

Concepts in Toxicology

Food Toxicology

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Learning Objectives

- Define toxicology and toxicity.
- Discuss different types of toxic responses.
- Explain how toxicants are classified.
- Describe the phases of toxicosis.
- Explain how concomitant exposure influences toxicity.
- Develop an introductory understanding of toxicity testing.

Toxicology

- The science that deal with the adverse effects of chemicals on living systems.
- Classifications.
 - Descriptive toxicology.
 - What?
 - Mechanistic toxicology.
 - Why?
 - Analytical toxicology.
 - How much?

Definition of Toxicity

- Toxicity: The degree to which a substance can harm humans or animals.
- Toxicity can be acute, subchronic, or chronic.

Acute Toxicity

- Involves harmful effects in an organism through a single or short-term exposure.

Subchronic Toxicity

- The ability of a toxic substance to cause effects for more than one year but less than the lifetime of the exposed organism.

Chronic Toxicity

- The ability of a substance or mixture of substances to cause harmful effects over an extended period, usually upon repeated or

continuous exposure, sometimes lasting for the entire life of the exposed organism.

Specialty Areas in Toxicology

- Target Organ/System.
 - Neurotoxicology, Genetic Toxicology, Reproductive Toxicology, Immunotoxicology, Endocrine Toxicology.
- Target Species/Systems.
 - Aquatic Toxicology, Environmental Toxicology, Wildlife Toxicology, Veterinary Toxicology.
- Selected Responses.
 - Teratology, Carcinogenesis.

Applied Toxicology

- Occupational toxicology.
- Clinical toxicology.
 - Toxic induced diseases and antidotes.
- Forensic toxicology.
 - Determining causes of death.
- Regulatory toxicology.
 - Risk assessment from descriptive tests
- Developmental toxicology.
 - New chemicals and uses.

Classification of Toxicants

- Target organ.
 - Hepatotoxin, neurotoxin.
- Intended use.
 - Pesticide, solvent.
- Source.
 - Natural, synthetic.
- Special effect.
 - Carcinogen, mutagen, endocrine disruptor.

Classification of Toxicants, 2

- Physical state.
 - Gas, solid.
- Toxicity.

- Extremely, slightly.
- Chemical composition.
 - Heavy metal, organophosphate.
- Mechanism of action.
 - Anticholinergic, inhibitor, uncoupler.

Types of Toxic Responses

- Immediate.
 - Minutes to hours after a single exposure.
- Delayed.
 - Days to years after exposure.
- Some both.

- Local.
 - Effect at site of contact.
 - GIT, lungs.
- Systemic.
 - Effect distant from exposure site.
 - CNS, kidney, lungs.
- Some both.

Types of Toxic Responses, 2

- Reversible vs. Irreversible
- Largely determined by
 - Tissue involved, length of exposure and magnitude of toxic insult.
- Reversible - rapidly regenerating tissue.
 - Liver, intestinal mucosa, blood cells.
- Irreversible
 - CNS damage, carcinogenesis, mutagenesis, teratogenesis.

Bioavailability

- Octanol-Water Partition Coefficient, K_{ow}
- An empirical solubility term that can be used to assess transmembrane movement potential.

- $K_{ow} = 10^2$ to 10^3 indicates good chemical for absorption (Log $K_{ow} = 2$ to 3).
 - OK lipid solubility and OK water solubility.

Three Phases of Toxicology

- Exposure phase.
- Toxicokinetic phase.
 - Absorption.
 - Distribution.
 - Metabolism.
 - Excretion.

- Toxicodynamic phase.

Exposure Phase

- Bioavailability.
 - The fraction of a dose available for absorption.
- Main factors.
 - Time and frequency of exposure, e.g. acute, subchronic...
 - Route of administration.
 - Animal: oral, lung, skin, injection.
 - Plant: roots, leaves.

Exposure Phase, 2

- Dose.
- Physical and chemical form of the toxicant.
 - Particle size, solubilization.

Absorption Phase

- Comparative aspects.
 - Cellular to organism.
- Membrane morphology.
 - Lipoprotein bilayer.
- Physiochemical processes that govern transmembrane movement.
 - Lipid-water solubility, K_{ow}
 - Ionization (pK_a), functional groups
 - Molecular size and conformation.

Absorption Phase, 2

- Transmembrane movement.
 - Simple diffusion – Fick’s Law.
 - Filtration – aqueous pores.
 - Carrier mediated.
- Sites of Absorption.
 - Animals – GIT, dermal, lung.
 - Plants – stomatal pores, cuticle, roots.
 - Insects – pore canals, oral.
 - Fish – gills, GIT, dermal.

Distribution Phase

- Four fates.
 - Site of toxic action, storage, metabolism, excretion.
- How it occurs.
 - Animals – blood, lymph.
 - Plants – xylem and/or phloem.
- Barriers of toxicological significance.
 - Blood/brain.
 - Placental (maternal - fetal).
 - Mammary (blood - milk).

Distribution Phase, 2

- Factors affecting distribution.
 - Affinity of tissues for the xenobiotic.
 - Blood flow, protein binding.
 - Route of administration, rate of metabolism.
- Redistribution.
 - Enterohepatic recirculation.

Metabolism Phase

- Phase I – Bioconversion.
 - Factors affecting toxicity and metabolism.
 - Environmental, genetic...
- Phase II – Conjugation.
 - “Grease to salt”

Factors Influencing Toxicity Concomitant Exposure

- Additive $2 + 2 = 4$

- 2 OP's leading to cholinesterase inhibition.
- Synergistic $2 + 2 = 10$
 - CCl_4 with ethanol leading to hepatotoxicity.
- Potentiation $2 + 0 = 6$
 - Isopropanol with CCl_4 , tumor promoters.
- Antagonism $2 + 2 = 0$
 - BAL with heavy metals, antidotes.

Excretion

- Toxicological significance.
- Renal excretion.
- Non-renal excretion.
 - Biliary, expiration, gastric secretion...
- Comparative aspects.
 - Animals, plants.

Toxicodynamics

Intrinsic Activity

Oxygen Transport Toxicants

- Methemoglobin formation (Fe^{2+} to Fe^{3+}).
 - Nitrate, nitrite.
 - Naphthalene.
 - Chlorate.
 - Acetaminophen.
- O_2 competition at Fe^{2+}
 - CO, carbon monoxide.
 - CN^- , cyanide.

O_2 Transport, Hemoglobin: Biochemistry

Toxicity Rating – Oral Human Dose

Spectrum of Toxic Dose