Concepts in Toxicology

Principles of Environmental Toxicology
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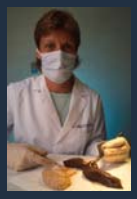
Learning Objectives

- 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.

The Death of Socrates, 1787 Jacques-Louis David (Metropolitan Museum of Art, New York)

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

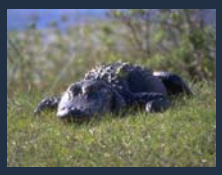
- Target Organ/System.
  - Neurotoxicology, Genetic Toxicology, Reproductive Toxicology, Immunotoxicology, Endocrine Toxicology.
- Target Species/Systems.
  - Aquatic Toxicology, Environmental Toxicology, Wildlife Toxicology, Veterinary Toxicology.
- Selected Responses.
  - Teratology, Carcinogenesis.

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

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

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

Types of Toxic Responses, 2

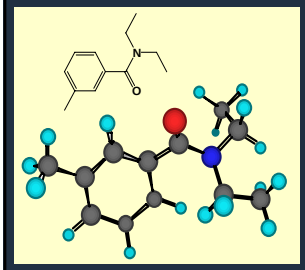
- Reversible vs. Irreversible
- Largely determined by
  - Tissue involved, length of exposure and magnitude of toxic insult.
- Reversible - rapidly regenerating tissue.
  - Liver, intestinal mucosa, blood cells.
- Irreversible
  - CNS damage, carcinogenesis, mutagenesis, teratagenesis.

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.

$$K_{ow} = [T]_{octanol} / [T]_{water}$$

N,N-diethyl-3-methylbenzamide



Diethyltoluamide,DEET

Experimental Log K_{ow} = 2.18

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.

–Host related factors.

–Pre-absorption metabolism.

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).

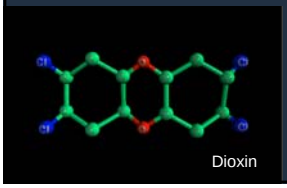

Sea snake neurotoxin

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"


Dioxin

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

Dose - Response Relationships

Toxic Chemical

↓ *Key interaction*

Critical Target

↓

Modified Critical Target

(*Key lesion*)

Progression ⇣

Overt Biological Response or Effect

Intrinsic Activity

- Intrinsic activity: response
  - Agonist - substances with intrinsic activity, e.g. O_2
  - Antagonist - substances that work against agonist, e.g. CO

$$T + R \rightleftharpoons TR$$

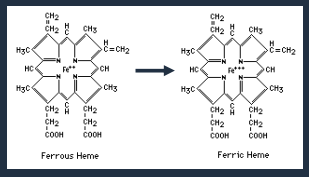
"Response"

Drugs – Typically reversible.
Toxicants – Typically non-reversible.

Oxygen Transport Toxicants

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

Methemaglobin Formation



O_2 Transport, Hemoglobin

Bar-headed goose Hemoglobin (oxy form)

Toxicity Rating – Oral Human Dose

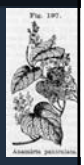
Class	Dose	For Average Adult
Practically non-toxic	>15 g/kg	More than a quart
Slightly toxic	5-15 g/kg	Between a pint and a quart
Moderately toxic	0.5-5 g/kg	Between an ounce and a pint
Very toxic	50-500 mg/kg	Between a teaspoonful and an ounce
Extremely toxic	5-50 mg/kg	Between 7 drops and a teaspoonful
Supertoxic	<5 mg/kg	A taste (<7 drops)

Cassarett and Doull

Spectrum of Toxic Dose

Agent	LD_{50} (mg/kg)
Ethanol	10,000
NaCl	4,000
Ferrous sulfate	1,500
Morphine sulfate	900
Phenobarbitol	150
DDT	100
Picrotoxin	5
Strychnine sulfate	2
Nicotine	1
d-Tubocurarine	0.5
Tetrodotoxin	0.1
Dioxin (TCDD)	0.001
Botulinus toxin	0.00001

Fish berry



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