Toxicology and Environmental Protection

Introduction to Toxicology

Refer lecturer for course updated notes.

Students are oblidged to follow the courses for evaluation process and presented notes are preliminary drafts for the whole evaluation process.

Definition

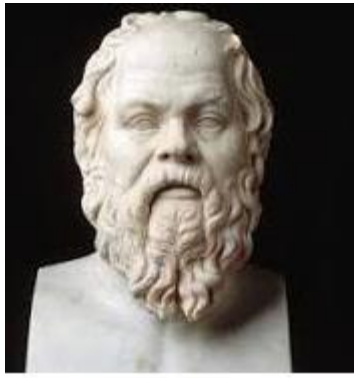
- Greek word poison (toxicon) + scientific study (logos)- conjoined as a term in 17th century
- The study of adverse effects of xenobiotics
- Before
  - «The science of poison»
- Now
  - «The science that deals with the adverse effects of chemicals on living organisms and assesses the probability of their occurrence»

History

- Early cave dwellers -poisonous plants and animals and used their extracts for hunting or in warfare
- 2700 B.C. - Chinese journals: plant and fish poisons
- 1900-1200 B.C. - Egyptian documents - directions for collection, preparation, and administration of > 800 medicinal and poisonous recipes.
- 800 B.C. - India - Hindu medicine includes notes on poisons and antidotes.

History

- 50-100 A.D. - Greek physicians classified over 600 plant, animal, and mineral poisons.
- 50- 400 A.D. - Romans used poisons for executions and assassinations.
- 399 BC- philosopher Socrates- mixture containing poison hemlock
- 30 BC in Alexandria- Cleopatra - suicide by asp (Egyptian cobra)



Socrates

Cleopatra

History

“...the appearance of disease in human populations is influenced by the quality of air, water, and food; the topography of the land; and general living habits.”

The ancient-Greek physician Hippocrates in his treatise Air, Water and Places

400 BC

History

- Avicenna (A.D. 980-1036)- Islamic authority on poisons and antidotes.
- 1200 A.D. - Spanish rabbi Maimonides- first-aid book for poisonings, poisons and antidotes

Avicena

Maimonides

History

- Developed as an empirical science from ancient prisoners - evolution to volumetric science by the emergence of chemistry and analytical science
- Until…

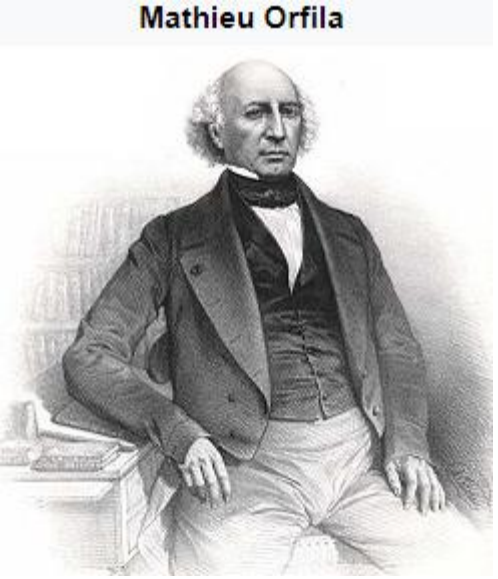
The Father of Modern Toxicology

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

Paracelsus (1493-1541)

(Philippus Theophrastus Aureolus Bombastus von Hohenheim)

History



- Spanish physician Orfila (1787-1853) established toxicology a

a distinct scientific discipline

- Forensic toxicology- criminal tasks- autopsy materials
- Founder of toxicology
- Systematic correlation-chemical and biological properties of poisons

The 20th century

- Paul Erlich- how toxicants affect living organisms
- Rache
- advanced level of understanding of toxicology
- All toxic effects are related to molecular effects- through specific changes in molecules (DNA etc) and biochemicals

Some recent cases

Assassination of Kim Jong-nam

13 February 2017

VX nerve agent,

Bosnian Croat war criminal dies after taking poison in UN courtroom

Former commander Slobodan Praljak drank from bottle moments after judges upheld 20-year sentence in The Hague

Nov 29, 2017

cyanide poisoning,

Toxicology= Science+ Art

In all branches of toxicology, mechanisms by which chemicals produce **adverse effects** in the biological systems

Biomedical area- mechanisms of action

Exposure to chemical agents- a cause of acute and chronic illness.

Physiology and pharmacology - to understand physiological phenomena

Classification

- Research Methodology
  - Descriptive
  - Mechanistic
  - Regulatory
  - Predictive
- Specific socio-medical issue
  - Occupational
  - Environmental
  - Clinical
  - Forensic
- Affected Organ/System
  - Cardiovascular
  - Renal
  - CNS
  - GI
  - Respiratory
  - Reproductive

Toxicologists

Occupational toxicology- Recognition, identification, and quantification of hazards resulting from occupational exposure to chemicals

Public health aspects of chemicals in air, water, other parts of the environment, foods, and drugs.

Discovery and development of new drugs and pesticides.

Development of standards and regulations designed to protect human health and the environment from the adverse effects of chemicals

involved in safety assessment and use of

data as basis for regulatory control of hazards

- determines risk associated with use of chemicals

Environmental toxicologists- study the effects of chemicals in flora and fauna

Molecular toxicologists-the mechanisms by which toxicants modulate cell growth and differentiation and cells respond to toxicants at the level of the gene.

Clinical toxicologists- develop antidotes and treatment regimes to ameliorate poisonings and xenobiotic injury.

Forensic toxicology: A branch of medicine that focuses on medical evidence of poisoning, and tries to establish the extent to which poisons were involved in human deaths

Descriptive toxicology deals with toxicity tests on chemicals exposed to human beings and environment as a whole.

Mechanistic toxicology deals with the mechanism of toxic effects of chemicals on living organisms.

Regulatory toxicology studies whether the chemical substances has low risk to be used in living systems

Predictive toxicology studies about the potential and actual risks of chemicals /drugs.

- Academic, industrial, and governmental organizations- complementary

Xenobiotic

- Greek «xeno» "foreigner."
- is the general term that is used for a foreign substance taken into the body. It is derived from the

Toxicants	substances that produce adverse biological effects of any nature may be chemical or physical in nature effects may be of various types *(acute, chronic, etc.)*
Toxins	specific proteins produced by living organisms *(mushroom toxin or tetanus toxin)* most exhibit immediate effects
Poisons	toxicants that cause immediate death or illness when experienced in very small amounts

Toxic agent- Toxicant

- A toxic agent is anything that can produce an adverse biological effect.
- Toxic agents may be: Chemical (cyanide), physical (radiation), or biological (snake venom) in form.

Factors deterimining the adverse effects

- Intrinsic toxicity
  - Chemical properties
    - Molecular structure- functional groups
    - Volatility
    - Reactivity
    - Solubility
    - Stability (light, water, acids, enzymes)
  - Physical properties
    - Gas (density,…)
    - Liquid (vapor pressure,…)
    - Solid (crystal structure, sice, shape,..)
- Dose
- Exposure conditions
- Exposure of host

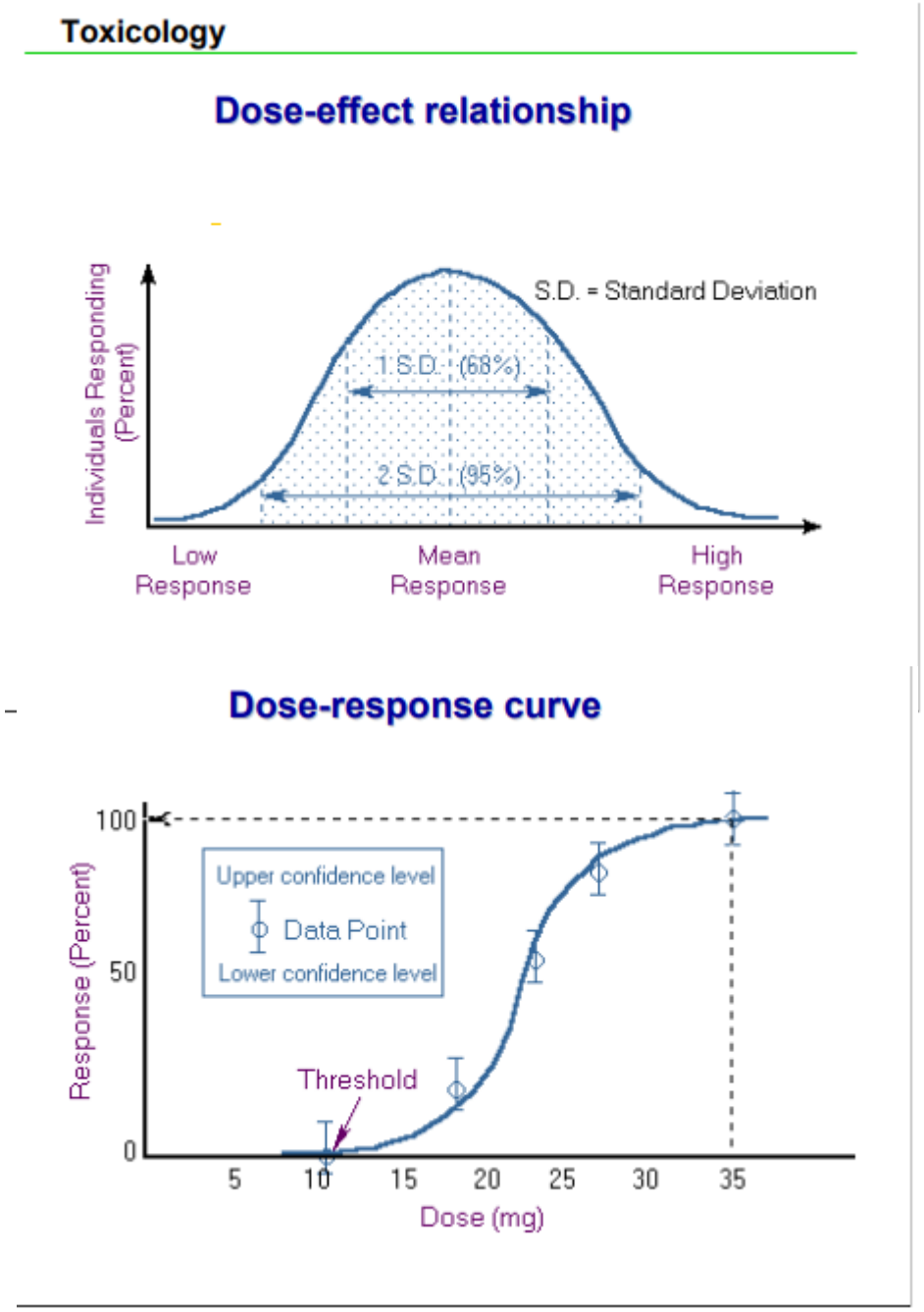
Terminology

- Toxicity - The adverse effects that a chemical may produce.
- Dose - The amount of a chemical that entering the body
  - the amount of a xenobiotic in a unit of the media (eg. Mg of chemical/kg of body weight= mg/kg)
  - mg/liter (mg/l) for liquids
  - mg/gram (mg/g) for solids
  - mg/cubic meter (mg/m3) for air
  - Ppm, ppb, ppt, ppq

  - Dependent upon= concentration, properties of the toxicant, timing and frequency of exposure, length of exposure, exposure route
- Exposure – Contact providing opportunity of obtaining a poisonous dose.
- Response- Dependent upon the dose and organism- change from the normal state
  - Molecular, cellular, organ, organism level
  - Loval/systemic

Response

- Reversible/ Irreversible
- Delayed/ Immediate
- Dose response
  - Monotonic (response increase with dose)/Nonmonotonic (response does not increase with dose- Endocrine disrupting compounds, hormones)
    - Hormesis- beneficial effect at low conc- decreases at high
  - Treshold/no treshold
    - A threshold for toxic effects occurs at the point where the body's ability to detoxify a xenobiotic or repair toxic injury has been exceeded (cirrhosis- %50)
  - Cancer/non cancer



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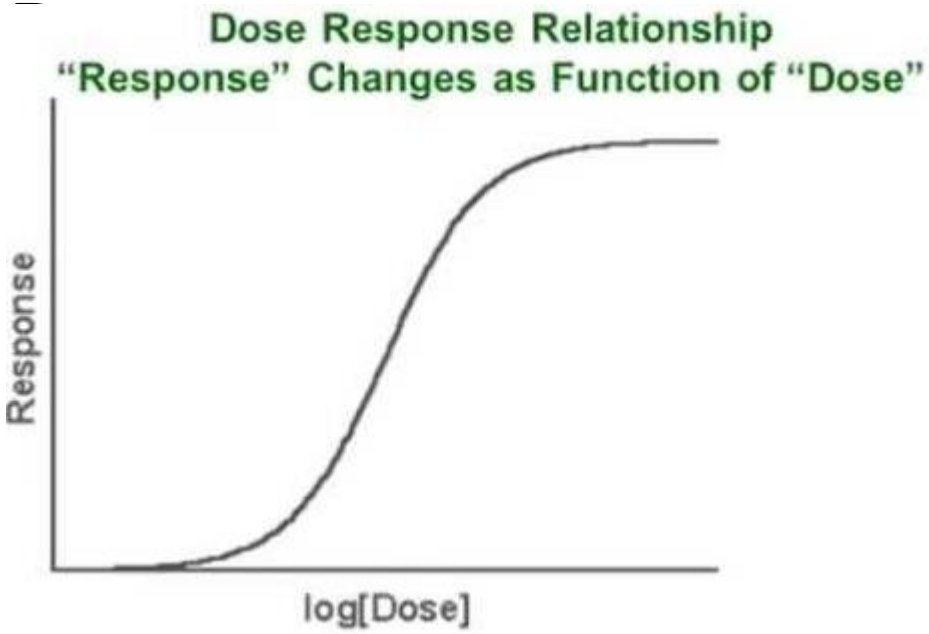
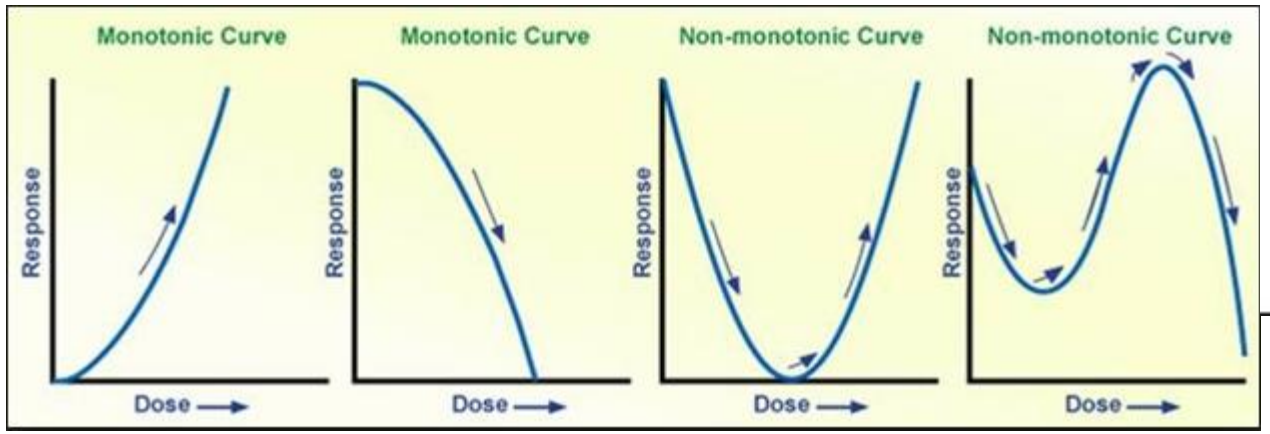
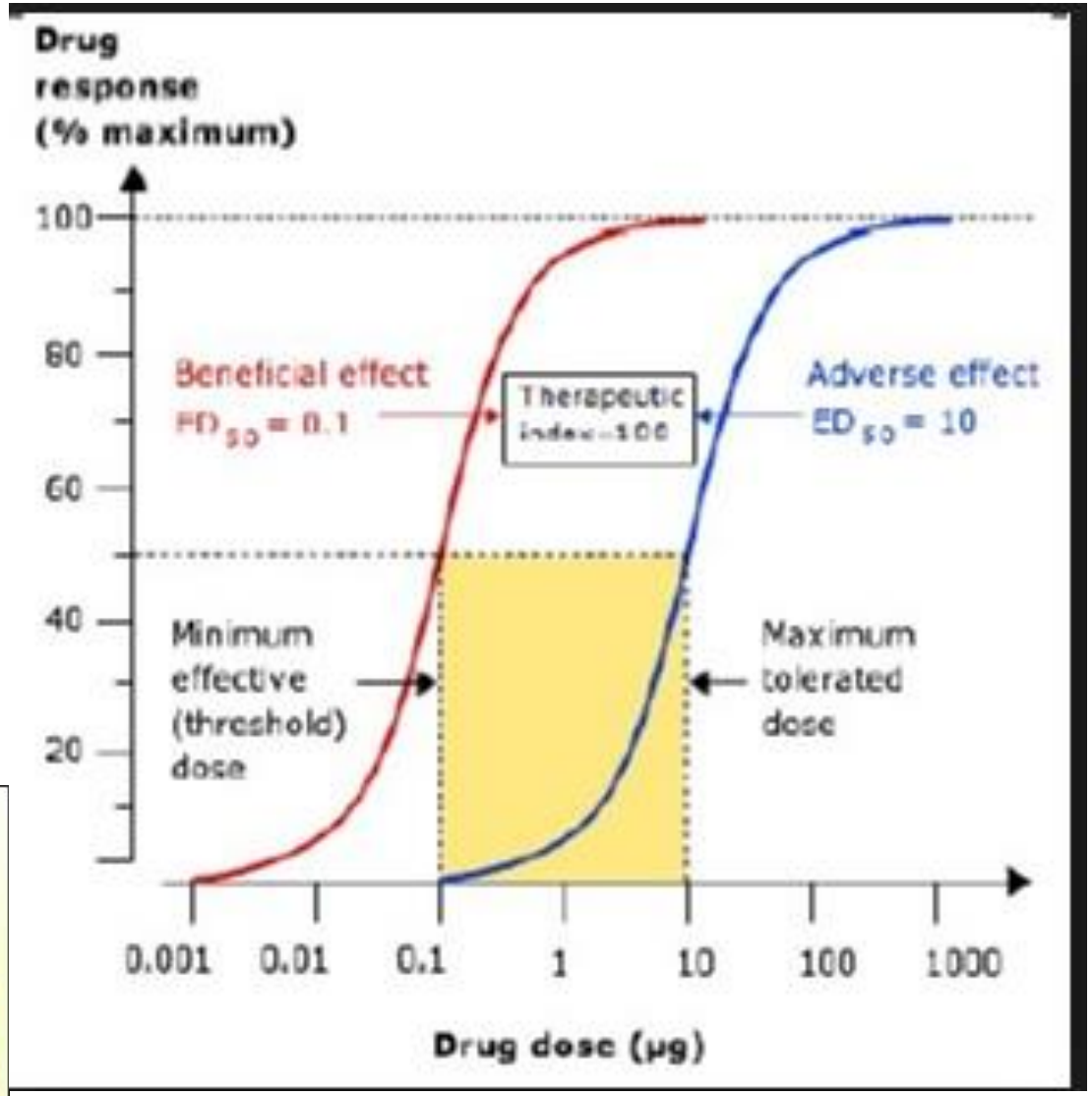
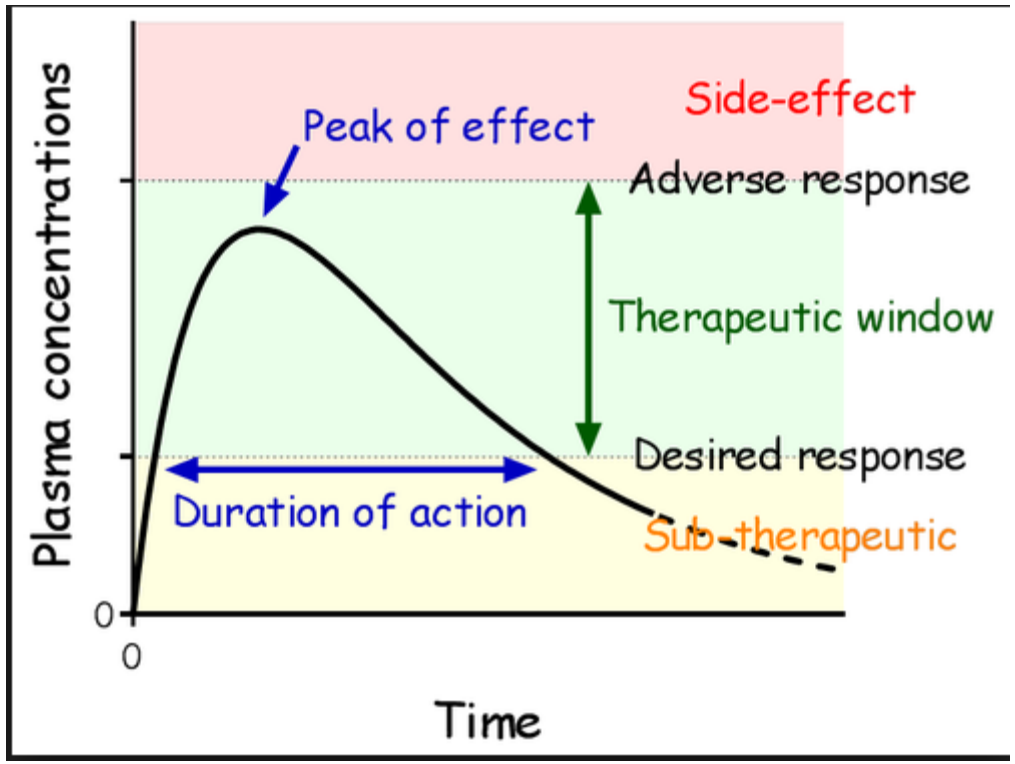
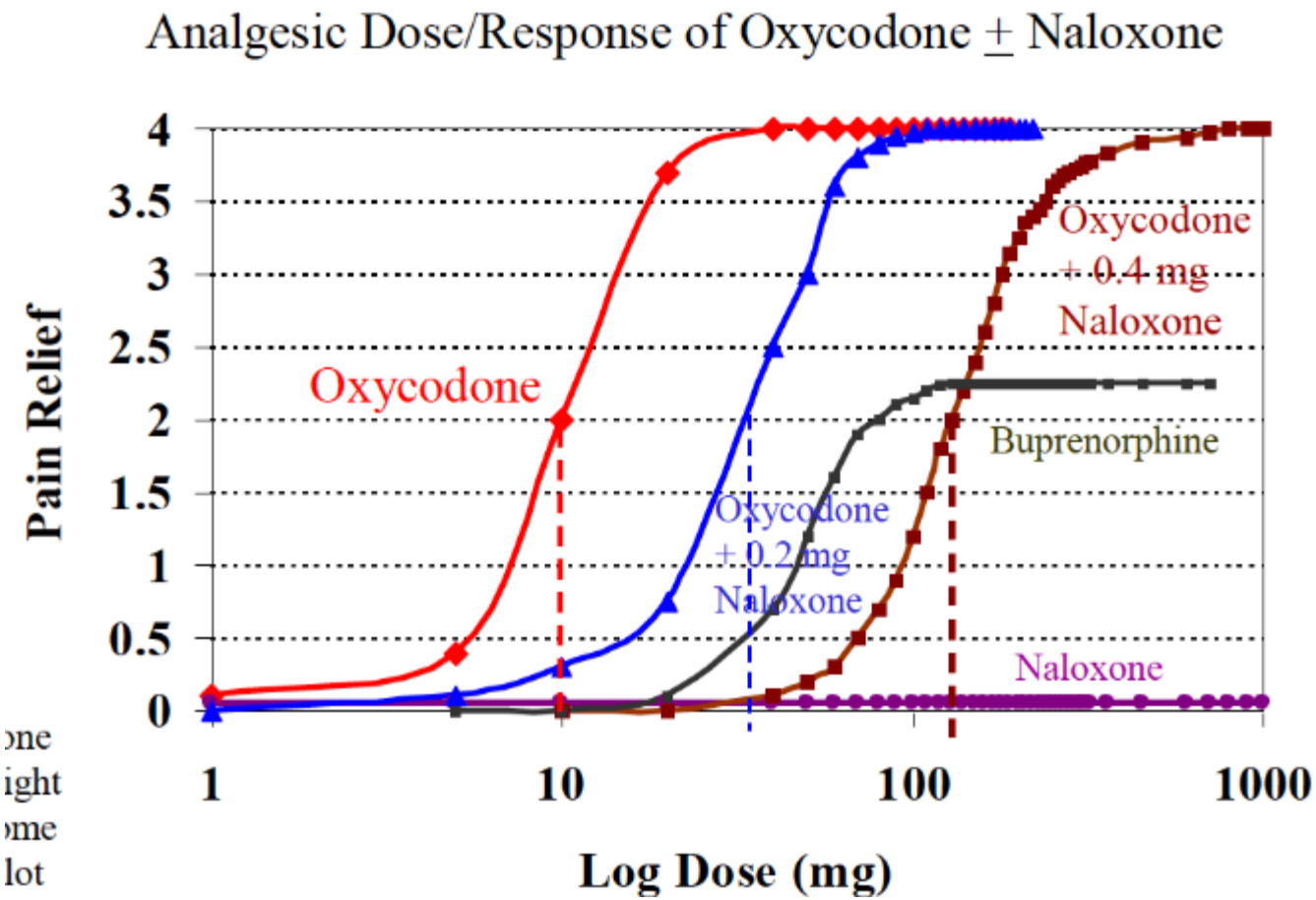

Dose Response Relationship
"Response" Changes as Function of "Dose"
Response
log[Dose]


Monotonic Curve
Monotonic Curve
Non-monotonic Curve
Non-monotonic Curve
Response
Dose


Drug response (% maximum)
100
80
60
40
20
Beneficial effect
ED50 = 0.1
Therapeutic index=100
Adverse effect
ED50 = 10
Minimum effective (threshold) dose
Maximum tolerated dose
0.001
0.01
0.1
1
10
100
1000
Drug dose (µg)


Plasma concentrations
Peak of effect
Side-effect
Adverse response
Therapeutic window
Desired response
Duration of action
Sub-therapeutic
0
0
Time


Analgesic Dose/Response of Oxycodone ± Naloxone
Pain Relief
4
3.5
3
2.5
2
1.5
1
0.5
0
Oxycodone
Oxycodone + 0.4 mg Naloxone
Buprenorphine
Oxycodone + 0.2mg Naloxone
Naloxone
1
10
100
1000
Log Dose (mg)

- Acute exposure is a single exposure – or multiple exposures occurring over 1 or 2 days.
- Chronic exposure is multiple exposures continuing over a longer period of time

Systemic/Organ toxicants

- Systemic toxicant-affects entire body/many organs
  potassium cyanide-every cell and organ-interfering with the cells' ability to use oxygen.

- Organ toxicant- affect only specific tissues or organs while not producing damage to the body as a whole.
  - Benzene- primarily toxic to the blood-forming tissues.
  - Lead- three target organs: CNS, kidneys, hematopoietic system.

Mixture interaction

- Additive
- Synergistic
- Potentiation
- Antagonism (functional, chemical, receptor= physiological, chemical, pharmacological)

Mixture

- Additive effect- total pharmacological action of two or more chemicals taken together is equivalent to the summation of their individual pharmacological action (1+1=2)
- Synergism-when the effect of two chemicals is greater than the effect of individual chemicals (1+1>2) (carbontetrachloride + alcohol)
- Potentiation effect - the capacity of a chemical to increase the effect of another chemical without having the effect (Disulfiram- alcohol)
- Antagonism - opposing actions of two chemicals on the same system, inhibition of the effects (paracetamol+alcohol&barbiturates= hepatotoxicity)

TOLERANCE

- state of decreased responsiveness to a toxic effect of a chemical, resulting from previous exposure
  - dispositional tolerance; a decreased amount of drug reaching the site
  - cellular; reduced responsiveness of a tissue

Estimation of Toxic Effects

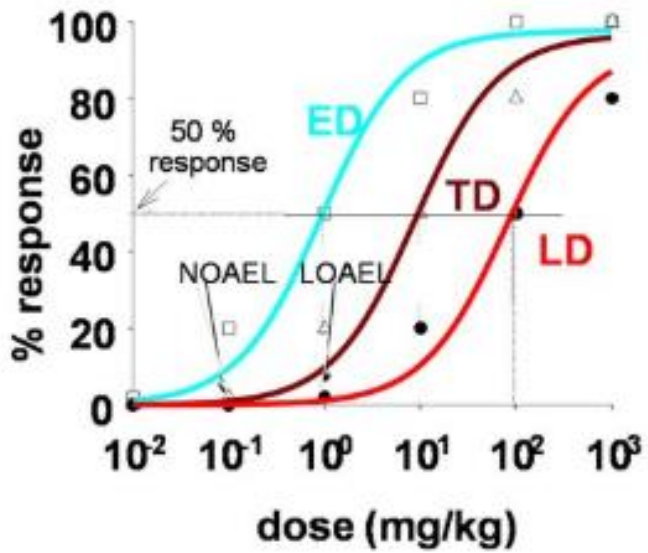
- From the dose-response curves,
  - LD50 (Lethal Dose 50%)- statistically derived dose at which 50% of the individuals will be expected to die
  - LD0 - the dose at which no individuals are expected to die. This is just below the threshold for lethality.
  - LD10- the dose at which 10% of the individuals will die.
- Effective Doses (EDs) are used to indicate the effectiveness of a substance. Usually beneficial effect (relief of pain).
- Toxic Doses (TDs) -to indicate doses that cause adverse toxic effects

Effective dose

ED0	effective for 0% of the population
ED10	effective for 10% of the population
ED50	effective for 50% of the population
ED90	effective for 90% of the population

Toxic dose

TD0	toxic to 0% of the population
TD10	toxic to 10% of the population
TD50	toxic to 50% of the population
TD90	toxic to 90% of the population



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

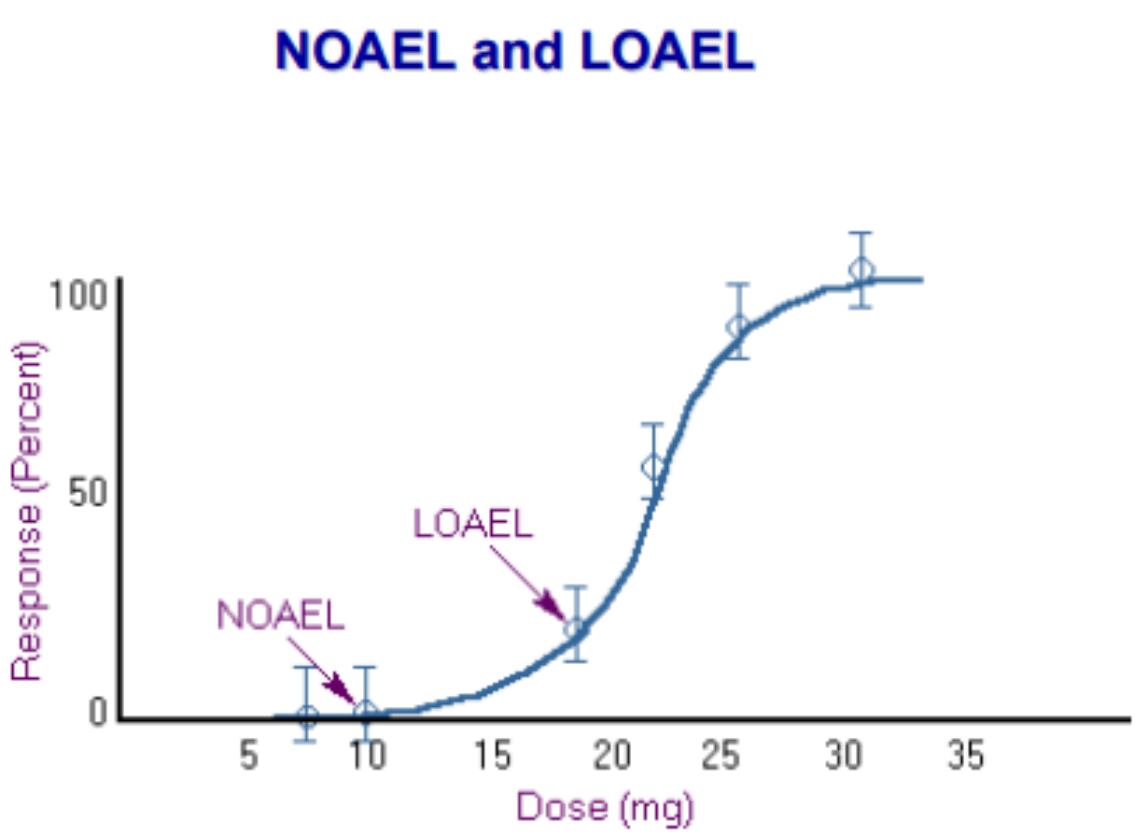
LOAEL: lowest observed adverse effect level

ED_{50}: dose at which 50% of population therapeutically responds.

(In this example, ED_{50}=1 mg/kg)

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

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



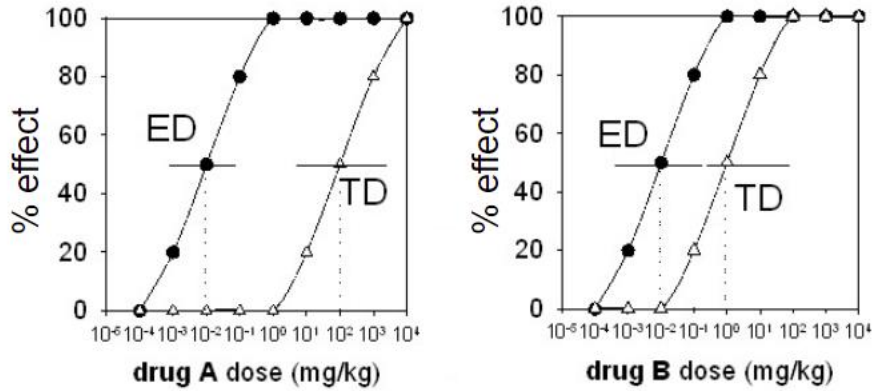
- No Observed Adverse Effect Level (NOAEL) and Low Observed Adverse Effect Level (LOAEL)
- Actual data points
- NOAEL, LOAEL, NOEL, and LOEL have great importance in the conduct of risk assessments.

Therapeutic Index (TI)

- Therapeutic Index (TI)

$$TI = LD_{50}/ED_{50}$$

or $$TI = TD_{50}/ED_{50}$$



- Comparative toxicity- relatively safe
- Larger ratio- greater the relative safety
- Meanwhile- TI does not take into account of the slope of DR curve

Margin of Safety

- Margin of safety= LD1/ED99 or TD1/ED99

Toxic Potency

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

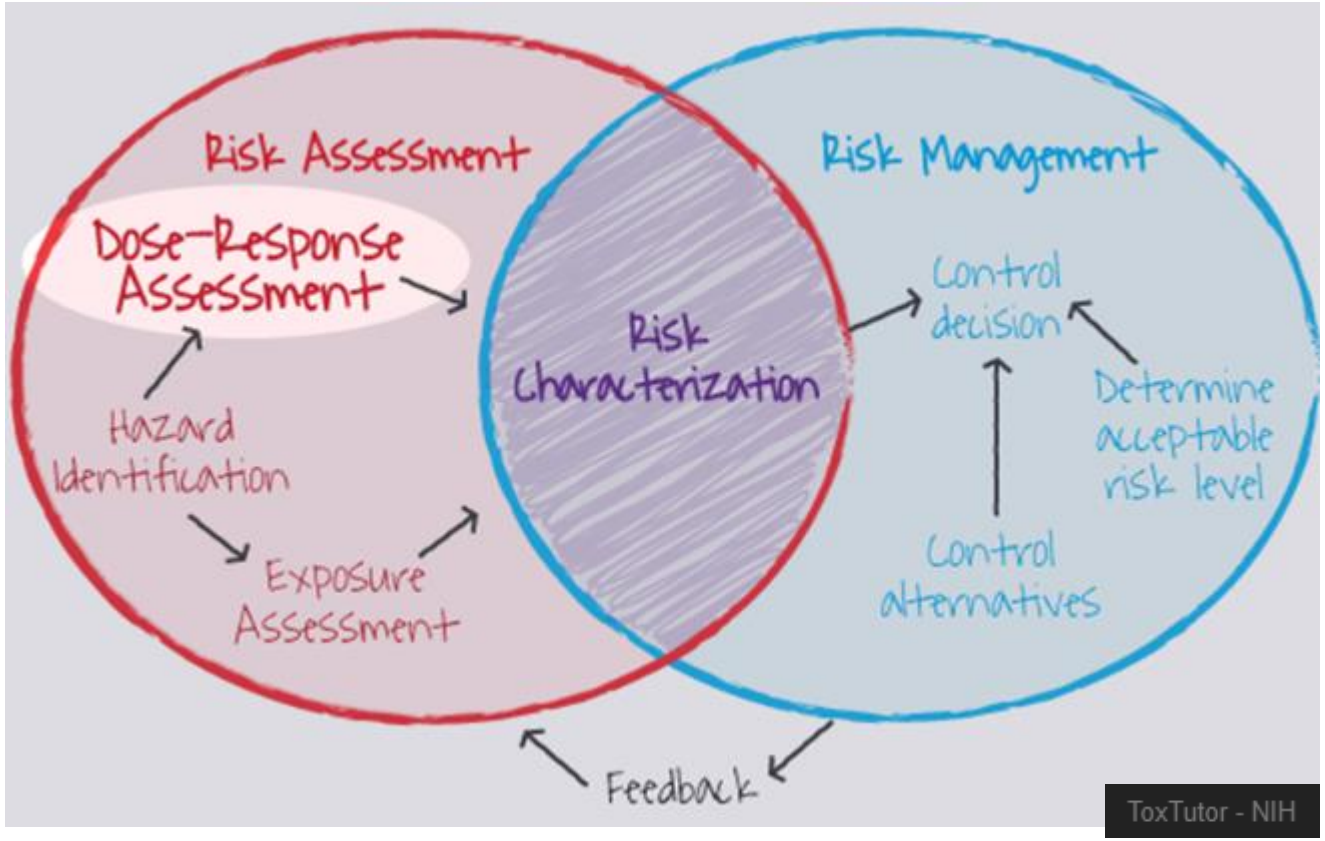
Hazard –likelihood that injury will occur in a given situation or setting

the conditions of use

exposure

Risk – is defined as the expected frequency of the occurrence of an undesirable effect arising from exposure to a chemical or physical agent

RISK RESEARCH	RISK ASSESSMENT	RISK MANAGEMENT	RISK COMMUNICATION
Understand the mechanistic linkage btw Sources of toxicants, exposure, doe-response	-Hazard identification -Dose Response Assessment -Exposure Assessment -Risk Characterization -Identiciation of Research Needs	- Decisions from the results of risk characterization, public health, economic consideration	- Communicate the risk process and risk characterization to risk holders


Risk Assessment
Dose-Response Assessment
Hazard Identification
Exposure Assessment
Risk Characterization
Risk Management
Control decision
Determine acceptable risk level
Control alternatives
Feedback
ToxTutor - NIH

Toxicokinetic and Toxicodynamics

- Toxicokinetics -absorption, distribution, biotransformation (biotransformation) and excretion of chemicals.
- Toxicodynamics -biochemical and physiological effects of chemicals to the body and mechanisms of their actions.

Concerning the oft forgotten wherefore of toxicology:

And even in our times it is said, venomous animals poison the water after the setting of the sun, so that the good animals cannot drink of it, but in the morning after the sunrise, comes the unicorn and dips his horn into the stream driving away the poison from it . . . this I have seen for myself.

—*John of Hesse*