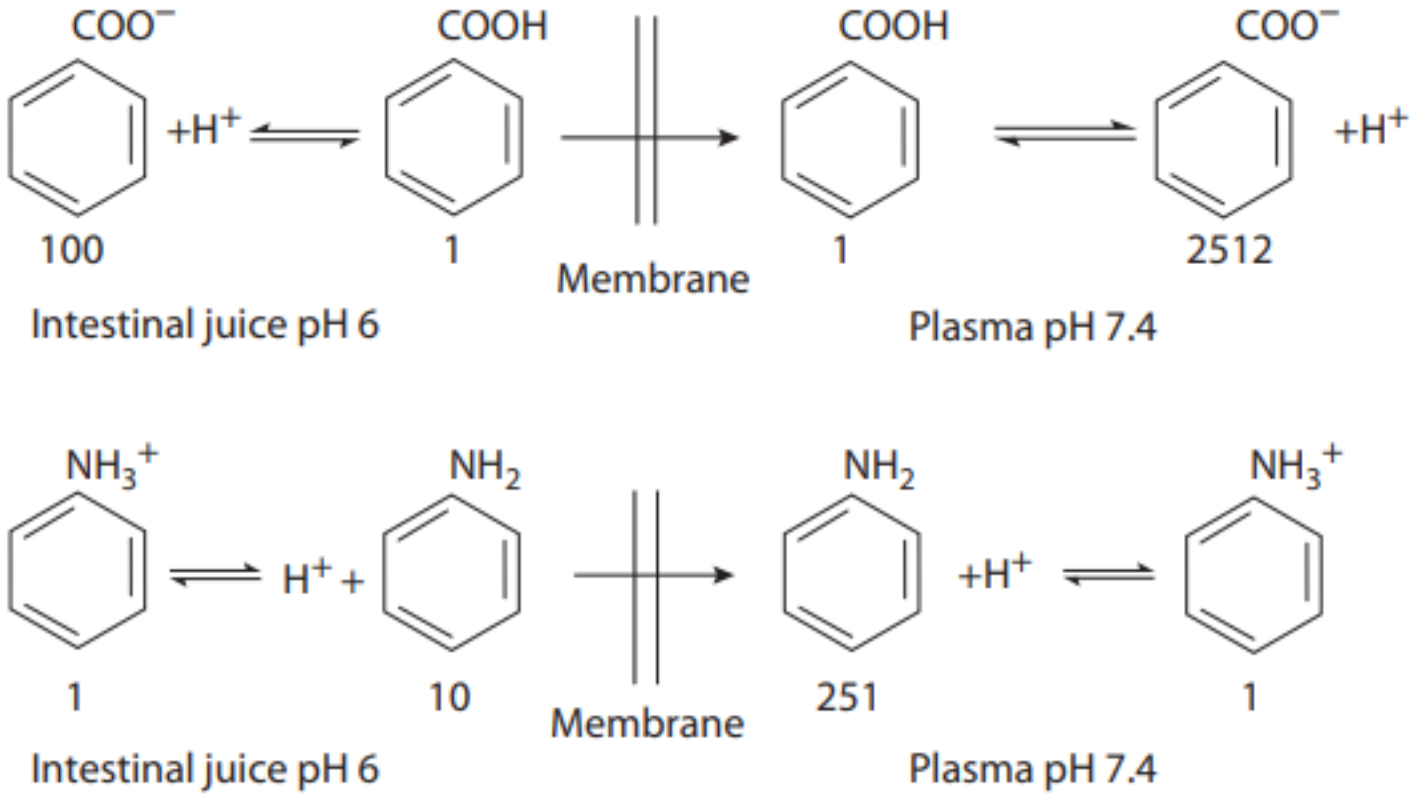


Figure 06. Disposition of benzoic acid and aniline in intestinal juice and plasma (Lee & Kacew, 2012).

Gastrointestinal (GI) tract

- The oral cavity, although, has thin epithelium and is rich in blood vessels, favoring absorption; the residence time is usually too brief for any substantial absorption.

- Absorption of toxicants from stomach is also limited due to its thick mucosal layer and relatively short residence time.

- Most of the absorption, therefore, occurs in the small intestine, which has a tremendously large surface area due to the presence of villi and microvilli, has more permeable membranes than those in the stomach, and has long residence time.

Gastrointestinal (GI) tract

- A small number of chemicals may be absorbed by
  - **Facilitated diffusion** (e.g., antimetabolic nucleotides),
  - **Active transport** (e.g., lead and 5-fluorouracil),
  - **Pinocytosis** (e.g., dyes and bacterial endotoxins).

- Chemicals or toxicants that reach the bloodstream by absorption through the GI tract are transported directly to the **liver** via the **portal circulation**, where they normally undergo metabolic biotransformation, mostly to **less active (toxic)** and in some cases to **more active chemical** forms, even before gaining access to other tissues of the body; **this phenomenon is known as the first-pass effect.**

Gastrointestinal (GI) tract

- **Factors influenced absorption in GI tract**

-pH

-**Presence of food** in the GI tract is one of the most important factors that modify GI absorption of ingested chemicals. Presence of food in the stomach delays/reduces the absorption of weak organic acids from the stomach. - **Presence of lipid-rich food** delays emptying of the gastric content into the small intestine, delaying the absorption of chemicals.

- **Chemical interactions** in the GI tract between **nutrients and drugs** may considerably reduce the absorption of some drugs; for example, calcium ions from dairy products form insoluble and nonabsorbable complexes with tetracycline and therefore, the antibiotic works best when taken on an empty stomach

Gastrointestinal (GI) tract

- Certain drugs are **irritants** to the GI tract (e.g., nonsteroidal anti-inflammatory drugs and potassium chloride tablets) and must be **ingested with food.**
- **Enterohepatic circulation** provides an example of a special case of intestinal absorption. Certain chemicals (toxicants), like methyl□mercury, after undergoing biotransformation in the liver, are excreted into the intestine via the bile. They then are reabsorbed in the intestine, sometimes after enzymatic modification by intestinal bacteria. This process can markedly prolong the stay of chemicals in the body. It can be interrupted by antibiotics that destroy the intestinal bacterial flora.

Gastrointestinal (GI) tract

-Digestive enzymes: of the stomach or intestine**,** For example, snake venoms, which are proteinaceous, are much less toxic by the oral route relative to intravenous exposure because they are broken down by digestive enzymes of the GI tract.

-Bile acids,

-Motility and permeability of the GI tract

Pesticide Residues in the Food Supply

- **Definitions**
  - According to the U.S. Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), a pesticide is defined as:
  - any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant, and any nitrogen stabilizer …
  - a pesticide is an agent used specifically to control any of a wide number of different types of pest [insect, rodent, nematode, fungus, weed, other forms of terrestrial or aquatic plant or animal life or viruses, bacteria, or other microorganisms on or in living man or other animals, which the Administrator declares to be a pest].

Pesticide Residues in the Food Supply

- **History and Development of Pesticides**

❖The idea of combating the ravages wrought by pests and crop diseases by the use of chemicals is not new.

❖Historically, pesticides have been used since as early as 1000 B.C., when sulfur was used by the Chinese to control powdery mildew on fruit.

❖In Sumeria, about 4,500 years ago, elemental sulfur dusting was used to protect crops from pests for the first time

The introduction of these and other synthetic pesticides has made an enormous contribution not only to agriculture but also to human health. For example, in Europe and Asia during and after World War II, thousands of lives were saved by the use of **DDT** to control the mosquito vector of **malaria transmission**

Pesticide Residues in the Food Supply

[redacted] Damage of Crops Caused by Pests Without Pesticides

Commodity	% Lost
Avocado	43
Banana	33
Cabbage	37
Carrot	44
Cauliflower	49
Grain	25
Lettuce	62
Mango	30
Orange	26
Pineapple	70
Sweet potato	95
Tomato	30

amage caused by pests on food rops is significant. An example of amage on typical crops without esticides is shown in Table 3.

One of the major benefits of pesticides is the protection of crop yields

Pesticide Residues in the Food Supply

- **Classifications**

Pesticide Types and Targets

Pesticide Type	Pest Controlled
Insecticide	Insect
Herbicide	Weeds
Fungicide	Fungi
Nematicide	Nematodes
Acaricide	Mites
Rodenticide	Rodents
Molluscicide	Snails
Algacide	Algae
Bacteriocide	Bacteria
Defoliant	Leaves

Toxicology Edited by William Helferich and Carl K. Winter

Pesticide Categories

- Pesticides are divided into four categories based on the LD50 to rats,

Table 3.1 Pesticide categories and their label markings

Category of toxicity	Oral LD50 (mg/kg)	Label markings[a]
I (Highly toxic)	<50	"DANGER POISON"; Skull and crossbones; "Keep out of reach of children"
II (Moderately toxic)	50–500	"Warning"; "Keep out of reach of children"
III (Slightly toxic)	500–5000	"Caution"; " Keep out of reach of children"
IV (Relatively nontoxic)	>5000	"Caution"; "Keep out of reach of children"

[a] The signal words "DANGER POISON" and the skull and crossbones symbol are all in red.

The Toxicology and Biochemistry of Insecticides. Simon J. Yu

PESTICIDES IN THE FOOD CHAIN

- In some areas, non-agricultural applications of pesticides may also be a source of environmental and water contamination.
- contaminated water used in the processing or preparation of food.
- Misuse or accidental poisoning in the home use of pestocide.

PESTICIDES IN THE FOOD CHAIN

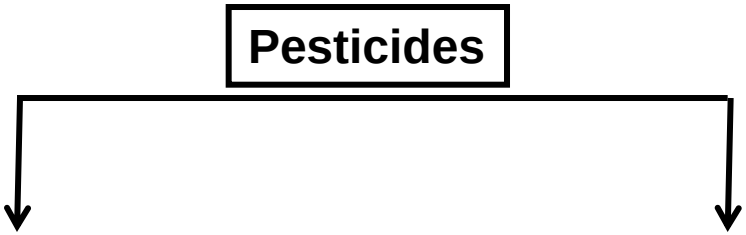
Home use of pesticides involves the least hazardous pesticides

Human exposure to contaminated water through drinking or washing also has an indirect effect on issues of pesticide residues in foods since it may comprise a significant portion of pesticide contamination within the exposed population.

Thousands of samples of food are examined by the FDA each year to determine compliance with established pesticide tolerances on raw agricultural products

PESTICIDES IN THE FOOD CHAIN

In recent years, contamination of surface and groundwater by pesticides has been recognized as a serious and growing problem in agricultural regions.



Many pesticides degrade rapidly in the environment, bind tightly to soil, or are simply too insoluble or nonvolatile to move throughout the environment

Others are both persistent and mobile

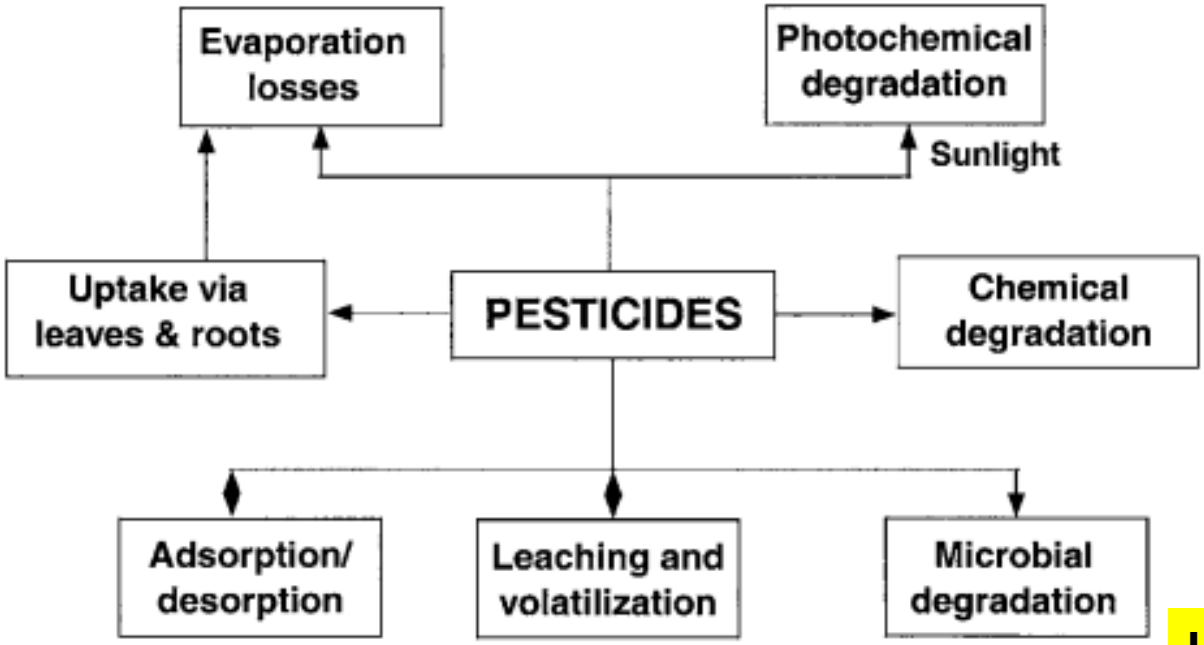


Figure XX. Pesticide movement in the environment.

Handbook of food toxicology, Deshpande, S. S 2002

Insecticides

- **Insecticides**
  - Insecticides exert their toxicity to insects in a number of ways, such as
    - damaging nerves,
    - poisoning muscles,
    - or serving as desiccants or sterilants.
  - The first major synthetic class of insecticides is known as the **chlorinated hydro□carbons**. This chemical family, developed during the 1930s and 1940s, includes insecticides such as DDT, aldrin, dieldrin, and chlordane.
  - At the present time, very few chlorinated hydrocarbon insecticides remain registered for agricultural use because of their **adverse environmental effect.**
  - they appear to be **nervous system poisons** (Coats, 1987). They also inhibit γ-aminobu□tyric acid– (**GABA**)-activated chloride uptake in nerves, producing destabilized, more easily stimulated nerve membranes

History of Development and Use of DDT Insecticide

- 1874, DDT synthesized (Zeidler)
- 1939, DDT insecticidal properties discovered (Muller).
- 1970, Beginning of DDT trial (Sweden, United States).
- 1972, DDTbanned in the United States.

DDT (dichloro diphenyl trichloroethane)

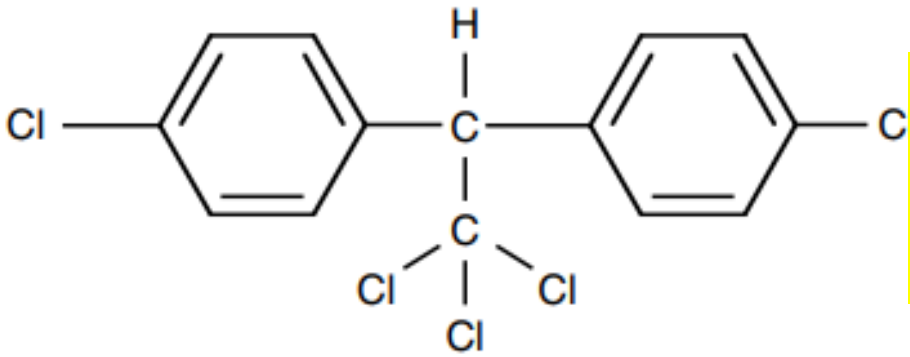
DDT (Definition)

Unfortunately, some pesticides, **such as DDT**, persist and remain in the environment and are consequently found in various foods grown on contaminated soil, or in the fish that live in contaminated waters.

DDT is a very nonpolar molecule

it has high lipid solubility,

it accumulates in animal tissues and in the food chain.
The DDT used to control insect-borne diseases (malaria).



Food and nutritional toxicology. Stanley T. Omaye

1,1'-(2,2,2-trichloroethylidene)bis(4-chlorobenzene) (DDT)

FIGURE 16.1 DDT (dichloro diphenyl trichloroethane).

DDT Residues in Food

- DDT was previously found in almost all major classes of food; the ban of its use initiated in the United States.
- particularly meats and dairy products, reflect its persistence in the adipose tissues of animals as well as the abiotic environment.

DDT Residues in Food

Table XX. Pesticide Residues Reported from Various Countries to Contaminate Major Classes of Foodstuffs

Food class	Pesticide residues[a]
Total diet	Aldrin, arsenicals, BHC and isomers, DDT and metabolites,[b] dieldrin,[b] hexachlorobenzene, PCB,[b] other chlorinated hydrocarbons,[b] various organophosphates[b]
Dairy products	Aldrin, BHC and isomers, carbaryl, heptachlor, heptachlor epoxide, hexachlorobenzene,[b] lindane,[b] DDT and metabolites,[b] dieldrin,[b] endrin, PCB,[b] TDE, other chlorinated hydrocarbons, various organophosphates
Fruits	Aldrin, benomyl, BHC and isomers, biphenyls, captafol, captan, carbamates, carbaryl, carbendazim, carbon disulfide, chlorpyrifos, ethylene dibromide, ethylene thiourea, fenitrothion, formothion, lindane, DDT and metabolites, dicofol, dieldrin, dimethoate, dinocap, disulfoton, endosulfan, ethion, methyl bromide, parathion, *o*-phenylphenol, phosmet, trichlorfon, zineb, other chlorinated hydrocarbons, organophosphates, thiabendazole, imazalil, methamidophos, methidathion, vinclozoline, procymidon
Vegetables	Acephate, aldicarb, aldrin, arsenicals, BHC and isomers, captafol, captan, carbamates, carbaryl, carbofuran, ethylene thiourea, funsulfothion, fenthion, folpet, hydroquinone, lindane, linuron, malathion, maneb, mercurials, dacthal, DCPA, DDT and metabolites, diazinon, dicamba, dieldrin, dimethoate, endrin, EPN, ethephon, ethion, ethoprop, methamidophos, methyl bromide, MSMA, parathion, phosalone, prometryne, pyrocatechol, TDE, terbutylazine, terbutryne, thiofanox, trichlormetaphos, zineb, ziram, other chlorinated hydrocarbons, organophosphates
Cereals, grains, and grain products	BPMC, chlordimeform, ethylene dibromide, fenitrothion, hexachlorobenzene, IBP, isoprocarb, malathion, MCPA, diazinon, MTMC, phthalide, piperazine, piperonjyl butoxide, PCB, propham, quintozene, triforine, other chlorinated hydrocarbons
Fish	BHC and isomers, mercurials, DDT and metabolites, dieldrin
Meat and meat products	BHC and isomers, chlordane, heptachlor, lindane, DDT and metabolites,[b] diazinon, dieldrin, dioxins, endrin, methoxychlor, 2,4,5-T, other chlorinated hydrocarbons[b]
Poultry	BHC and isomers, hexachlorobenzene, other chlorinated hydrocarbons
Wines	Parathion
Honey	Various chlorinated hydrocarbons

Handbook of food toxicology, Deshpande, S. S 2002

DDT (Toxicity)

TABLE 16.2
Acute Oral LD_{50} of DDT in Animals

Species	Oral LD_{50} (mg/kg)
Rat	500–2500
Mouse	300–1600
Guinea pig	250–560
Rabbit	300–1770
Dog	>300
Cat	100–410

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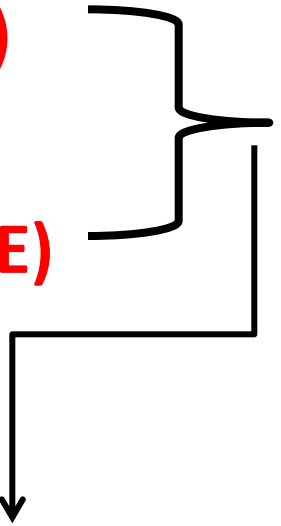
DDT metabolites

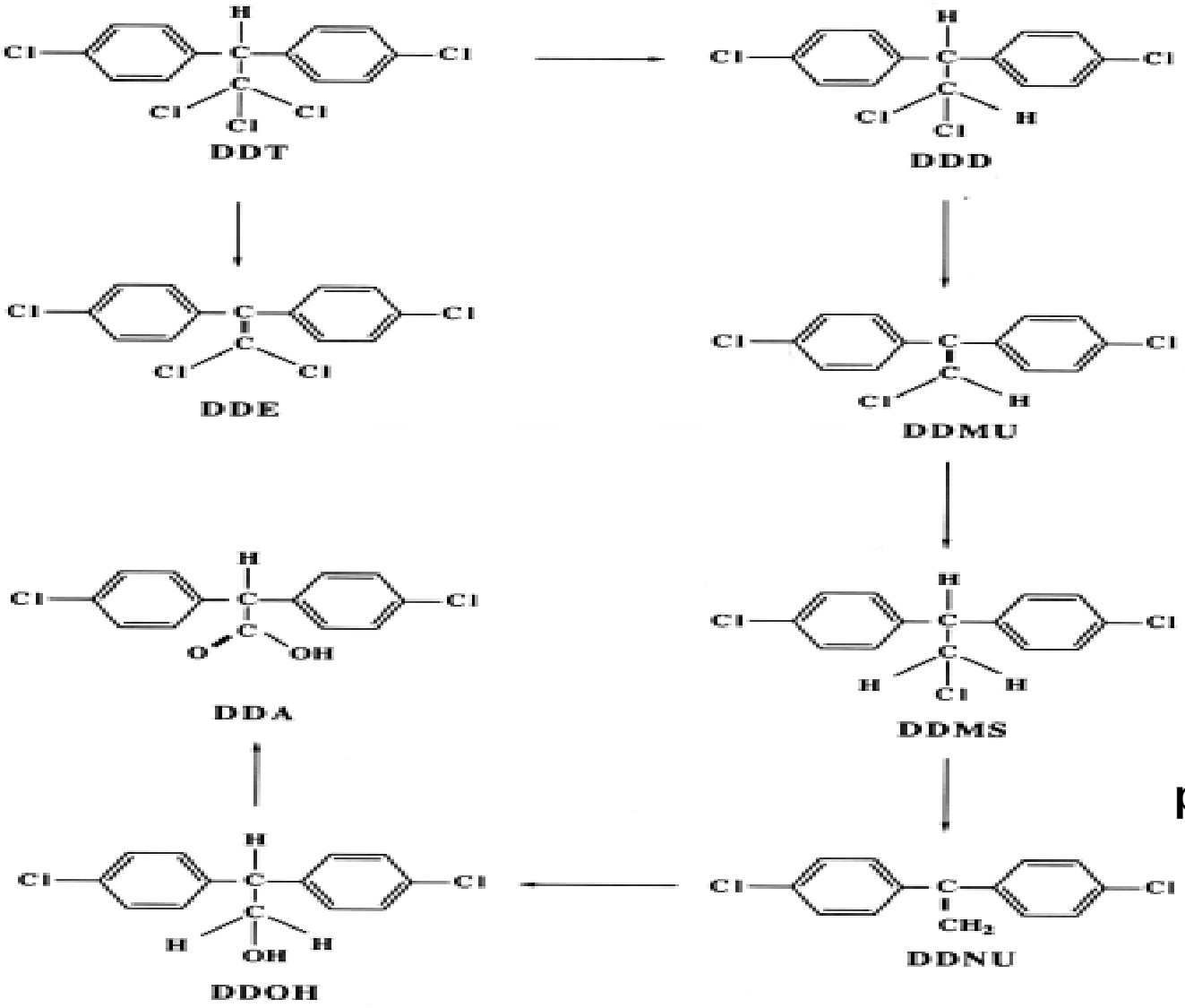
- DDT could degrade into
  - **dichlorodiphenyldichloroethane (DDD)**

  And
  - **dichlorodiphenyldichloroethylene (DDE)**



these metabolites were stored in human and animal fat tissues

DDT (In Vivo Metabolism)



INTRODUCTION TO FOOD TOXICOLOGY, Takayuki Shibamoto and Leonard F. Bjeldanes

Metabolic conversion pathways of DDT

DDT (In Vivo Metabolism)

- DDT insecticide is known to be hydroxylated by cytochrome P450 monooxygenases as shown in Figures XX and 8.4. Microsomal hydroxylation usually results in detoxification.

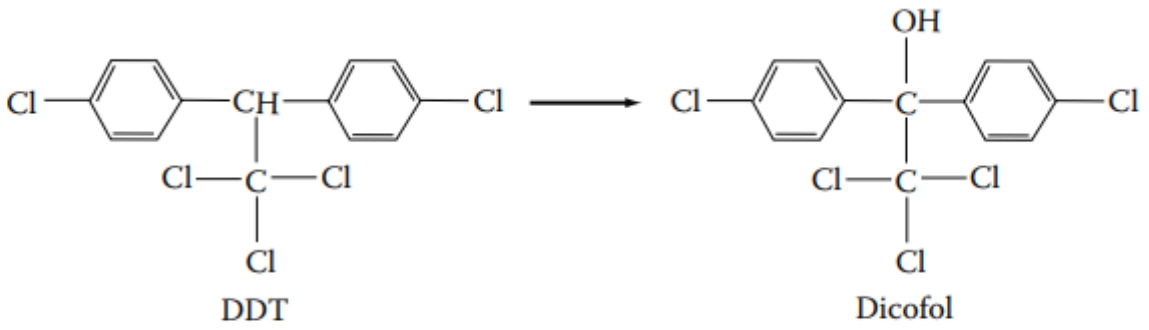


Figure 8.3 Aliphatic hydroxylation of DDT.

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DDT (In Vivo Metabolism)

- DDT can be reductively dechlorinated to TDE (DDD) by anaerobic liver plus NADPH, dead tissues, and some microorganisms (Figure 8.17). It is not known whether the reaction proceeds enzymatically or nonenzymatically.

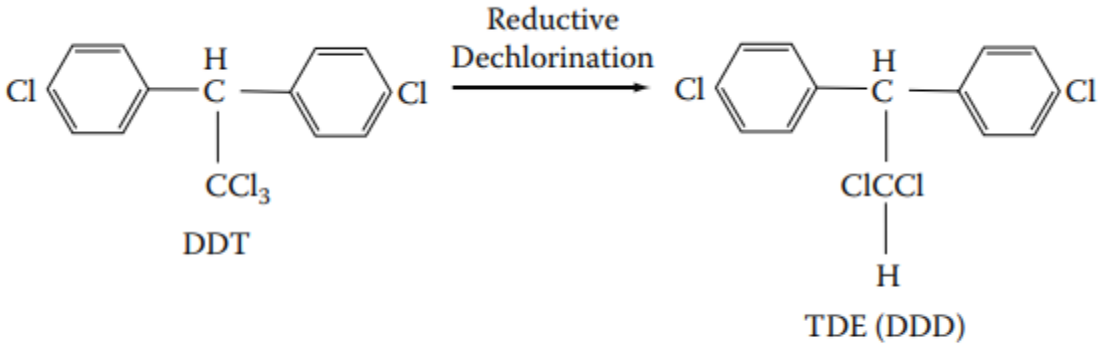

Figure 8.17 Reductive dechlorination of DDT.

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DDT (In Vivo Metabolism)

- Interestingly, a glutathione S-transferase isozyme isolated from the housefly exhibits DDT-dehydrochlorinase activity, showing that DDT-dehydrochlorinase (DDTase) is one of glutathione S-transferases (Clark and Shamaan, 1984). DDT-dehydrochlorinase converts DDT to DDE, resulting in detoxification (Figure 8.23).

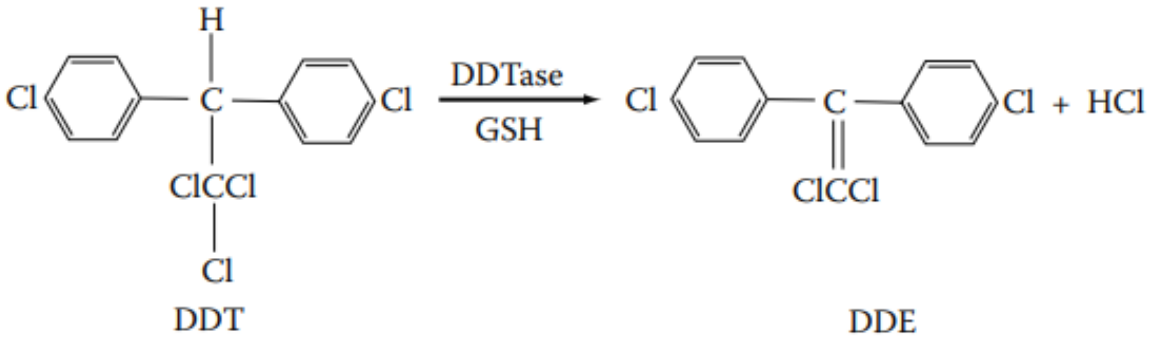

Figure 8.23 Dehydrochlorination of DDT

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Mechanisms of Toxicity of pesticides

- a pesticide can **bioaccumulate** significantly only if it is of **high lipid solubility**, of **low water solubility** (not easy to excrete), **persistent** (not easily degraded in vivo), and **stable enough** in the environment to allow adequate uptake into biological components

Mechanisms of Toxicity of pesticides

- When pesticides are applied improperly, resulting residues in foods can pose significant health risks to consumers. The use of pesticides in agricultural production represents three related but distinct risks defined as the quantifiable probability that harm or injury will occur:
- 1. The environmental risks associated with adverse effects on nontarget organisms and groundwater contamination.

- 2. Occupational risks to agricultural workers and pesticide factory workers, which are considerably higher than those of other sources of human exposure and pose the foremost human health concern related to pesticides.

- 3. The occurrence of pesticides as residues on or in edible foods

- **FUNGAL TOXINS**

FUNGAL TOXINS

Molds=filamentous organisms

Certain fungal metabolites are highly **desired** components in some **foods** such as **cheese**, whereas other metabolites are important **antibiotics**, such as **penicillin** and **cephalosporin**

HOWEVER

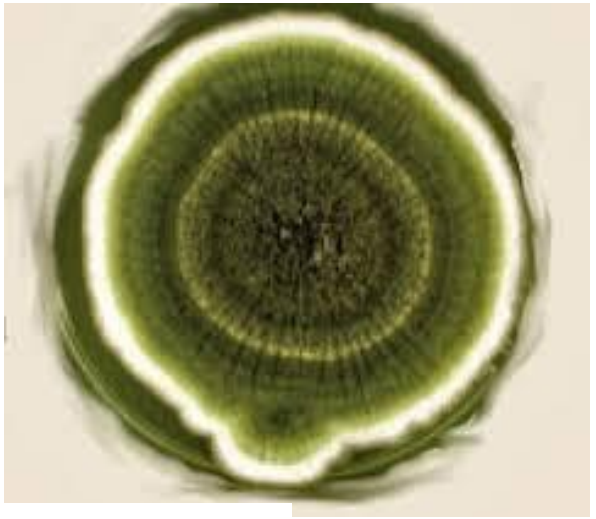
Some fungi, can produce substances that are potent **acute** or **chronic toxins** or **carcinogens**. These toxic agents are called mycotoxins, a term that usually is reserved for toxins produced by filamentous fungi.

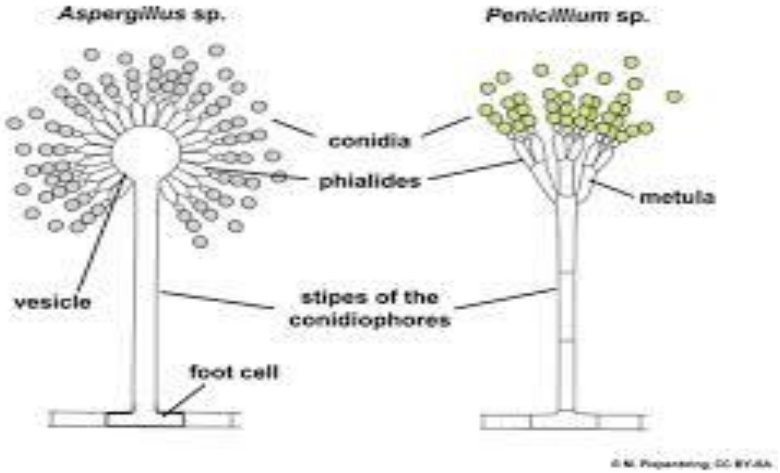
Mycotoxins

Toxins that are produced in favorable conditions by mold-fungi (molds=filamentous organisms).

The most important and most studied mycotoxins, originating from the species of the genera *Aspergillus*, *Fusarium*, *Penicillium*, and *Claviceps*


Décontamination Québec inc.




Aspergillus sp.
Penicillium sp.
conidia
phialides
metula
vesicle
stipes of the conidiophores
foot cell

FUNGAL TOXINS

- The **mycotoxicoses** are the diseases these fungi cause.
- Most clinical syndromes associated with the mycotoxins involve the ingestion of **contaminated food** **(Table XX)**.
- The most common fungal genera associated with mycotoxin production in **food** are ***Aspergillus***, ***Fusarium*** , and ***Penicillium***.

FUNGAL TOXINS

TABLE 5. Potential Mycotoxins in Human Foods and Animal Feed Barceloux, (2008).

Commodity	Situation	Mycotoxins
Cereals	Preharvest fungal infection	Deoxynivalenol, T-2 toxin, nivalenol, zearalenone, alternariol, alternariol monomethyl ether, tenuazonic acid fumonisins
Maize, peanuts	Preharvest fungal infection	Aflatoxins
Maize, sorghum	Preharvest fungal infection	Fumonisins
Stored cereals, nuts, spices	Damp, inadequate storage conditions	Aflatoxins, ochratoxin
Fruit juice	Fruit mold	Patulin
Dairy products	Animal consumption of mold-contaminated feeds	Aflatoxin M_1, cyclopiazonic acid, ochratoxin, compactin, cyclopaldic acid
Meat and eggs	Animal consumption of mold-contaminated feeds	Patulin, citrinin, ochratoxin, cyclopiazonic acid, cyclopaldic acid, citromycetin, roquefortine, fumonisins
Oilseeds	Preharvest fungal infection	Tenuazonic acid, alternariol

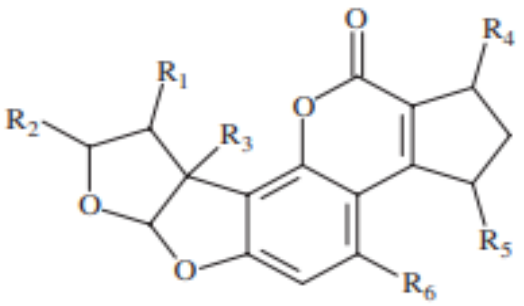
Source: Adapted from Ref 15.

FUNGAL TOXINS: AFLATOXINS

- Isolation of the first aflatoxins occurred in 1959.
- Aflatoxins (AT) are structurally related coumarin derivatives.
- They are produced by microfungi, mostly belonging to the species *Aspergillus flavus.*
- The four main aflatoxins, namely, B1, B2, G1, and G2 are produced by the microfung.
- Letters B (blue) and G (green) indicate the color of the respective aflatoxin band at the thin layer chromatography (TLC) plate irradiated by ultraviolet (UV)

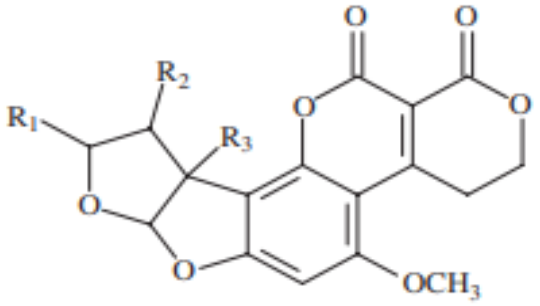
FUNGAL TOXINS: AFLATOXINS

Aflatoxin B_1 and its derivatives



Aflatoxin	R_1	R_2	R_3	R_4	R_5	R_6
B_1	H	H	H	=O	H	OCH_3
B_2	H_2	H_2	H	=O	H	OCH_3
B_{2a}	HOH	H_2	H	=O	H	OCH_3
M_1	H	H	OH	=O	H	OCH_3
M_2	H_2	H_2	OH	=O	H	OCH_3
P_1	H	H	H	=O	H	OH
Q_1	H	H	H	=O	OH	OCH_3
R_0	H	H	H	OH	H	OCH_3

Aflatoxin G_1 and its derivatives



Aflatoxin	R_1	R_2	R_3
G_1	H	H	H
G_2	H_2	H_2	H
G_{2a}	OH	H_2	H
GM_1	H	H	OH

FIGURE. Structure of aflatoxin compounds and metabolites (Barceloux, (2008).

FUNGAL TOXINS: AFLATOXINS (TOXICOKINETICS)

- TOXICOKINETICS

Absorption
involve ingestion

Biotransformation
The cytochrome P450 (CYP450) isoenzyme system in the liver metabolizes aflatoxin B1 primarily via hydroxylation. The human CYP450 isoforms, CYP3A4 and CYP1A2, catalyze the epoxidation reaction of afl atoxin B 1 to afl atoxin B 1 exo - 8,9 - epoxide.

Elimination
Renal excretion of aflatoxin M 1 (AFM 1) occurs after the ingestion of aflatoxin B1 ,but there are few human data on the toxicokinetics of aflatoxins or the relative amount of M 1 eliminated in human urine.

TOXICOKINETICS

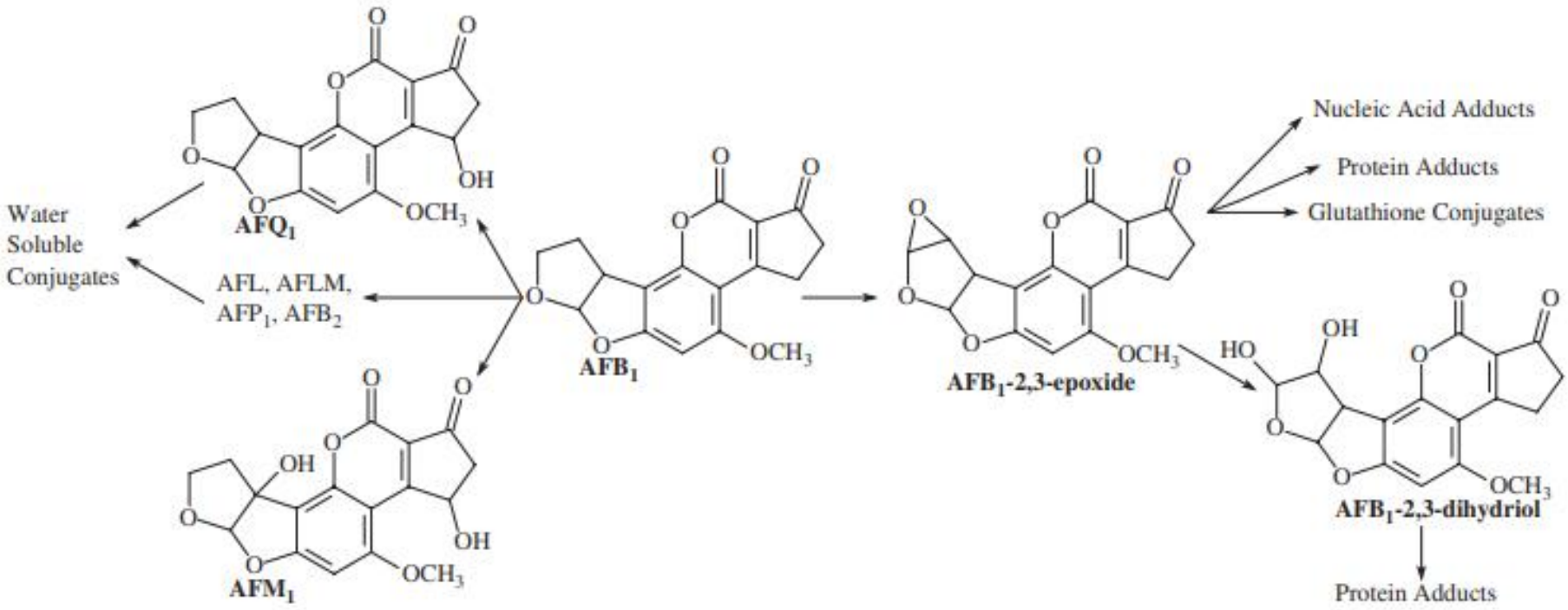


FIGURE . Aflatoxin B 1 (AFB 1) Metabolism. Reduction of AFB 1 by cytoplasmic reductase produces afl atoxicol. Hydroxyl ation of AFB 1 forms AFQ 1 and AFM 1 . O - demethylation of AFB 1 produces AFP 1 . AFB 2 results from the hydration of AFB 1 .

Toxicological Information Sources

- **A. The Agency for Toxic Substances and Disease Registry (ATSDR**): is mostly concerned with the health effects that may occur from exposure to toxic chemicals.
- B. **The United States Environmental Protection Agency (EPA) :**studies the effects of toxic exposure on people and the environment.
- **C. The Centers for Disease Control and Prevention (CDC) :**its mission is to promote health and quality of life by preventing and controlling disease, injury, and disability

Toxicological Information Sources

- **D. The Nuclear Regulatory Commission (NRC):**established in 1974, regulates the use of nuclear materials for commercial, industrial, academic, and medical purposes.
- **E. The Food and Drug Administration (FDA):**promotes and protects the public health by helping safe and effective products reach the market in a timely way, and monitoring products for continued safety after they are in use.
- **F. The American Conference of Governmental Industrial Hygienists (ACGIH):**is a professional organization that produces a listing of Threshold Limit Values (TLV) and Biological Exposure Indices (BEI) for several hundred chemicals, updating 29 them every year.

Toxicological Information Sources

- **G. Electronic Databases:**
  - Toxicology Data Network (TOXNET - www.toxnet.nlm.nih.gov.
  - CHEMTREC (Chemical Transportation Emergency Center - www.chemtrec.org).
  - Material Safety Data Sheets (MSDS) are available on the Occupational Safety and Health Administration website: www.osha.gov.
  - Hazardous Substances and Health Effects Database (HazDat), available on ATSDR's website at www.atsdr.cdc.gov.

Toxicological Information Sources

- National Institute of Occupational Safety & Health (NIOSH) – Reduce Contamination at Home - http://www.cdc.gov/niosh/thttext.html

- NIOSH – Pocket Guide to Chemical Hazards - http://www.cdc.gov/niosh/npg/npg.html

- New Jersey Dept. of Health – Hazardous Substance Fact Sheets - http://www.state.nj.us/health/eoh/rtkweb/rtkhsfs.htm

V. Test Your Knowledge Quiz

1. Which of these groups is usually designated as one of the most sensitive sub-populations for exposures to toxic substances?

   a. Adult women
   b. Infants
   c. Adult men
   d. Adolescents

2. You have worked at a chemical facility for 10 years. The facility does not require protective equipment, and you have developed a number of serious health affects in the last 7 years. You are possibly experiencing what type of exposure?

   a. Chronic
   b. Acute

3. You are worried about contamination of vegetables grown in contaminated soils. What type of toxicologist would you contact?

   a. Descriptive
   b. Environmental
   c. Regulatory
   d. Food

4. You are concerned about risks associated with growing vegetables in soil with high lead and arsenic concentrations. You are speaking of what type of substance?

   a. Toxin
   b. Toxicant

5. The larger the amount of exposure and the greater the dose, the greater the observed response, or effect.

   a. True
   b. False

6. What type of toxicologist takes samples of your blood, urine and hair for testing?

   a. Descriptive
   b. Analytical
   c. Mechanistic
   d. Forensic

7. Toxic agents can be classified in terms of their physical state, their effects, and their source.

   a. True
   b. False

8. Which agency deals with the health effects that may occur from environmental exposure to toxic chemicals?

a. The Environmental Protection Agency
b. The Centers for Disease Control and Prevention
c. The Agency for Toxic Substances and Disease Registry
d. The Nuclear Regulatory Commission

9. Which database has information on emergency handling procedures, environmental data, regulatory status and human exposure?

a. TOXNET
b. HazDat
c. IRIS
d. CHEMTREC

10. HazDat contains information on hazardous substances found at NPL and non-NPL waste sites, and on emergency events.

a. True b. False

11. The no observed adverse effect level (NOAEL) is the same as the no effect level (NEL).

a. True b. False

12. The term *toxicant* is used when talking about toxic substances that are produced by or are a by-product of human-made activities.

a. True b. False

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