Introduction to Toxicology

WATER BIOLOGY
PHC 6937; Section 4858

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"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)

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 chronic
- 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…

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.

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

Occupational Toxicology: Combines occupational medicine and occupational hygiene.

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 & molecular basis by which chemicals exert toxic effects.

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

An interdisciplinary field…

Federal agencies:

FDA (FDCA- Federal Food, Drug & Cosmetic Act)

EPA (FIFRA-Federal Insecticide, Fungicide and Rodenticide Act)

EPA (TSCA-Toxic Substance Control Act) PCBs, asbestos, Pb-based paint

EPA (CERCLA- Comprehensive Env Response, Compensation, & Liability Act); Superfund

DOL (OSHA-Occupational Safety and Health Administration)

Environmental Contaminants

- **Inorganics**
  (e.g., metals, N,P, ions)
- **Organics**
  (e.g., solvents, hydrocarbons, pesticides, EDCs, detergents)
- **Particulates**
- **Gases**
- **Biologicals**

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

"All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy."

Paracelsus 1493-1541

Relative Toxicity

Approximate 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.

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

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 medicine, chronic effects of a chemical exposure may manifest themselves as a common disease and go unnoticed**
- **SARs and K_{ow} predictors**

Dose vs Exposure

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

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

Exposure concentrations

Concentrations in liquids or solids:

ppt = parts per thousand (g/L; ‰; PSU); easily confused
ppm = parts per million (µg/mL = mg/L or µg/g = mg/kg)
ppb = parts per billion (ng/mL = µg/L or ng/g = µg/kg)

Concentrations in air:

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

The Dose Makes The Poison

- **A** Absorption
- **D** Distribution to tissues
- **M** Metabolism
- **E** Excretion

Primary Routes of Exposure

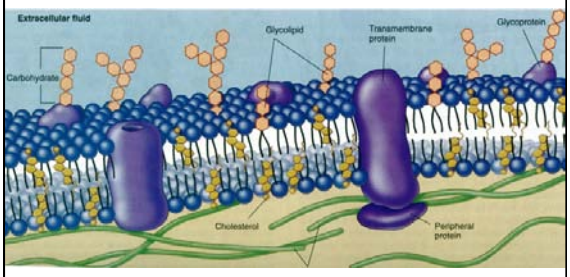
Gastrointestinal

Respiratory

Dermal (skin)

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

Cell Membrane

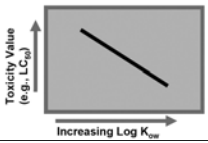


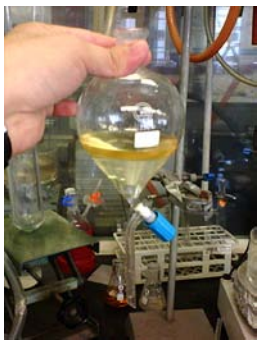
Semi-permeable lipid bilayer

Pharmacokinetic Parameters

Octanol Water Partition Coefficient (K_{ow})

- Ratio of the concentration of a chemical in octanol and in water at equilibrium and at a specified temperature.
- Predict solubility
- Predict bioaccumulation





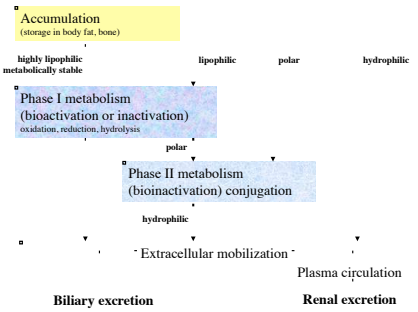
Metabolism

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

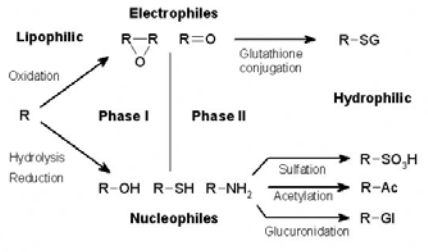
Bioactivation (activation): production of metabolites that are more toxic than the parent substance.

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

Xenobiotics



Metabolism



Routes of Elimination

Biliary

Renal

Fecal

Respiratory

Bioaccumulation

- Accumulation of substances, such as pesticides or other organic chemicals in an organism or part of an organism.
- Biological sequestering through respiration, diet, epidermal (skin) contact.
- Results in the organism having a higher concentration of the substance than the concentration in the surrounding environment.
- Amount depends on the rate of uptake, the mode of uptake, how quickly the substance is eliminated, transformation of the substance, the lipid content of the organism, the K_{ow} of the substance, and environmental factors, and other biological and physical factors.
- General rule: the more hydrophobic (i.e., lipophilic) a substance is the more likely it is to bioaccumulate in organisms.
- Bioconcentration refers only to the uptake of substances into the organism from water alone. Bioaccumlation is the more general term because it includes all means of uptake into the organism. Biomagnification refers to increased concentration going up a food chain.

Chemical Interactions

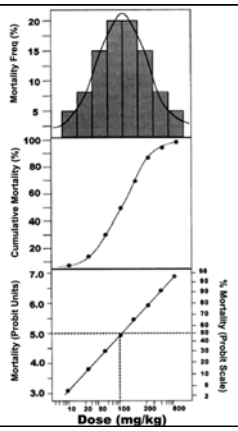
Additive: **2+3=5** (parathion + diazinon)

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

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

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

Diagram of quantal dose-response relationships



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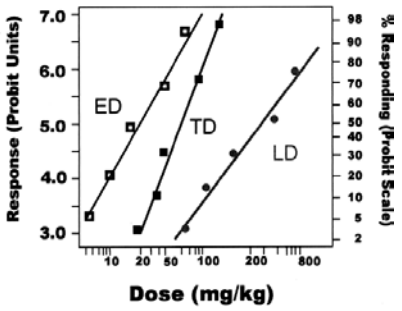
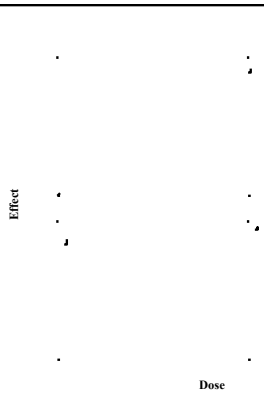
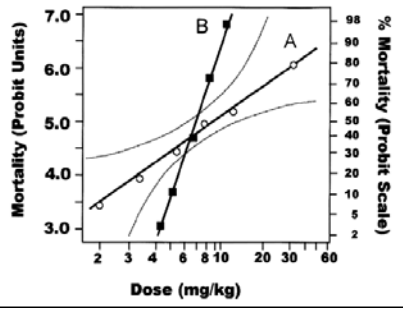
Effective, toxic and lethal dosages



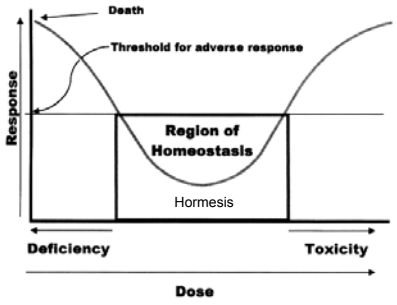


Comparison of dose-response relationship for two different chemicals plotted on a log dose-probit scale



The U Shaped Curve

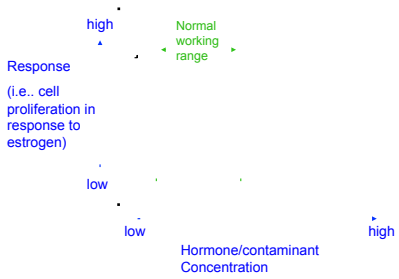
Dose-response relationship for representative essential substances, such as vitamins or trace elements (e.g., Cr, Co, Se)



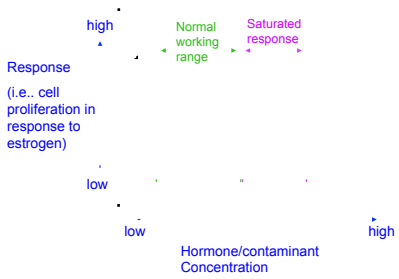
EDCs

An **endocrine disruptor** is an exogenous chemical substance or mixture that alters the functions(s) of the endocrine system and thereby causes adverse effects to an organism, its progeny, or (sub) population.

- "Inverted U" common hormone dose-response.
- Linear working range: small change in concentration → relatively large change in response. Not representative of other exposure ranges.

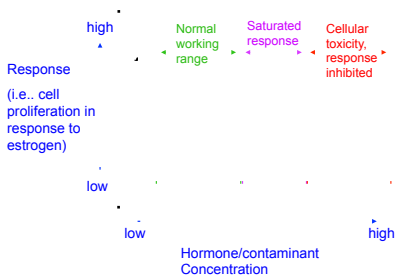


However, if the hormone concentration exceeds the working range, the response quickly saturates.



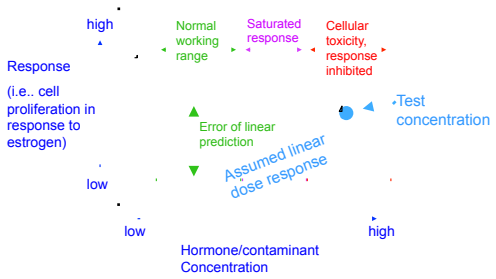
At even higher hormone concentrations, cellular toxicity (i.e. cell death) occurs and the response is inhibited.

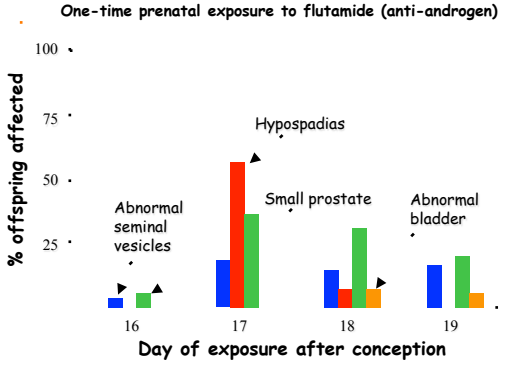
So, why is it important to understand the inverted U dose response curve?



The reason is because most chemicals are tested at concentrations that cause cellular toxicity.

For many chemicals the response curve is unknown. The working range for many chemicals is far below the test ranges. E.G., working range for estradiol is 10^6 < cytotoxic range.





STPE: A complex mixture of EDCs

- naturally occurring hormones (e.g., progesterone, testosterone, estradiol)
- synthetic hormones (birth control estrogen - EE_2)
- neuroactive pharmaceuticals (antidepressant, -anxiety, ADHD meds)
- surfactants, plasticizers, and antimicrobials

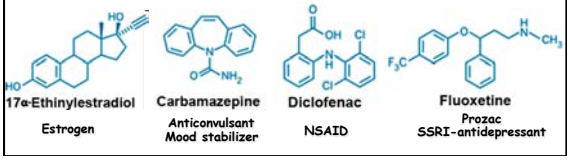
Phthalates

- Coatings of pharm pills
- Adhesives & glues
- Agricultural adjuvants
- Building materials
- Personal care products
- Detergents & surfactants
- Firm plastics (eg PVC pipes)
- Paints and caulk
- Printing inks and coatings
- Food products
- Textiles
- Soft plastics (eg vinyl, shower curtains, toys)
- Nail polish
- Perfumes &fragrances
- Electronics
- Medical tubing & catheters

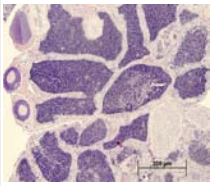
PPCPs

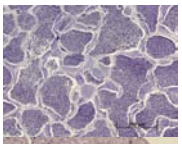
Ilene Ruhoy & Christian Daughton (2007) Sci Total Environ (338): 137-148
19.7 tons orphaned pharmaceuticals per year

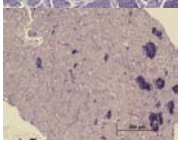
Fish as sentinels

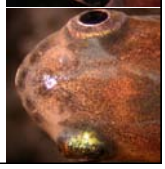


Fish as sentinels









Intersex

The Dose Makes the Poison

Detection does not infer health risk and non-detection does not ensure safety.

EPA United States Environmental Protection Agency

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

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