General Toxicology

General Considerations in Toxicology

Lec. 1 & Lec. 2
4th Year
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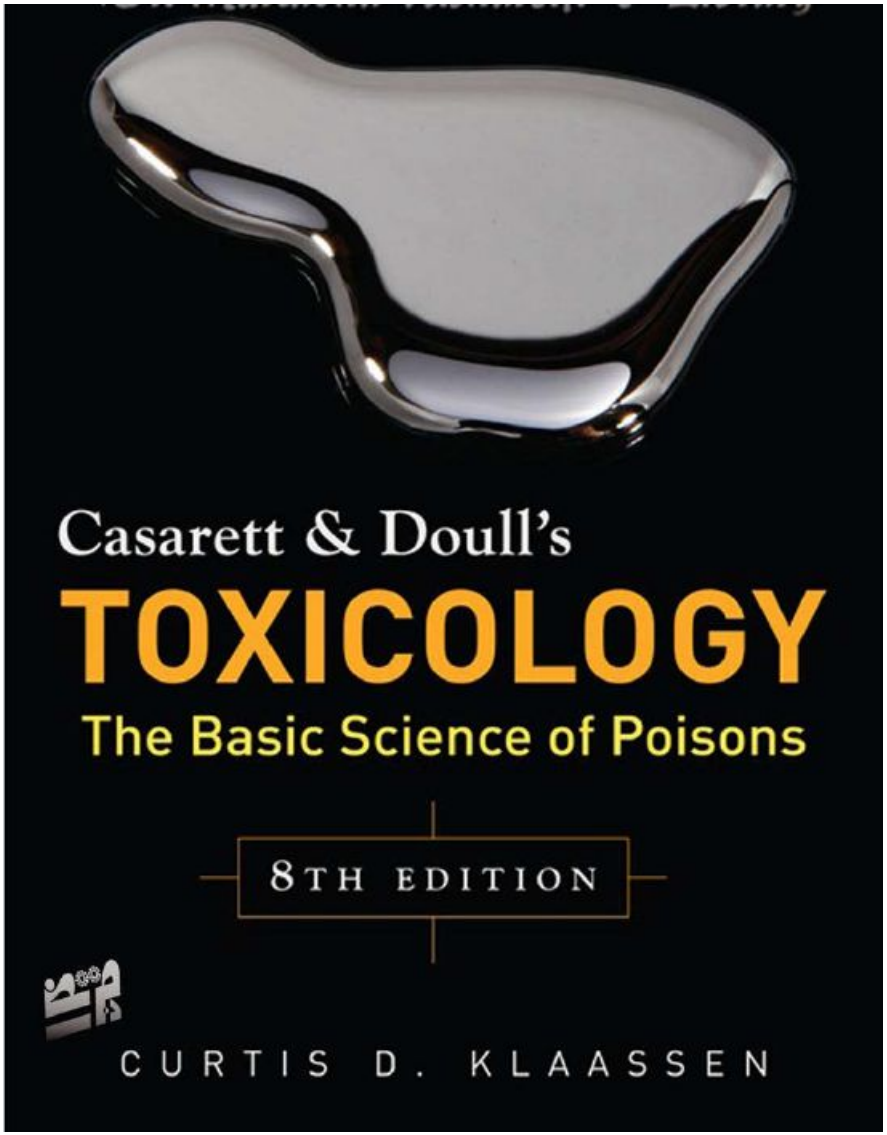
Syllabus:

No	Lecture title
1	Introduction: general consideration; host factor, environmental factors of toxic effects.
2	Carcinogenesis.
3	Mutagenesis:
4	Target organs and systemic toxicology; Respiratory system, Liver, Kidney, Skin, Nervous system, cardiovascular system, Blood.
5	Toxic substances: Food additive and contaminants, Pesticides, Metals, Radiation and radio active materials, plants, Solvents,
6	Environmental toxicology: Air pollution, water and soil pollutants, Gases (Tear gas, Pepper spray), CO, Cyanide(H_2S).

Textbook:


Casarett & Doull's
TOXICOLOGY
The Basic Science of Poisons
8TH EDITION
CURTIS D. KLAASSEN

Objectives of this lecture are to:

- Define toxicology & identify its different areas.
- Determine how to classify toxic agents.
- Determine spectrum of undesired effects.
- Explain the difference between reversible & irreversible toxic effects.
- Explain the difference between local & systemic toxic effect, &
- Determine characteristics of exposure (route, site, duration & frequency).

“What is there that is not poison?
All things are poison and nothing (is) without poison. Solely the dose determines that a thing is not a poison.”

Paracelsus (1493–1541)

Dose and dose-rate matter:

Toxicology:

- Toxicology is the study of the adverse effects of chemicals on living organisms.

- A toxicologist is trained to examine the nature of those effects (including their cellular, biochemical, & molecular mechanisms of action) & assess the probability of their occurrence.

- Fundamental to this process is characterizing the relation of exposure (or dose) to the response.

Areas of Toxicology:

- Mechanistic toxicology
- Toxicogenomics
- Descriptive toxicology
- Regulatory toxicology
- Forensic toxicology
- Clinical toxicology
- Environmental toxicology
- Developmental toxicology
- Teratology
- Reproductive toxicology

Mechanistic toxicologist:

A mechanistic toxicologist identifies the cellular, biochemical, & molecular mechanisms by which chemicals exert toxic effects on living organisms.

Toxicogenomics:

Toxicogenomics permits the application of genomic, transcriptomic technologies to:

- identify descriptive & mechanistic information that can protect genetically susceptible individuals from harmful environmental exposures,
- & to customize drug therapies based on their individual genetic makeup.

Descriptive toxicologist:

A descriptive toxicologist is concerned directly with toxicity testing, which provides information for safety evaluation & regulatory requirements.

Regulatory toxicologist:

- A regulatory toxicologist has the responsibility for deciding, on the basis of data provided by descriptive & mechanistic toxicologists, whether a drug or another chemical poses a sufficiently low risk to be marketed for a stated purpose.

- Regulatory toxicologists are involved in the establishment of standards for the amount of chemicals permitted in foods, drugs, ambient air, industrial atmospheres, & drinking water.

Forensic toxicology:

Forensic toxicology focuses primarily on the medicolegal aspects of the harmful effects of chemicals on humans & animals.

Clinical toxicology:

Clinical toxicology is concerned with disease caused by or uniquely associated with toxic substances in humans.

Environmental toxicology:

Environmental toxicology focuses on the impacts of chemical pollutants in the environment on biological organisms, specifically studying the impacts of chemicals on nonhuman organisms such as fish, birds, terrestrial animals, & plants.

Ecotoxicology:

Ecotoxicology is a specialized area within environmental toxicology focuses specifically on the impacts of toxic substances on population dynamics in an ecosystem.

Developmental toxicology:

Developmental toxicology is the study of adverse effects on the developing organism that may result from exposure to chemical or physical agents before conception (either parent), during prenatal development, or postnatally until the time of puberty.

Teratology:

Teratology is the study of defects induced during development between conception & birth.

Reproductive toxicology:

Reproductive toxicology is the study of the occurrence of adverse effects on the male or female reproductive system that may result from exposure to chemical or physical agents.

Classification of toxic agents:

- Toxic agents are classified depending on the interests & needs of the classifier.

- These agents may be discussed in terms of their target organs, use, source, & effects.

- The term toxin generally refers to toxic substances that are produced by biological systems such as plants, animals, fungi, or bacteria.

- The term toxicant is used in speaking of toxic substances that are produced by or are a by-product of human activities.

- Toxic agents may be classified in terms of their physical state, chemical stability or reactivity, general chemical structure, or poisoning potential.

- No single classification is applicable to the entire spectrum of toxic agents & therefore, a combination of classifications is needed to provide the best characterization of a toxic substance.

Spectrum of undesired effects:

- In therapeutics, each drug produces a number of effects, but usually only one effect is associated with the primary objective of the therapy; all the other effects are referred to as side effects.

- Some side effects of drugs are always deleterious to the well-being of humans.

  These are referred to as the adverse, deleterious, or toxic effects of the drug.

Allergic reactions:

- Chemical allergy is an immunologically mediated adverse reaction to a chemical resulting from previous sensitization to that chemical or to a structurally similar one.

- The terms hypersensitivity, allergic reaction, & sensitization reaction are used to describe this situation.

- Once sensitization has occurred, allergic reactions may result from exposure to relatively very low doses of chemicals.

- Importantly, for a given allergic individual, allergic reactions are dose-related.

- Most chemicals & their metabolic products are not sufficiently large to be recognized by the immune system as a foreign substance & thus must first combine with an endogenous protein to form an antigen (or immunogen). Such a molecule is called a hapten.

- Subsequent exposure to the chemical results in an antigen–antibody interaction.

- This interaction provokes the typical manifestations of an allergy that range in severity from minor skin disturbance to fatal anaphylactic shock.

Idiosyncratic reactions:

- Chemical idiosyncrasy refers to a genetically determined abnormal reactivity to a chemical.

- The response observed is usually qualitatively similar to that observed in all individuals but may take the form of extreme sensitivity to low doses or extreme insensitivity to high doses of the chemical.

- Specific genetic polymorphisms in drug-metabolizing enzymes, transporters, or receptors are responsible for many of the observed differences among individuals.

- An example of idiosyncratic reaction is that: some individuals are abnormally sensitive to nitrites & other substances capable of oxidizing the iron in hemoglobin, whereas normal individuals would be unaffected. Which produces methemoglobin which is incapable of binding & transporting oxygen to tissues.

Reversible versus irreversible toxic effects:

- Some toxic effects of chemicals are reversible, & others are irreversible.

- If a chemical produces pathological injury to a tissue, the ability of that tissue to regenerate largely determines whether the effect is reversible or irreversible.

- Liver tissue has high regeneration ability & most injuries are, therefore, reversible.

- CNS injury is largely irreversible because its cells are differentiated & cannot be replaced.

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

Local versus systemic effects:

- Local effects occur at the site of first contact between the biological system & the toxicant.

- In contrast, systemic effects require absorption & distribution of a toxicant from its entry point to a distant site, at which deleterious effects are produced.

- Most substances, except for highly reactive materials, produce systemic effects.

- Some materials can produce both effects.

- Most chemicals that produce systemic toxicity usually elicit their major toxicity in only one or two organs, which are referred to as the target organs of toxicity of a particular chemical.

- Paradoxically, the target organ of toxicity is often not the site of the highest concentration of the chemical.

- Target organs in order of frequency of involvement in systemic toxicity are:

- the CNS;
- the circulatory system;
- the blood & hematopoietic system;
- visceral organs such as the liver, kidney, & lung; & the skin.
- Muscle & bone are seldom target tissues for systemic effects.

Characteristics of exposure:

- Toxic effects in a biological system are not produced by a chemical agent unless that agent or its metabolic breakdown (biotransformation) products:
  - reach appropriate sites in the body,
  - at a concentration &/or a length of time sufficient to produce a toxic manifestation.

- Whether a toxic response occurs is dependent on:
  - the chemical & physical properties of the agent,
  - the exposure situation,
  - how the agent is metabolized by the system,
  - & the overall susceptibility of the biological system or subject.

Route & site of exposure:

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

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

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

- The route of administration can influence the toxicity of agents.

  For example, an agent that acts on the CNS, but is efficiently detoxified in the liver, would be expected to be less toxic when given orally than when inhaled.

Duration & frequency of exposure:

❖ Duration of exposure:

Toxicologists usually divide the exposure of experimental animals to chemicals into four categories:

- Acute exposure is defined as exposure to a chemical for less than 24 h.

- Subacute exposure: refers to repeated exposure to a chemical for 1 month or less,

- Subchronic exposure: for 1 to 3 months, &

- Chronic exposure: for more than 3 months.

- In human exposure situations, the frequency & duration of exposure are usually not as clearly defined as in controlled animal studies.

- Workplace or environmental exposures may be described as acute (occurring from a single incident or episode)

- Subchronic (occurring repeatedly over several weeks or months),

- Chronic (occurring repeatedly for many months or years).

Frequency of exposure:

- The other time-related factor that is important in the temporal characterization of repeated exposures is the frequency of exposure.

- The relationship between elimination rate & frequency of exposure is shown in (Figure 1).

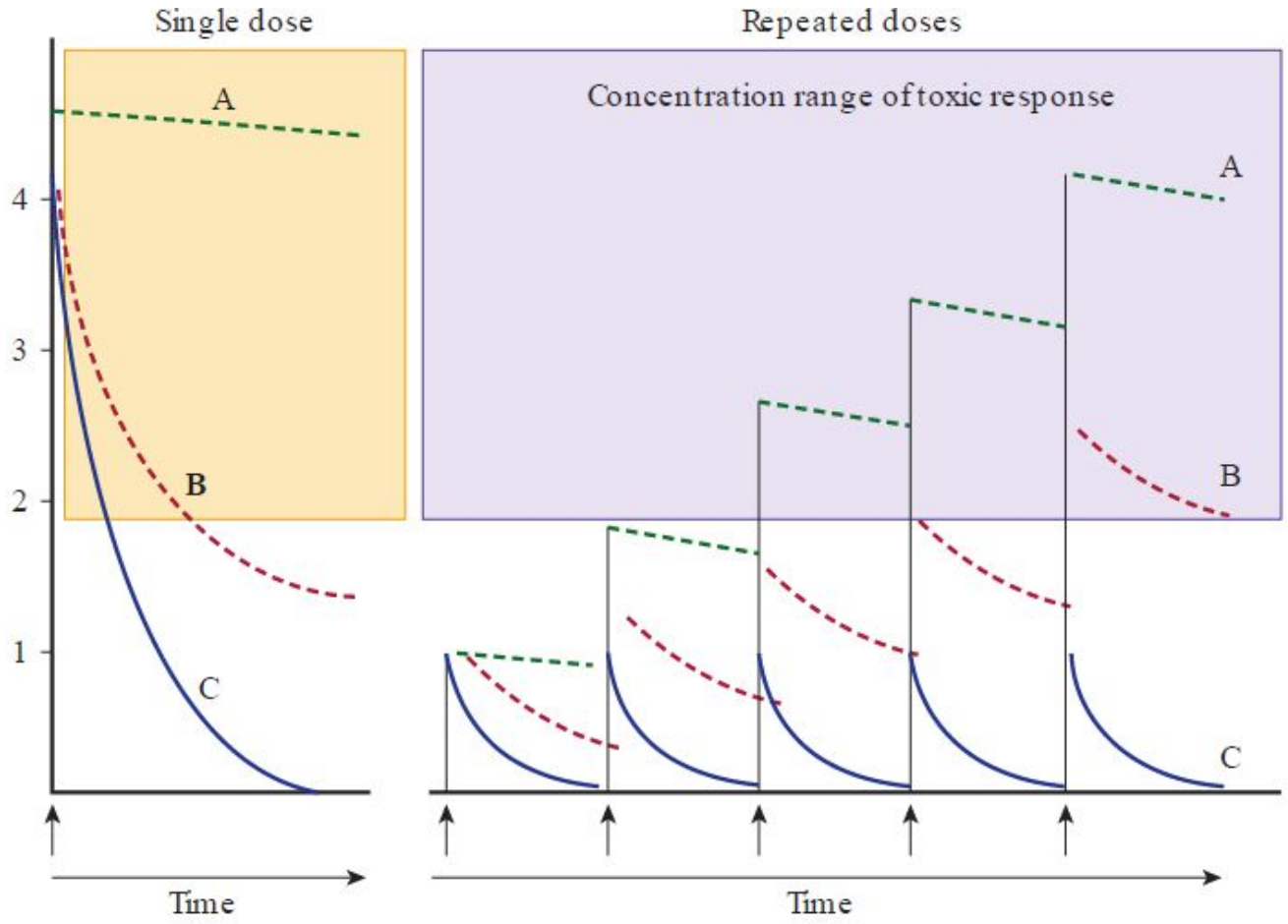


Figure 1. Diagrammatic view of the relationship between dose and concentration at the target site under different conditions of dose frequency and elimination rate. Line A. A chemical with very slow elimination (e.g., half -life of 1 year). Line B. A chemical with a rate of elimination equal to frequency of dosing (e.g., 1 day). Line C. Rate of elimination faster than the dosing frequency (e.g., 5 h). Purple shaded area is representative of the concentration of chemical at the target site necessary to elicit a toxic response.

- The important consideration, is whether the interval between doses is sufficient to allow for complete repair of tissue damage.

- Chronic toxic effects may occur, if:

- the chemical accumulates in the biological system (rate of absorption exceeds the rate of biotransformation and/or excretion),

- if it produces irreversible toxic effects,

- or if there is insufficient time for the system to recover from the toxic damage within the exposure frequency interval.


Thank
you