

Concepts in Toxicology

Food Toxicology
Instructor: Gregory Möller, Ph.D.
University of Idaho

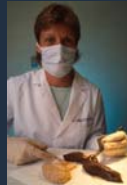
Learning Objectives

- 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.

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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?



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Definition of Toxicity

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

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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)

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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.



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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.



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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.

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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.

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Classification of Toxicants

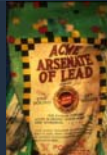
- Target organ.
 - Hepatotoxin, neurotoxin.
- Intended use.
 - Pesticide, solvent.
- Source.
 - Natural, synthetic.
- Special effect.
 - Carcinogen, mutagen, endocrine disruptor.



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Classification of Toxicants, 2

- Physical state.
 - Gas, solid.
- Toxicity.
 - Extremely, slightly.
- Chemical composition.
 - Heavy metal, organophosphate.
- Mechanism of action.
 - Anticholinergic, inhibitor, uncoupler.



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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.

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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.



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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.


$$K_{ow} = \frac{[T]_{\text{octanol}}}{[T]_{\text{water}}}$$

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Food Toxicology

Three Phases of Toxicology

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



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Food Toxicology

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.

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Food Toxicology

Exposure Phase, 2

Ukrainian President Viktor Yushchenko
Dioxin Poisoning



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

- Host related factors.
- Pre-absorption metabolism.

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Food Toxicology

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.

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Absorption Phase, 2

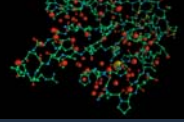
- Transmembrane movement.
 - Simple diffusion – Fick's Law.
 - Filtration – aqueous pores.
 - Carrier mediated.
- Sites of Absorption.
 - Animals – GIT, dermal, lung.
 - Plants – stomatal pores, cuticle, roots.
 - Insects – pore canals, oral.
 - Fish – gills, GIT, dermal.

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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



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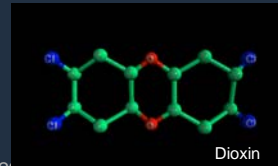
Distribution Phase, 2

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

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Metabolism Phase

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



Dioxin

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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.

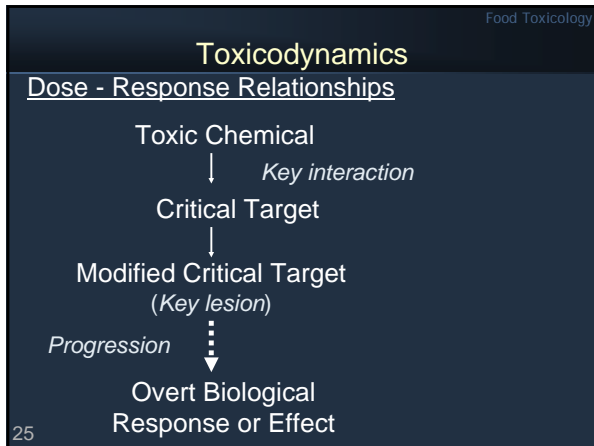
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Excretion

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



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Intrinsic Activity

- Intrinsic activity: response
 - Agonist - substances with intrinsic activity, e.g. O₂
 - Antagonist - substances that work against agonist, e.g. CO

$$T + R \rightleftharpoons TR$$

"Response"

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


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Food Toxicology


Oxygen Transport Toxicants

- Methemoglobin formation (Fe²⁺ to Fe³⁺).
 - Nitrate, nitrite.
 - Naphthalene.
 - Chlorate.
 - Acetaminophen.
- O₂ competition at Fe²⁺
 - CO, carbon monoxide.
 - CN⁻, cyanide.

Normal



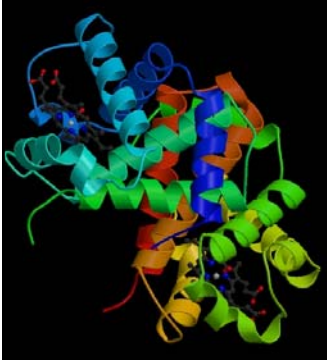
Abnormal



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Food Toxicology

O₂ Transport, Hemoglobin: Biochemistry



Bar-headed goose Hemoglobin (oxy form)

Food Toxicology

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)

29 Cassarett and Doull

Food Toxicology

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

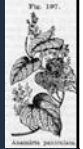


Fig. 1397
HARRISON, 1931

30 Cassarett and Doull