

~~To Die For~~

To Die From

Toxicology for Non-Chemists

**Devens EHS Roundtable
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I. What is Toxicology?

No substance is a poison by itself.
It is the dose that makes the poison.

Paracelsus, c. 1530

II. Major Routes of Entry

- Outer Surface of Body
- Gastrointestinal
- Lungs

Outer Surface of Body

- Skin generally impermeable; good barrier
- Hair follicles, sweat glands. Minor route only
- Percutaneous: through epidermis, dermis
- Epidermis: dry, dead protein filaments
 - Pretty good barrier
- Dermis: living, porous, aqueous
 - Not a very good barrier. Cuts, abrasions, etc.

Gastrointestinal

- Enter with food and water
- Enter as drugs or chemicals
- Usually no toxic effects until absorbed (exc. corrosives)
- Absorption all along GI tract, not in mouth

Lungs

- Main site of entry: alveoli
- If $>10\ \mu\text{m}$ – too big
- If $<0.01\ \mu\text{m}$ – too small
- Between $0.01\ \mu\text{m}$ and $10\ \mu\text{m}$ – just right
 - 2/3 upper respiratory tract, 1/3 lower respiratory tract
- Safety devices:
 - Nose hair
 - Mucociliary elevator
 - Phagocytes

III. Distribution

- General Distribution
- Barriers
- Binding and Storage

General Distribution

- Toxic material enters blood stream
- Distributed rapidly
- Rate of distribution to organs is function of:
 - Blood flow through organ
 - Ease of crossing capillary wall and cell membrane
 - Affinity of organ for toxic material

Barriers

- Blood-brain barrier
- Blood-nerve barrier

Binding and Storage

- Creates higher concentration than expected
- Liver and kidneys good at binding
- Adipose tissue good for nonpolar materials

IV. Major Routes of Exit

- Urine
- Liver
- Lungs
- Others
 - GI tract
 - Milk
 - Saliva, sweat

V. Biotransformation

- Toxic material broken down by chemical reactions
- Breakdown product may be more toxic than the original - Bioactivation

Bioactivation

- Breakdown product is more toxic than original toxic substance
- Benign material may become toxic through metabolic process
- Examples:
 - Ethanol >> acetaldehyde>> acetic acid
 - Methanol>> formaldehyde>> formic acid

VI. Toxic Effects

- Local vs. systemic
- Reversible vs. irreversible
- Immediate vs. delayed
- Morphologic
- Functional
- Biochemical
- Sensitization
- Idiosyncratic reaction
- Graded vs. quantal

VII. Factors that Modify Toxic Effects

- Species
- Sex
- Age

Species

- Basis of specificity of pesticides
- Within mammals, differences less pronounced

Sex

- Chloroform acutely toxic to male rats but not females
- Estrogens neutralize the effect
- Castration neutralizes the effect
- Androgens make females susceptible

Age

- Newborn, young: 1.5X – 10X susceptibility to many toxics
- Not just size, also development of detox system
- Opposite effect for bioactivation. Ex: DDT
 - Adult LD₅₀ = 200 mg/kg
 - Newborn LD₅₀ = >4000 mg/kg
- Some fetus 50X susceptible to carcinogens
- Elderly – impaired detoxification system

VIII. Target Organs

- Respiratory system
- Liver
- Kidneys
- Skin
- Eyes
- Nervous system

Respiratory system

- Gas – vapor – mist – dust – fume
- Nasopharynx – trachea – bronchia – lungs
- Effects: local irritation, cellular damage, edema, fibrosis, allergic response, sensitization, carcinogenesis

Liver

- Largest, metabolically most complex organ
- Metabolism of nutrients as well as toxicants
- Don't forget bioactivation and biotransformation
- Types of liver injury: fatty liver, liver necrosis, cirrhosis, hepatitis, carcinogenesis

Kidney

- High blood flow
- Concentrates toxicants in filtrate
- Bioactivates certain toxicants
- Fortunately, remarkable compensatory ability

Skin

- Remember epidermis, dermis
- Primary irritation
- Sensitization

Eyes

- Cornea – delicate, subject to exposure: acids, bases, solvents, irritants
- aqueous humor – secreted near iris, drains through canal. Glaucoma.
- Lens – cataracts
- Retina – polycyclics, hyperoxia, vasoconstriction
- Optic nerve – methanol/central vision; CO/peripheral vision

Nervous system

- Safety features: blood/brain barrier, blood/nerve barrier
- Problems: long axons, lots of surface area, neurons do not reproduce
- CNS: brain, spinal cord
- Peripheral NS: motor, sensory, sympathetic, parasympathetic

Nervous system

- Types of effects:
 - Neuropathy
 - Axonopathy
 - Interference with synaptic transmission

IX. Some Classes of Toxic Chemicals

- Corrosive
- Metabolic
- Neurotoxic
- Carcinogenic

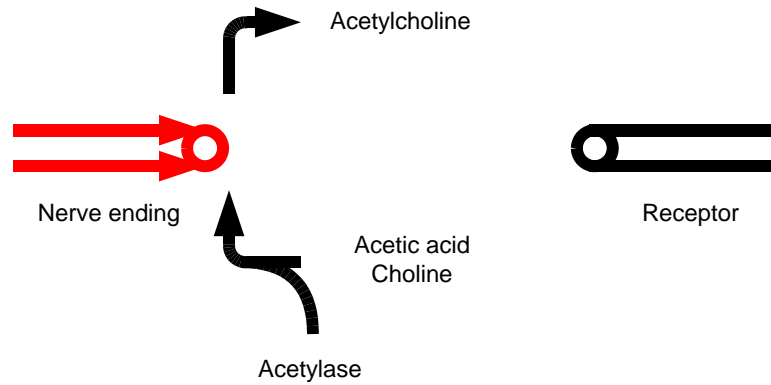
Corrosive

- Local action
- Dehydration
- Protein break
- Acids and bases
- Meat tenderizer

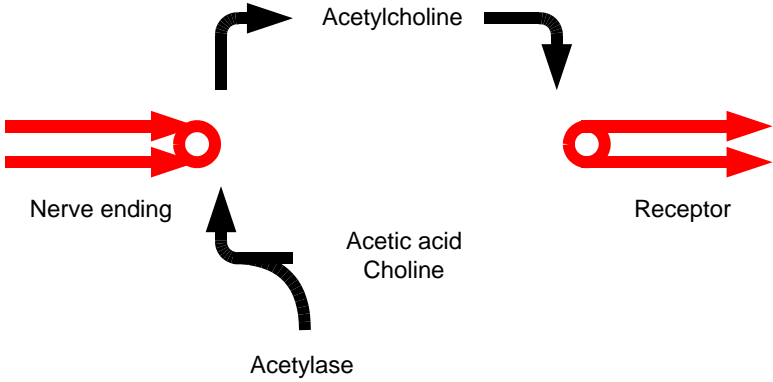
Metabolic

- Interfere with vital reaction in body
- Subtle – sometimes no signs until too late
- Carbon monoxide
- Cyanide
- Heavy metals

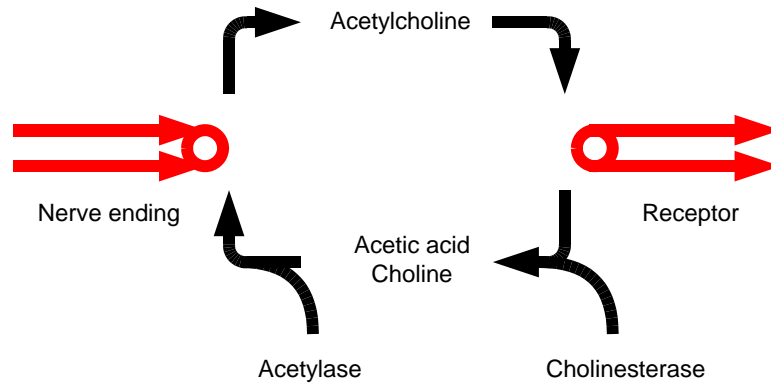
Acetylcholine cycle



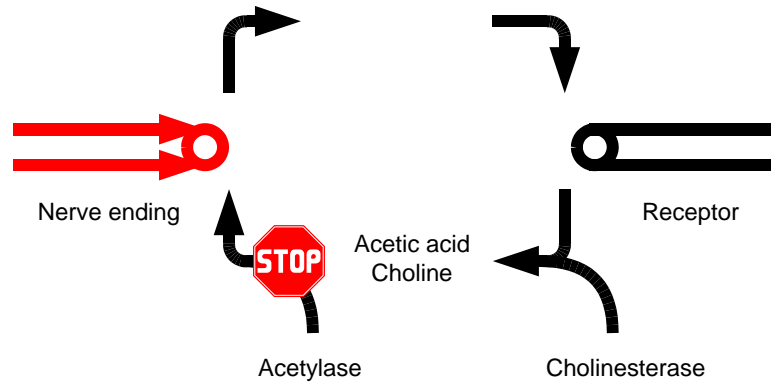
Acetylcholine cycle



Acetylcholine cycle



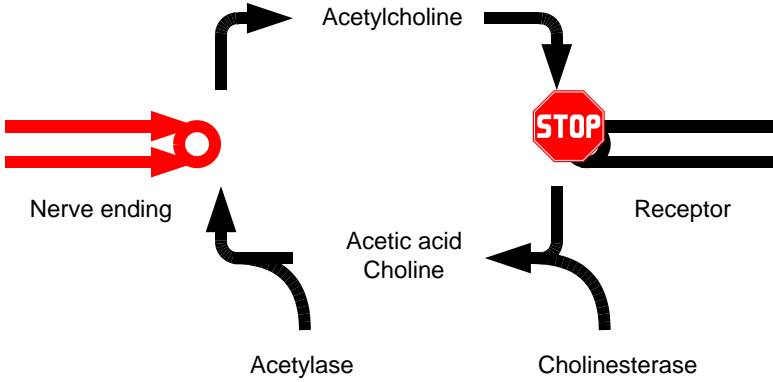
Acetylcholine cycle



Antiacetylase poisons

- Prevent formation of acetylcholine
- Impulse isn't carried across synapse
- Depressant
- Paralysis and death from respiratory failure
- Botulism

Acetylcholine cycle



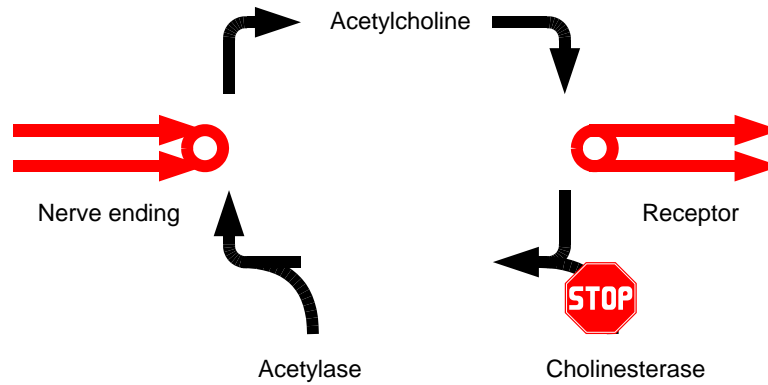
Receptor-blocking poisons

- Acetylcholine is created, but can't deliver the impulse
- Sensory messages don't get sent
- Anesthetics

Receptor-blocking alkaloids

- Atropine 100 mg/kg
- Curare 20 mg/kg
- Morphine 100 mg/kg
- Codeine 300 mg/kg

Acetylcholine cycle



Anticholinesterase poisons

- Acetylcholine can't break down
- Delivers the impulse over and over
- Overstimulation, convulsions, muscle cramps
- Insecticides, phosphates, black widow

Carcinogenic

- Carcinogens
 - Exposed individual only
 - Aniline, carbon tet, benzene, chromium, vinyl chloride
- Teratogens
 - Offspring only – not transmitted
 - Glycol ethers, thalidomide
- Mutagens
 - Offspring only – transmitted
 - ????

X. Levels and Categories of Toxicity

- None - Slight - Moderate - Severe
- Acute – Chronic (Exposure)
- Acute – Chronic (Effects)
- Local – Systemic
- How toxic is toxic?

How toxic is toxic?

LD50, per kg	Degree of toxicity	Probable lethal dose for a 70-kg man
<1.0 mg	dangerously toxic	a taste
1 - 50 mg	seriously toxic	a teaspoon
50 - 500 mg	highly toxic	an ounce
0.5 - 5 g	moderately toxic	a pint
5 - 15 g	slightly toxic	a quart
>15 g	extremely low toxicity	more than a quart