

NST110: Advanced Toxicology

Lecture 1: Principles of Toxicology

Principles of Toxicity

1. Defining toxicology
2. History of toxicology
3. Dose response
4. Evaluating safety

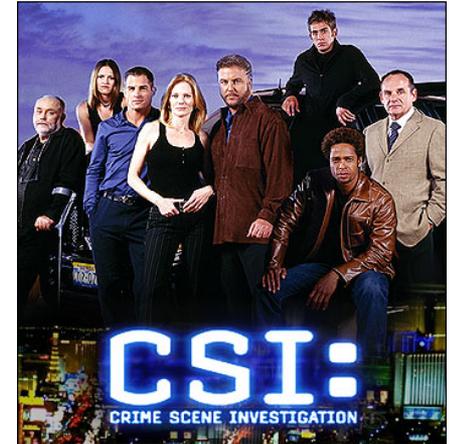
Toxicology

Toxicology is the study of adverse effects of chemicals on living systems, including:

- Mechanisms of action and exposure to chemicals as a cause of acute and chronic illness.
- Understanding physiology and pharmacology by using toxic agents as chemical probes.
- Recognition, identification, quantification of hazards from occupational exposure to chemicals.
- Discovery of new drugs and pesticides.
- Development of standards and regulations to protect humans and the environment from adverse effects of chemicals.

Branches of Toxicology

- 1. Mechanistic**—cellular, biochemical and molecular mechanisms by which chemicals cause toxic responses
- 2. Forensic**—cause of death, legal aspects
- 3. Clinical**—treatments for poisonings and injuries caused by xenobiotics
- 4. Environmental**—environmental pollutants, effects on flora and fauna
- 5. Food**—adverse effects of processed or natural food components
- 6. Regulatory**—assigns risk to substances of commercial importance.

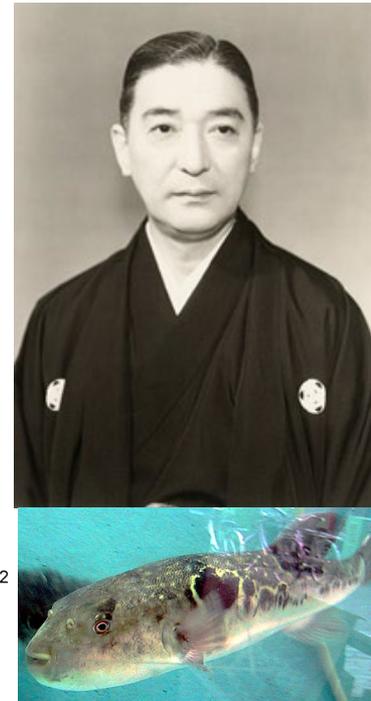


Origins of Toxicology

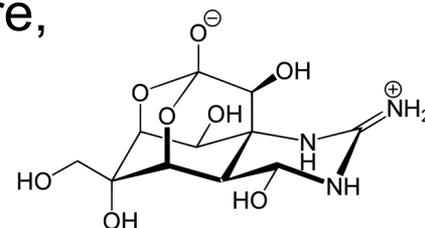
- Earliest humans used animal venoms and plant extracts for hunting, warfare and assassination.
- 400 BC: Hippocrates compiled a listing of a number of poisons and outlined some clinical toxicology principles.
- 1493-1541: Paracelsus—physician and philosopher
 - All substances are poisons; the right dose differentiates a poisons from a remedy.
 - “Dose determines toxicity.”
- 1775: Percival Pott found that soot caused scrotal cancer in chimney sweeps. Much later the carcinogens in soot found to be polycyclic aromatic hydrocarbons.
- 1972: Rachel Carson/EPA led to ban of insecticide DDT for environmental and health concerns



Examples of Toxicological Cases



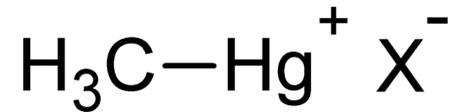
- April 30th, 1945, Eva Braun, long-time companion of Hitler committed suicide with a cyanide capsule
 - Inhibitor of cytochrome c oxidase, part of complex IV of the electron transport chain and inhibits ATP production leading to brain death and heart cessation, hypoxia, and death
- Jan 16th, 1975 Bando Mitsugoro VIII, a famous Japanese Kabuki actor died from eating 4 livers of pufferfish
 - Active toxic ingredient is tetrodotoxin
 - Tetrodotoxin blocks voltage-gated sodium channels leading to suppression of neurotransmission, numbness, bronchospasms, coma, respiratory failure, death



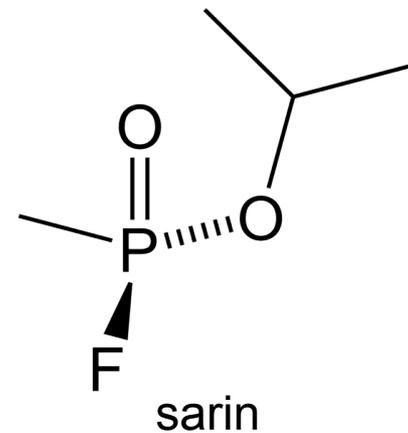
tetrodotoxin

Examples of Toxicological Cases

- 1932-1968: Minamata disaster—caused by methylmercury toxicity from industrial wastewater from Chisso Corporation in Minamata City in Japan
 - 2265 victims
 - Caused neurological syndrome associated with methyl mercury poisoning including ataxia, numbness, insanity, muscle weakness, hearing and speech loss, birth defects, paralysis, coma, death
 - Alters neurochemistry and neurotransmission through multiple mechanisms
- 1988, Saddam Hussein used sarin on Kurds, 1995, Japanese subway sarin attack by terrorist group; 2006 day 5 of “24”—Jack Bauer saves LA from VX attack in TV show; 2013 Assad uses sarin against rebels
 - Sarin and VX are an organophosphorus chemical warfare agents that inhibits acetylcholinesterase, leading to excess acetylcholine and hyperstimulation of neurons, resulting in seizures, tremoring, convulsions, excess salivation, excess tearing, urination, defecation, bronchoconstriction, respiratory failure, death



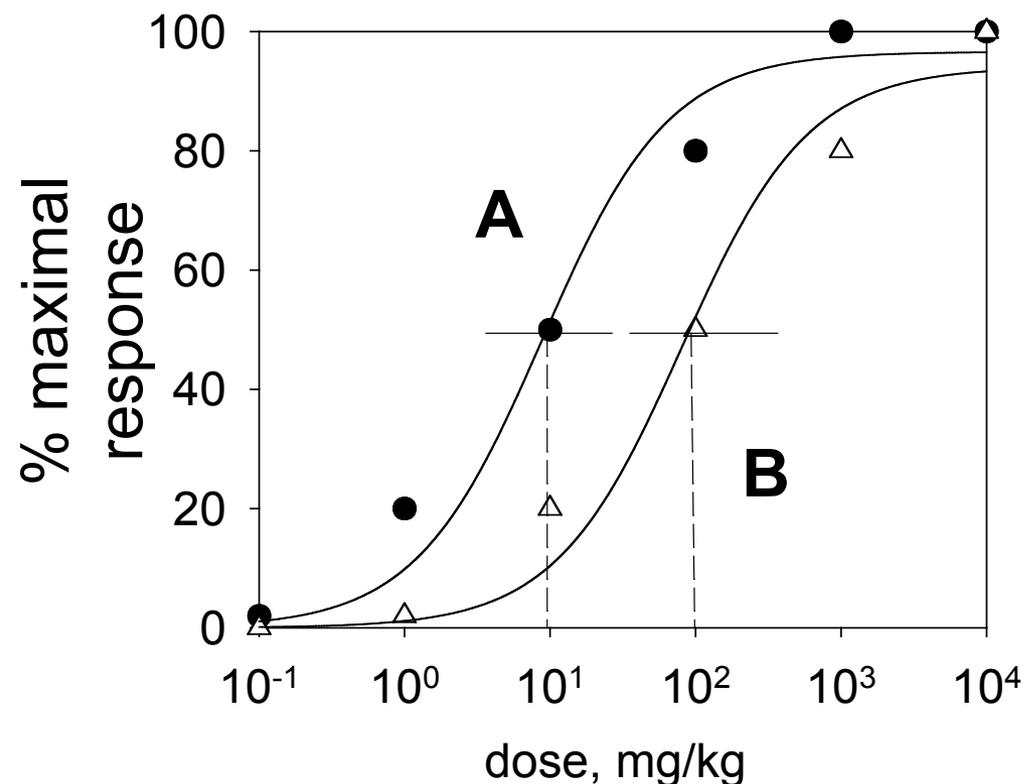
Methyl mercury



Dose-Response

Individual dose-response

Response of an *individual* organism to varying doses of a chemical (also called “graded” response because effect is continuous over a dose range) (e.g. enzyme activity, blood pressure).



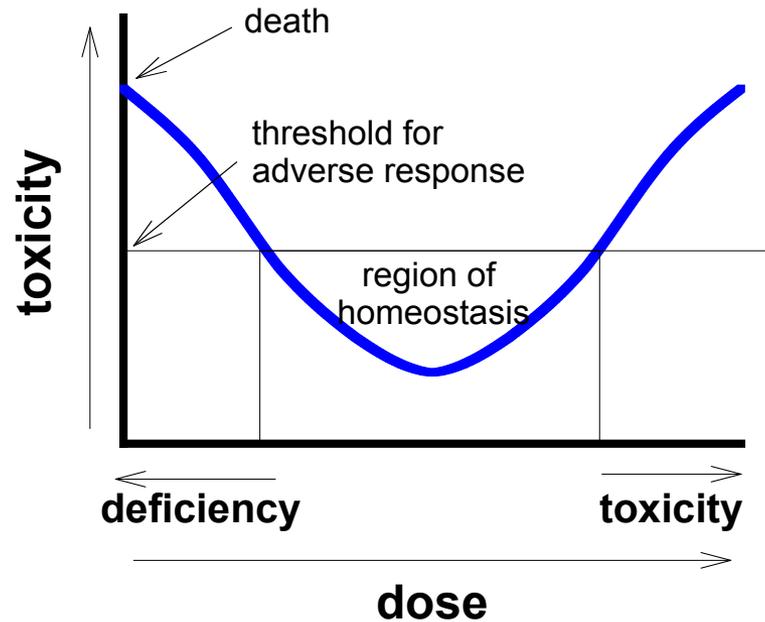
Y-axis: % of max. response
(linear in middle range)

X-axis: dose (e.g. mg/kg or molar concentration) (plotted as log base 10)

Can derive lethal dose (LD₅₀), toxic dose (TD₅₀), effective dose (ED₅₀) values from dose-response data.

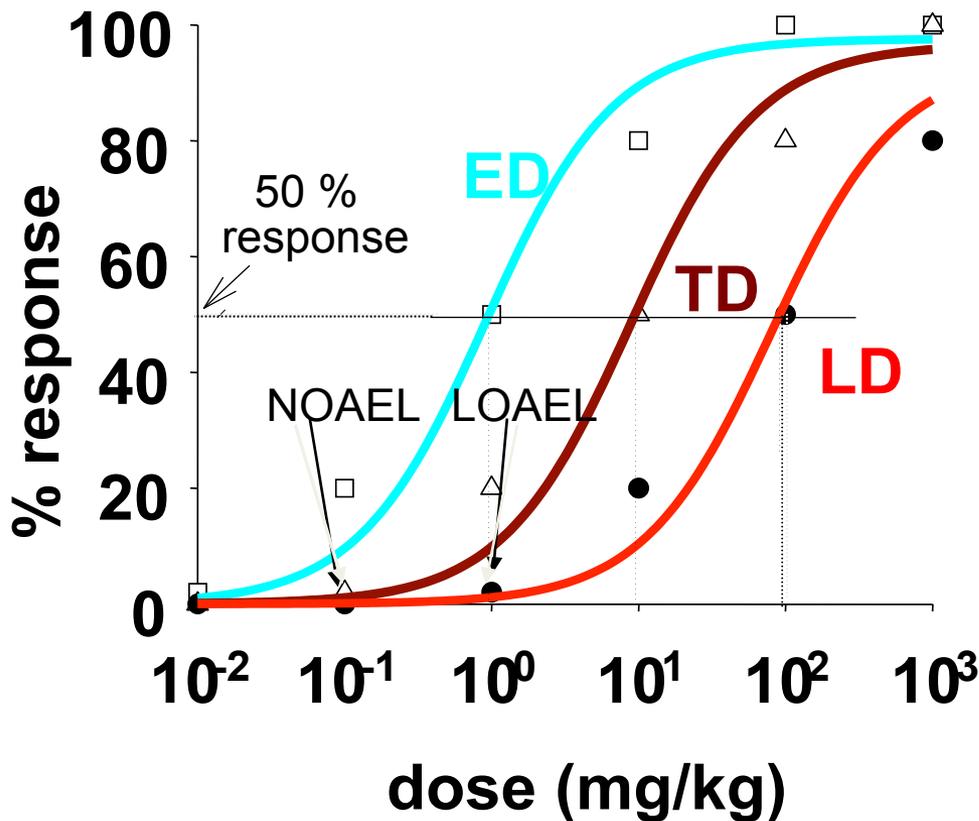
Inhibitory concentration (IC₅₀) can also be determined from concentration-response curves.

Dose-Response Curves for Beneficial Substances



- For substances required for normal physiological function and survival, the dose-response curves will be U- or J-shaped.
- At very low doses, there is an adverse effect (deficiency), which decreases with increasing dose (homeostasis). At very high doses, an adverse response appears from toxicity.
- For example, vitamin A can cause liver toxicity and birth defects at high doses and vitamin A deficiency is lethal.

Evaluating Dose-Response Relationships



ED: Effective dose
(therapeutic dose of a drug)

TD: Toxic dose
(dose at which toxicity occurs)

LD: Lethal dose
(dose at which death occurs)

NOAEL: no observed adverse effect level

LOAEL: lowest observed adverse effect level

ED₅₀: dose at which 50% of population therapeutically responds.

(In this example, ED₅₀=1 mg/kg)

TD₅₀: dose at which 50% of population experiences toxicity (**TD₅₀=10 mg/kg**).

LD₅₀: dose at which 50% of population dies (**LD₅₀=100 mg/kg**).

Comparing Toxicity of Compounds

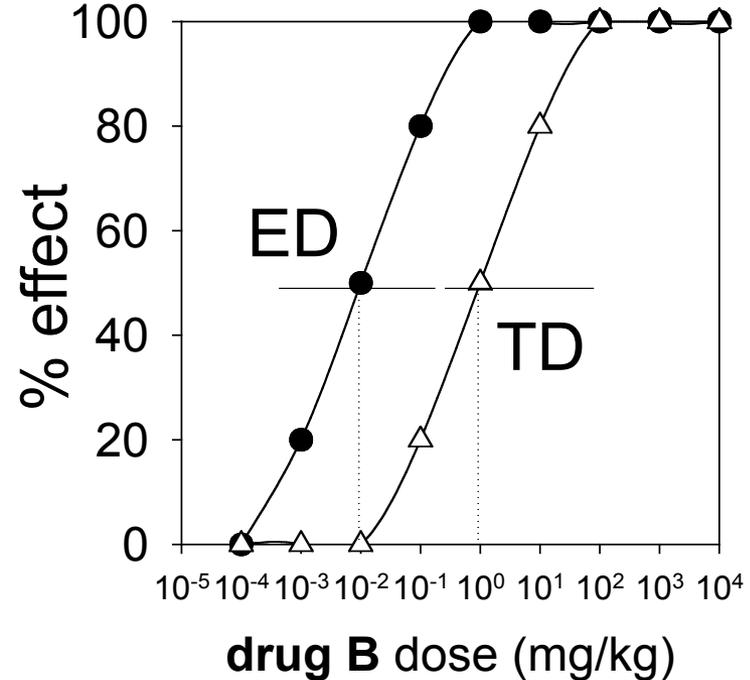
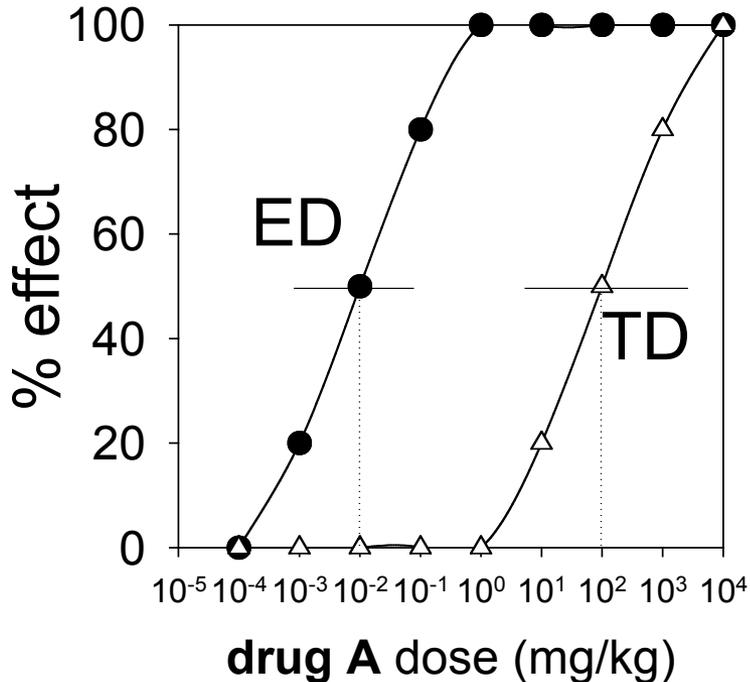
Therapeutic Index (TI)

$$\text{TI} = \text{LD}_{50}/\text{ED}_{50}$$

or
$$\text{TI} = \text{TD}_{50}/\text{ED}_{50}$$

- TI is the ratio of the doses of the toxic and the desired responses.
- TI is used as an index of comparative toxicity of two different materials; approximate statement of the relative safety of a drug.
- The larger the ratio, the greater the relative safety.

Example of using TI to compare relative safety of 2 drugs.

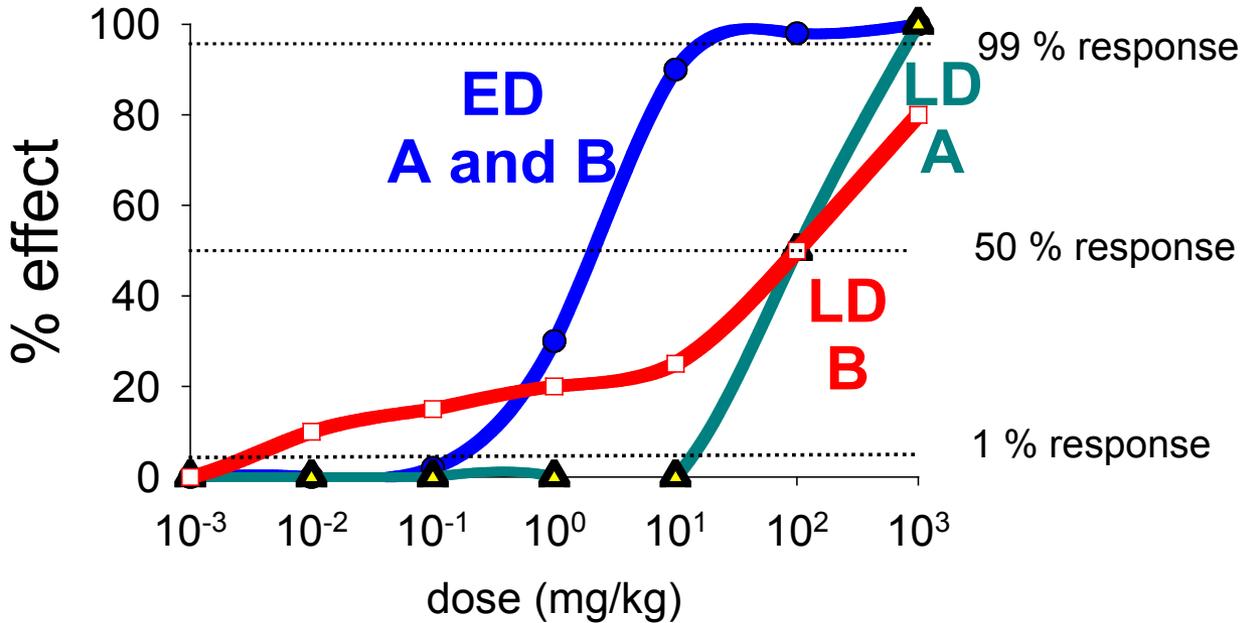


Drug A: $TI = TD_{50}/ED_{50} = 100/0.01 = 10000$

Drug B: $TI = TD_{50}/ED_{50} = 1/0.01 = 100$

Which drug is safer?

Disadvantages of Using TI



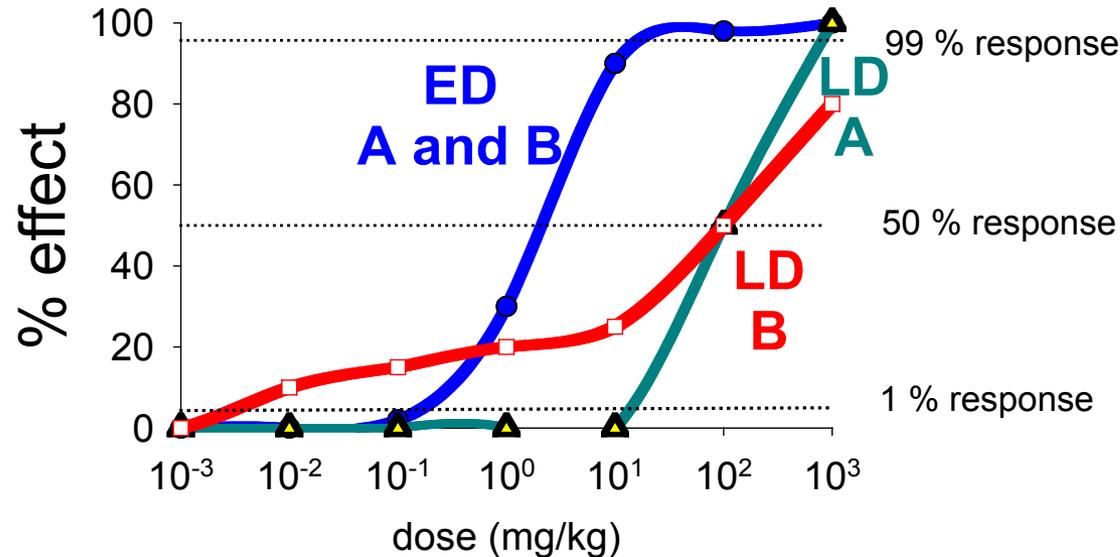
Drug A: $ED_{50} = 2 \text{ mg/kg}$; $LD_{50} = 100 \text{ mg/kg}$

Drug B: $ED_{50} = 2 \text{ mg/kg}$; $LD_{50} = 100 \text{ mg/kg}$

Drugs A and B both have the same TI = $100/2 = 50$

Therapeutic index does not take into account the slope of the dose-response curves.

Margin of Safety



Margin of safety can overcome this deficiency by using ED₉₉ for the desired effect and LD₁ for the undesired effect.

$$\text{Margin of safety} = \text{LD}_1 / \text{ED}_{99}$$

$$\text{Drug A: } \text{LD}_1 / \text{ED}_{99} = 10 / 10 = 1$$

$$\text{Drug B: } \text{LD}_1 / \text{ED}_{99} = 0.002 / 10 = 0.0002$$

Thus, Drug B is much less safe than Drug A.

Toxic Potency

Agent	LD ₅₀ (mg/kg)		
Ethyl alcohol	10,000	}	
Sodium chloride	4,000		} slight
BHA/BHT (antioxidants)	2,000		
Morphine sulfate	900	} moderate	
Caffeine	200		
Nicotine	1	} high	
Curare	0.5		
Shellfish toxin	0.01	} Extremely high (<1 mg/kg)	
sarin	0.001		
Botulinum toxin	0.00001		