Principles of Toxicology

The Study of Poisons

WATER BIOLOGY
PHC 6937; Section 4858

Andrew S. Kane, Ph.D.
Environmental Health Program
College of Public Health & Health Professions
KANE@UFL.EDU

Toxicology……

- Is the study of the harmful effects of chemicals and physical agents on living organisms
- Examines adverse effects ranging from acute to long-term
- Is used to assess the probability of hazards caused by adverse effects
- Is used to predict effects on individuals, populations and ecosystems

An interdisciplinary field……

Descriptive Toxicology: The science of toxicity testing to provide information for safety evaluation and regulatory requirements.

Mechanistic Toxicology: Identification and understanding cellular, biochemical and molecular basis by which chemicals exert toxic effects.

Regulatory Toxicology: Determination of risk based on descriptive and mechanistic studies, and developing safety regulations.

Federal agencies: FDA (FDCA- Federal Food, Drug and Cosmetic Act)
EPA (FIFRA-Federal Insecticide, Fungicide and Rodenticide Act)
EPA (TSCA-Toxic Substance Control Act)
EPA (CERCLA- Comprehensive Env Response, Compensation, & Liability Act); Superfund
DOL (OSHA-Occupational Safety and Health Administration)

An interdisciplinary field……

Clinical Toxicology: Diagnosis and treatment of poisoning; evaluation of methods of detection and intoxication, mechanism of action in humans (human tox, pharmaceutical tox) and animals (veterinary tox). Integrates toxicology, clinical medicine, clinical biochemistry/pharmacology.

Occupational Toxicology: Combines occupational medicine and occupational hygeine.

Environmental Toxicology: Integrates toxicology with sub-disciplines such as ecology, wildlife and aquatic biology, environmental chemistry.

Approach

Classical Toxicology → **Mechanistic Toxicology**

Whole Animal Studies

ADME

Target Organ Effects

In vitro/In vivo Models

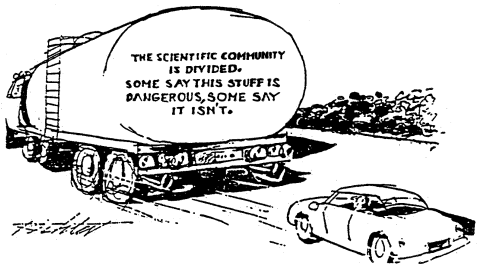
Gene Environment Interactions

Susceptible Populations

Mechanisms of Cell Injury and Cell Death

"The problem with toxicology is not the practicing toxicologists, but chemists who can detect, precisely, toxicologically insignificant amounts of chemicals"

Rene Truhaut, University of Paris (1909-1994)

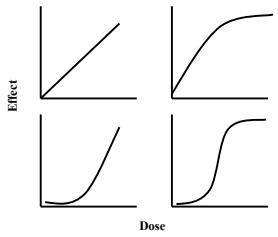


Approximate/relative acute LD50s for selected chemical agents

AGENT	LD_{50}, mg/kg*
Ethyl alcohol	10,000
Sodium chloride	4,000
Ferrous sulfate	1,500
Morphine sulfate	900
Phenobarbital sodium	150
Picrotoxin	5
Strychnine sulfate	2
Nicotine	1
d-Tubocurarine	0.5
Hemicholinium-3	0.2
Tetrodotoxin	0.10
Dioxin (TCDD)	0.001
Botulinum toxin	0.00001

*LD_{50} is the dosage (mg/kg body weight) causing death in 50 percent of exposed animals.

"All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy." **Paracelsus (1493-1541)**



Sources of Environmental Chemicals

- **Air Emissions**
  - **Industrial Processes**
  - **Incinerators**
  - **Gasoline and diesel exhaust**
  - **Spraying of agricultural chemicals**
- **Water Discharges**
  - **Industrial effluents**
  - **Sewage effluent**
- **Non-Point Sources**
  - **Surface run-off from roads and agricultural land**
  - **Leachate from dump-sites**
  - **Accidental spills**
- **Household Chemical Use**

Factors that determine dose to target organs

Absorption

Distribution to tissues

Metabolism

Excretion

Dose: **The amount of chemical an organism is exposed to per unit of body weight (mg/kg b.wt)**

Exposure Dose: **Concentration of a chemical in either the air, water or food through which the exposure occurs**

Concentrations in liquids or solids:

ppm = parts per million (ug/ml or mg/L)

ppb = parts per billion (ug/L or ng/ml)

Concentrations in air:

mg vapor/m^3 =molecular weight (ppm)/24.45

ppm = ug/m^3

Primary Routes of Exposure

Gastrointestinal (oral)

Respiratory/Inhalation

Dermal (skin)

➡ **There are tremendous differences in the absorption of compounds depending on the route of exposure due to physiological differences between these organs.**

Metabolism

Metabolites: conversion products of substances, often mediated by enzyme reactions.

Bioactivation (activation): production of metabolites that are more toxic than the parent substance.

Detoxication: production of metabolites that are less toxic than the parent substance.

Routes of Elimination

Biliary

Renal

Fecal

Respiratory

Pharmacokinetic Parameters

One Compartment Model

Elimination rate constant	k_{el} = 2.303 x slope
Volume of Distribution	$V_d = Dose_{IV}/C_o$
Half-life	$t_{1/2} = 0.693/ k_{el}$

Relationship between dose and concentration at the target site under different conditions of dose frequency and elimination rate

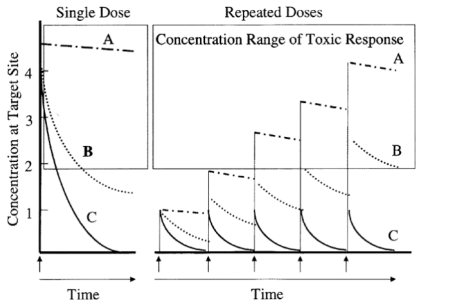
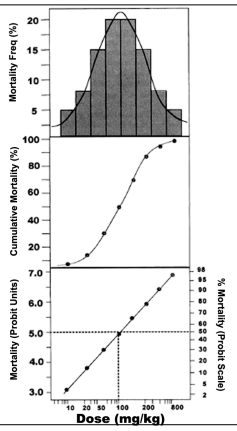
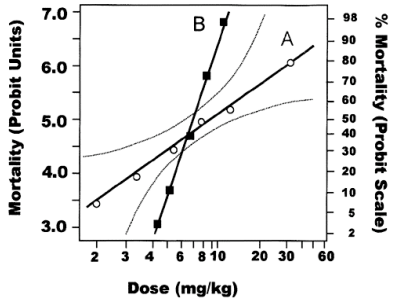


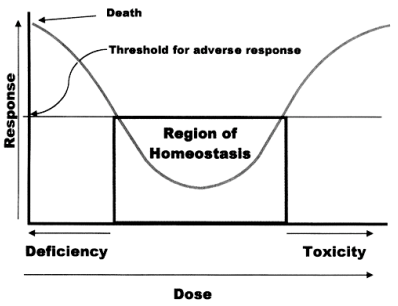
Diagram of quantal dose-response relationships



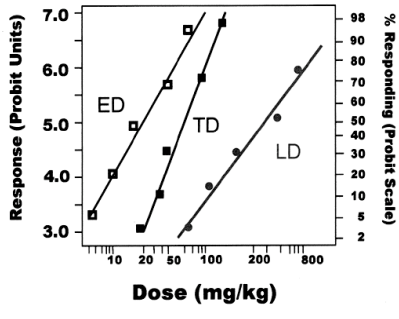
Comparison of dose-response relationship for two different chemicals plotted on a log dose-probit scale



Dose-response relationship for representative essential substances, such as vitamins or trace elements (e.g., Cr, Co, Se)



Comparison of effective, toxic and lethal dosages



Acute vs Chronic Toxicity

- **Acute effects do not predict chronic effects**
- **Doses causing chronic effects may not cause acute or sub-acute effects**
- **In human and veterinary arenas chronic effects of a chemical exposure may manifest themselves as a common disease and go unnoticed**

Haber's Law

For many compounds…

The toxic effect of a substance is determined by the product of the concentration and the duration of the exposure

Chemical Interactions

Additive: **2+3=5** (2 OPs - cholinesterase inhibition)

Synergistic: **2+2=20** (CCl_4 + EtOH)

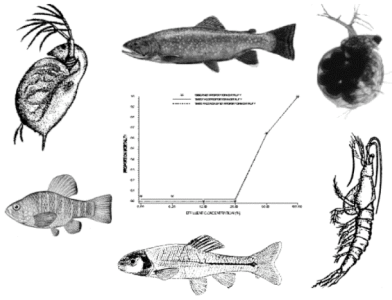
Potentiation: **0+2=10** (isopropanol + CCl_4)

Antagonism: **4+6=8; 4+0=1**

- **Functional antagonism:** 2 chemicals counterbalance each other by producing opposite effects on the same physiologic function (eg epinephrine + diazepam).
- **Chemical antagonism** (inactivation): chemical rxn between 2 compounds that produces a less toxic product (eg chelators and metals).
- **Dispositional antagonism:** alters A,D,M or E to that conc or duration at target site is diminished (eg ipacac, charcoal, diuretics, SKF-525A or piperonyl butoxide).
- **Receptor anatagonists** (blockers): clinical trtmt by competitive binding to same receptor (eg atropine and OPs to block cholinesterase receptors; tamoxifen as an anti-estrogen to lower risk of breast cancer).

EPA United States Environmental Protection Agency

Methods for Measuring the Acute Toxicity of Effluents and Receiving Waters to Freshwater and Marine Organisms



EPA United States Environmental Protection Agency

Methods for Measuring the Acute Toxicity of Effluents and Receiving Waters to Freshwater and Marine Organisms

Freshwater:
Ceriodaphnia dubia (daphnid)
Daphnia pulex and D. magna (daphnids)
Pimephales promelas (fathead minnow)
Oncorhyncus mykiss (rainbow trout)

Estuarine & Marine:
Mysidopsis bahia (mysid)
Cyprinodon variegatus (daphnids)
Menidia beryllina, M. menidia & M. peninsulae
(inland, Atlantic & tidewater silversides)

EPA United States Environmental Protection Agency

Methods for Measuring the Acute Toxicity of Effluents and Receiving Waters to Freshwater and Marine Organisms

Temperature
Light quality
Light intensity
Photoperiod
Test chamber size
Test solution volume
Renewal of test solutions
Density of test organisms
Aeration
Dilution water
Number of replicates
Age of test organisms
Test concentrations
Dilution factor
Test duration
Endpoints