Mechanisms of blood toxicity

Dr. Muhammed Malik Al-Ani

Mechanisms of toxicity

- Inhibition of oxygen transport
- Inhibition of electron transport chain
- Irritating, corrosivity
- Inhibition of enzymes
- Penetrating lipid structures, predominantly in the CNS
- Carcinogenic activity
- Teratogenic activity
- Radical damage
- Block of neurotransmission

The effect depends on:

- Physical and chemical properties of the substance:
  - state, solubility…
- Exposure:
  - dose, concentration, duration …
- Organism:
  - sex, age, condition…

1) Inhibition of oxygen transport

- **CO**:
  - produced by the **incomplete burning** of organic compounds.
  - binds to hemoglobin (⇒ carboxyhemoglobin) with higher affinity than oxygen, thus delaying the transport of oxygen
  - symptoms: at 30-40% of HbCO – headache, dizziness, unconsciousness; at 60-65% of HbCO – coma
  - intervention: mechanical ventilation (oxygen displaces CO)

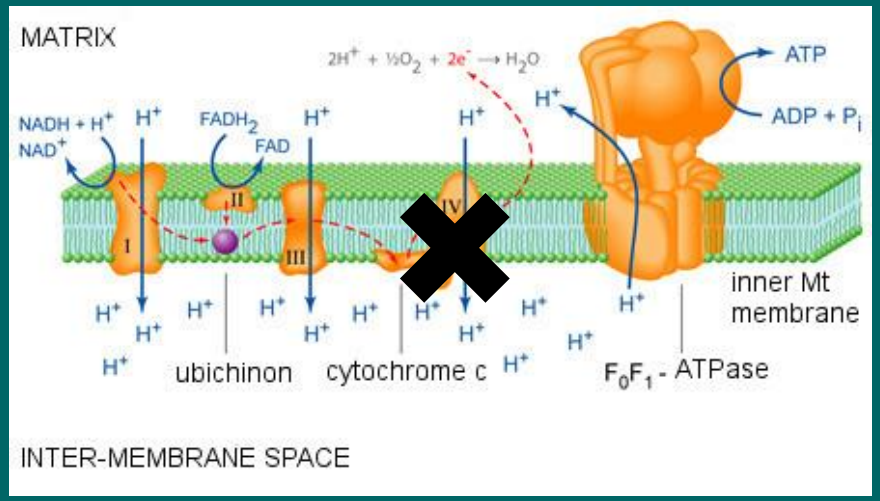
Poisons forming methemoglobin:

- nitrites, derivatives of aniline, certain drugs (esters of HNO_3)
- Fe^{2+} in the molecule of Hb is oxidized to Fe^{3+} $\Rightarrow$ Hb is converted to methemoglobin which is unable to bind O_2
- symptoms: cyanosis
- treatment: toluidine blue:
  - speeds up the reduction of MetHb to Hb

. Cl^-

2) Inhibition of electron transport chain

- **HCN and cyanides**:
  - inhibition of enzymes containing iron, predominantly of cytochrome oxidase



  - symptoms: headache, unconsciousness, respiratory failure
  - treatment: metals that bind CN.

3) Irritating gases

- **Cl_2, HCl, HF, halogen derivatives** – some of them are used as tear gases
  - irritate the mucous membranes in the eyes, nose, mouth and lungs: react with –SH groups of proteins
  - symptoms: conjunctivitis, rhinitis, bronchitis, sometimes even pulmonary edema.

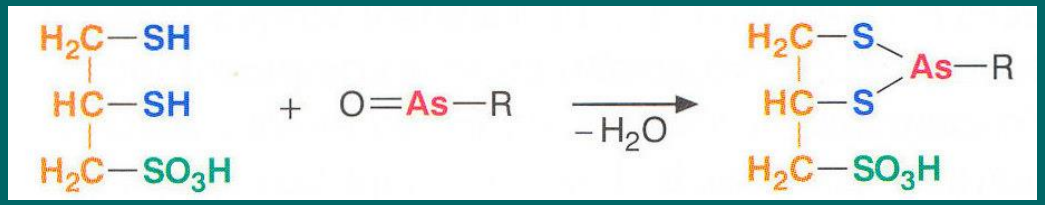
4) Inhibition of enzymes

- **HCN** – …..
- **H_2S**:
  - forms insoluble sulfides with transition metals, especially iron
    $\Rightarrow$ inhibits cytochrome oxidase and electron transport chain
  - symptoms: respiratory difficulties, circulation failure
- **α-amanitin**:
  - poison of „death cap“
  - inhibits RNA-polymerase
    $\Rightarrow$ liver damage, heart and kidney failure

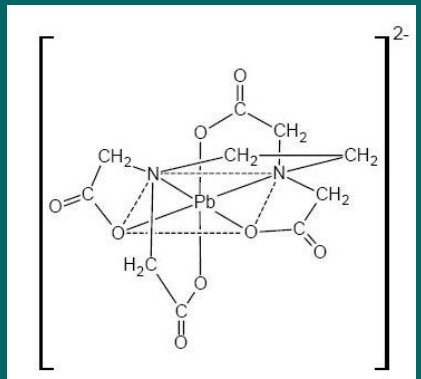
- **Metals**:
  - react with –SH groups of enzymes
  - e.g. lead inhibits enzymes participating in the synthesis of porphyrin, and thus hematopoiesis
  - metals can accumulate in the liver, kidney, and bones
  - symptoms: glomerular nephritis, neurological symptoms, a grey line along the gum (lead, mercury), anemia (lead)

Antidotes for metals

- Bind metals into stable, non-toxic complexes:
  - compounds containing –SH groups, e.g. derivatives of **dimercaprol**:



  - **EDTA**:



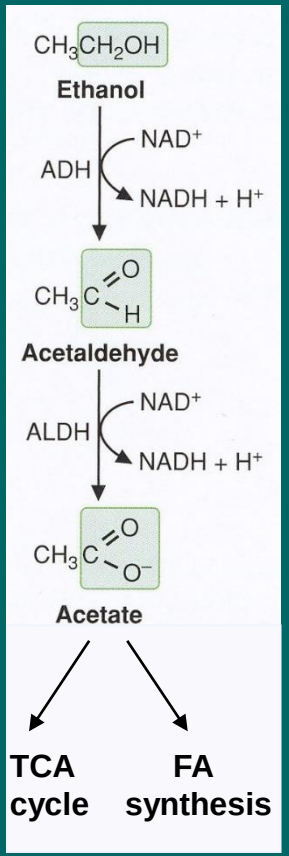
5) Corrosivity, acidosis

- **Acids:**
  - **local effects** (hydrolysis of biomolecules, protein coagulation)
  - moreover, **intake of H^+ can cause acidosis**: fall of blood pH
    - compensation: hyperventilation, ↑ tubular secretion of H^+
    - treatment: neutralization using MgO
- **Bases**: tissue damage is more severe than by acids.
  - treatment: large volume of water acidified with a weak acid (acetic)

6) Organic solvents: penetrating the membranes

- Organic solvents can easily penetrate lipid structures of the cell
- In CNS, they act as anesthetics, sedatives, and hypnotics, they can cause excitation, inhibition, as well as neurotoxicity
- **Halogen derivatives**
  - chloroform, vinyl chloride
  - they can also damage the liver and kidney

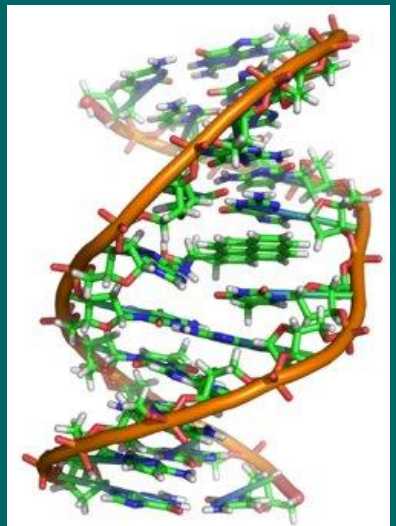
- **Ethanol**:
  - readily gets into CNS
  - interacts with membrane proteins, i.e. with ion channels
  - short-term effects: depresses inhibition control in the brain ⇒ mood swings, impaired motor and sensory function
  - chronic abuse ⇒ cirrhosis, brain damage
  - alcoholism treatment: disulfiram (antabuse)



7) Carcinogens

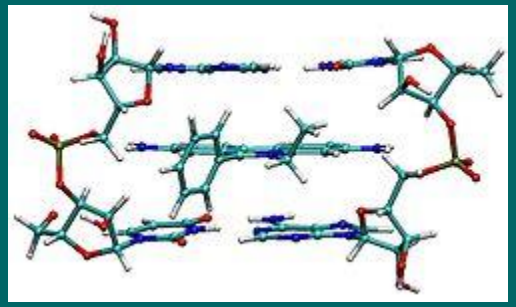
- Involved in causing cancer
- Often require prior metabolic transformation to become carcinogenic…metabolic activation
- Usually electrophiles ⇒ attack nucleophilic groups of NA and proteins ⇒ damage of cellular macromolecules

a DNA adduct of benzo[a]pyrene



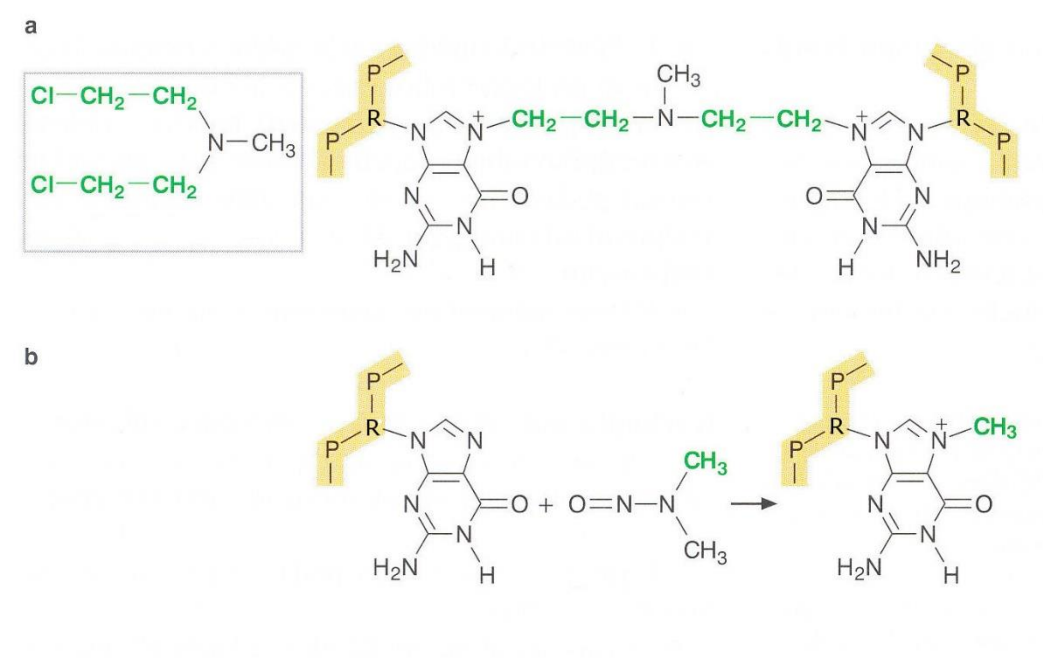
Damage to DNA

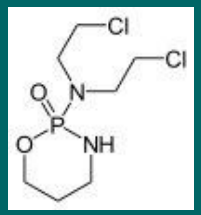
- Mutations – can be caused by:
  - alkylating agents.
  - DNA crosslinkers.
  - DNA intercalating agents – usually cationic planar (aromatic)
  - compounds that form DNA adducts
- Some of these agents can also inhibit transcription and replication



Types of carcinogens

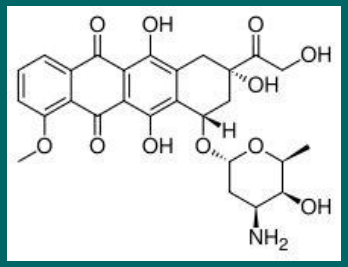
- **Alkylating agent**: inhibit cell division ⇒ some of them are used as antineoplastic drugs (cyclophosphamide)



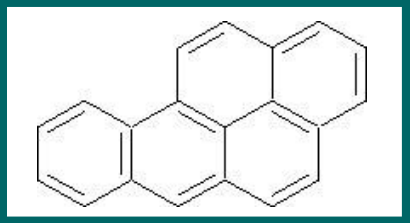


cyclophosphamide

- **Polycyclic aromatic hydrocarbons** (PAHs):
  - often activated by biotransformation → intercalation, adduct formation…



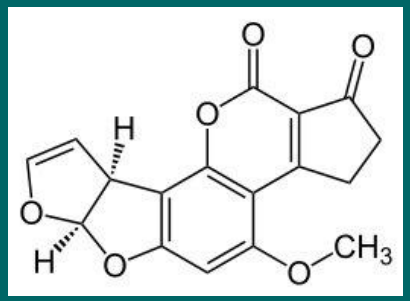
doxorubicin – used in cancer chemotherapy



benzo[a]pyrene

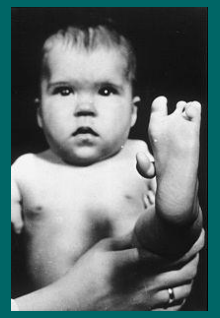
- **Inorganic substances**: arsenic, chromium salts, asbestos:
  - Asbestos = silicate minerals exploited commercially; dust inhalation → phagocytosis, pulmonary fibrosis → carcinoma

- **Naturally occurring compounds**:
  - aflatoxin produced by *Aspergillus flavus* (a fungus, contaminating peanuts, cereals…)



8) Teratogenic agents

- Impair fetal development (depends on developmental stage)
- Most of the **carcinogens** listed above, certain **drugs**
  - Thalidomide (Contergan): birth defects



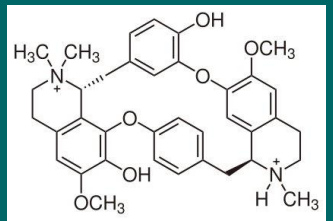
- Potential mechanism:
  - folate antagonism
  - endocrine disruption
  - oxidative stress
  - receptor- or enzyme-mediated teratogenesis

9) Damage by reactive species

- Compounds increasing the formation of reactive oxygen species (ROS): H_2O_2, OH•, $O^{\bullet -}$ $\Rightarrow$
  - peroxidation of membrane lipids
  - oxidation of amino acids in proteins
  - damage to DNA
- **Paraquat**: herbicide, impairs transport of electrons in the electron transport chain and stimulates ROS formation
  - $\Rightarrow$ damage to the liver, kidney, and lung

10) Block of neurotransmission

- Plant as well as animal toxins
  - **snake venoms**:
    - α-bungarotoxin – binds to the acetylcholine receptor at the neuromuscular junction, causing paralysis, respir. failure
  - **tetrodotoxin** – concentrated in internal organs of members of the order Tetraodontiformes (fish); blocks Na^+ channels $\Rightarrow$ paralysis of the diaphragm, respiratory failure
  - **curare**: alkaloid; blocks neuromuscular transmission $\Rightarrow$ paralysis of the respiratory muscles



Thank you

ACUTE TOXICITY STUDY

DETERMINATION OF LD50

Dr. Muhammed Malik Al-Ani

Type of toxicity

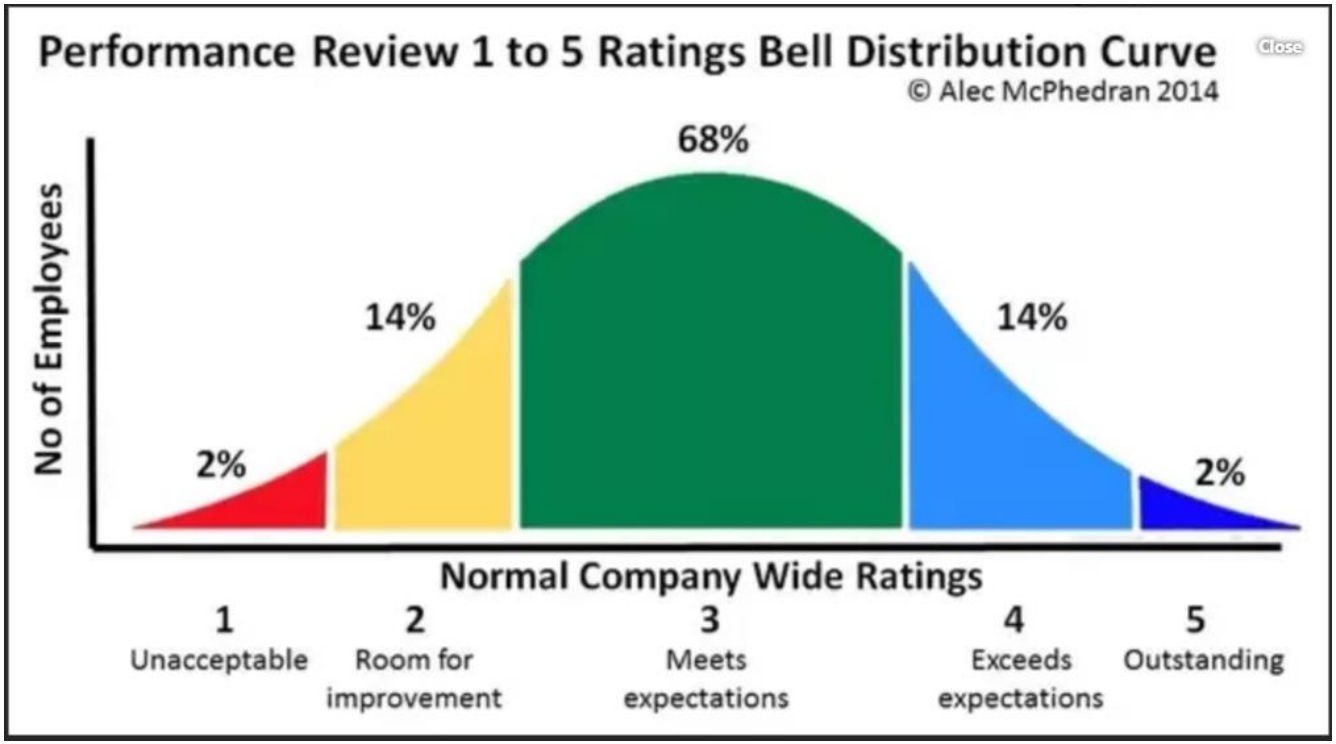
They can be divided according to the dose and period of exposure

1- Acute toxicity: sudden violent syndrome caused by single large dose of toxicant with high mortality and sever toxic symptoms.

2- Sub acute toxicity: repeated large toxic doses for a period less than one month, with sever toxic symptoms and some mortality.

3- Sub chronic toxicity: repeated moderated to low toxic doses for a period less than three months with moderated toxic symptoms.

4- Chronic toxicity: Long term condition by repeated small doses for a period more than three months with or without any toxicity symptoms, its used to study carcinogenicity and accumulation.


Performance Review 1 to 5 Ratings Bell Distribution Curve
© Alec McPhedran 2014
No of Employees
68%
14%
14%
2%
2%
Normal Company Wide Ratings
1
Unacceptable
2
Room for improvement
3
Meets expectations
4
Exceeds expectations
5
Outstanding

LD50 : MEDIAN LETHAL DOSE

- LD 50 is the amount of a material, given all at once, which causes the death of 50% of a group of test animals.
- The LD 50 is one way to measure the short-term poisoning (acute toxicity) of a material.

- It is an index to determination of medicine and poison's virulence. The lower LD 50 dose, the more toxic.
- It is usually expressed as the amount of chemical administered (e.g. in mg) per 100 gm (for smaller animals) or per kg (for bigger test subjects) of the body weight of the test animal.
- The LD 50 can be found for any route of entry or administration **but dermal & oral** administration methods are the most common.

ED50 :

- ED 50 : Is a medical term that stands for "**effective dose**“
- The 50 stands for 50 percent, which is the amount of people who experience a positive therapeutic effect of the treatment in order to be deemed to be effective.
- ED 50 is occasionally used to describe the effectiveness of drugs, most often it's used in radiology to describe the effects of radiation treatment.

DRUG VARIABILITY & TOXICITY ASSESMENT:

- ED 50 : Effective dose for 50% of the subject.
- LD 50 : Lethal Dose for 50% of subject.
- The Therapeutic Index : TI= LD 50 /ED 50
- **No drug is 100% safe.**

Significance:

1. To compare the toxic potency or intensity of different chemicals.
2. One way is to carry out lethality testing by measuring how much of a chemical is required to cause death.
3. This type of test is also referred to as a "QUANTAL" test because it measures an effect that "OCCURS" or "DOES NOT OCCUR".

4. As an aid in developing emergency procedures in case of a major spill or accident.
5. To help develop guidelines for the use of *appropriate safety clothing and equipment*.
6. For the development of transportation regulations.
7. As an aid in establishing occupational exposure limits.
8. As a part of the information in Material Safety Data Sheets.

- LD50 gives a measure of the immediate or acute toxicity of a chemical in the strain, sex, and age group of a particular animal species being tested.

- **Two most common scales are used:**

1. Hodge and Sterner Scale
2. Gosselin, Smith and Hodge Scale

Hodge and Sterner Scale:

Toxicity Rating	Commonly used term	LD50 (Rat , Oral)
1	Extremely Toxic	Less than 1 mg/Kg
2	Highly Toxic	1-50 mg/Kg
3	Moderately Toxic	50-500 mg/Kg
4	Slightly Toxic	500-5000 mg/Kg
5	Practically Non Toxic	>5000 mg/Kg

Gosselin, Smith and Hodge Scale

Toxicity Rating or Class	Dose	For 70-kg Person (150 lbs)
6 Super Toxic	Less than 5 mg/kg	1 grain (a taste - less than 7 drops)
5 Extremely Toxic	5-50 mg/kg	4 ml (between 7 drops and 1 tsp)
4 Very Toxic	50-500 mg/kg	30 ml (between 1 tsp and 1 fl ounce)
3 Moderately Toxic	0.5-5 g/kg	30-600 ml (between 1 fl oz and 1 pint)
2 Slightly Toxic	5-15 g/kg	600-1200 ml (between 1 pint to 1 quart)
1 Practically Non-Toxic	Above 15 g/kg	More than 1200 ml (more than 1 quart)

COMMON STEPS PERFORMED IN ALL TESTS:

1. The test substance must administered in **graduated doses** to several groups of experimental animals.

2. **Two species** must select- one rodent & other non-rodent, because species differ in their response to toxic agents. Ruminant

3. The substance used in toxicity tests should be as **pure** as the material eventually to be given to humans.

4. The volume of dose administered depends on the size of the test animal. **In rodents** it should not exceed 1ml/100g body wt. and max. of 50 mg/kg.

5. The LD50 value depends on the route of administration. Usually the value are found to increase with the following sequence of routes:

intravenous< intraperitoneal < subcutaneous< oral

What is the difference between a toxic and a non-toxic substance?

- **Toxic substance** is any liquid, solid or gas, which when introduced into the water supply creates, or may create a danger to health and well being of the consumer. An example is Arsenic, Chlorine and snake venom.

- A non-toxic substance is any substance that may create a non-health hazard but its aesthetically objectionable.

- For example, foodstuff, such as **sugar, dog and cat food and the hormones in birth control pills.**

METHODS TO DETERMINE LD 50:

- Different methods used to determine LD 50 are as follows:

1. Karber's method.
2. Fixed dose method.
3. Reed- Muench method.
4. Miller & Tainter method.
5. Lorke method.
6. Up & down method.

UP & DOWN METHOD :

- also called as **staircase** method.

- it occur in two way:

  A- Main Test.

  B- Limit Test.

UP & DOWN method occur by two way:

1. MAIN TEST :

- This test must be performed In those situations where there is little or no information about material toxicity, or in which the test material is expected to be **toxic**.
- A single ordered dose progression in which animals are dosed , one at a time , at a minimum of 48-hour intervals.
- The first animal receives a dose a step below the level of the **best estimate of the LD50** .

- If the animal survives, the dose for the next animal is increased by a factor of (3.2 times) the original dose ; if it dies, the dose for the next animal is decreased by a similar dose progression.

2. LIMIT TEST :

The limit test is primarily used in situation where the experiment has information indicating that test material is likely to be **non-toxic** . **Such as food additive.**

is a serial test that uses a maximum of 5 animals. A test dose of 5 g or ml /kg used, after overnight fasting for rats.

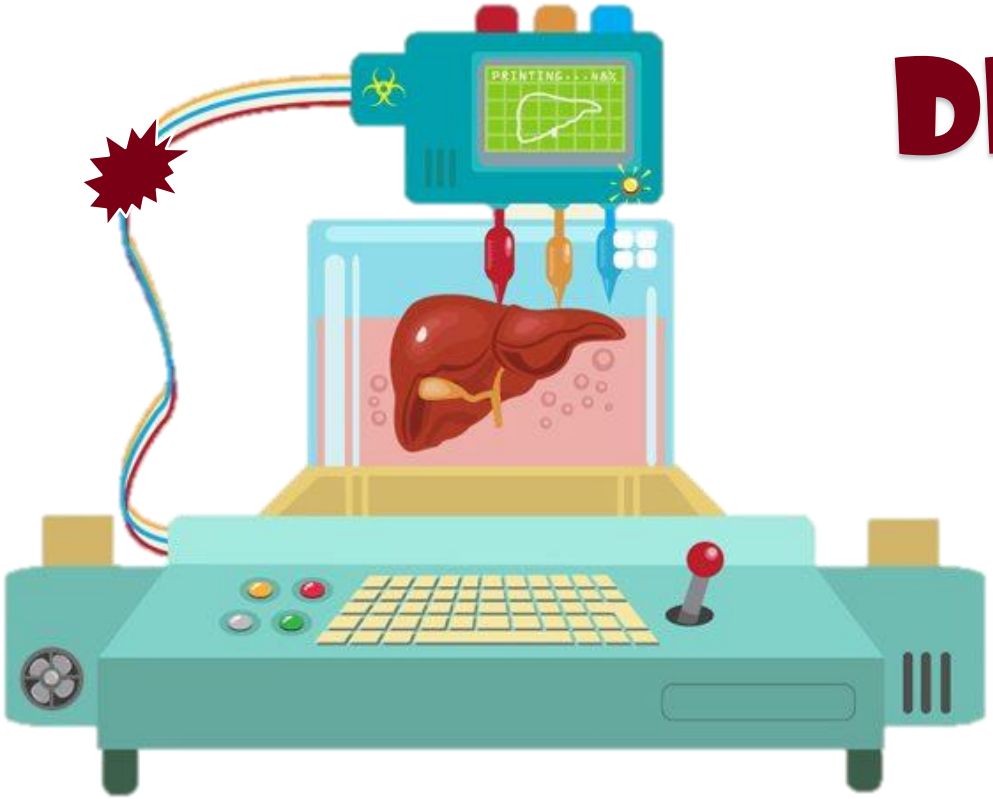
- Test animals should be observed closely for up to 14 days; symptoms of toxicity and recovery should be noted.
- Gross and histopathological examination of the test animals at the end of the study may help identify toxic effects on target organs.
- If no animals die as a result of this dose, there is no need to test higher dosages.
- The acute toxicity of the compound can then be expressed as being greater than 5 gm (or ml)/kg body weight of the test animal.

- This method is called the "limit test." In general, 5 gm or 5 ml of the test substance/kg body weight is the practical upper limit for the amount of test material that can be administered in one oral gavage dose to a rodent

Lethal Dose Table

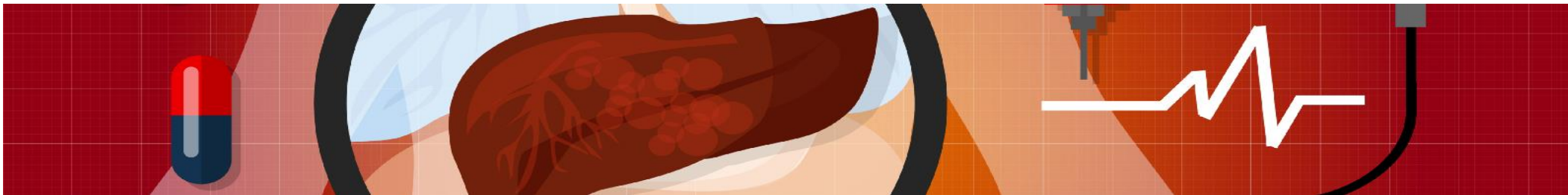
Lethal dose (LD_{50}) is the amount of an ingested substance that kills 50 percent of a test sample. It is expressed in mg/kg, or milligrams of substance per kilogram of body weight.

Common name	Toxin	Lethal doses	Description	Toxic response
Aspirin	Acetyl- salicylic acid $C_9H_8O_4$	LD_{50} 200 mg/kg (rat, oral)	Odorless white crystal	Gastric distress, confusion, psychosis, stupor, ringing in ears, drowsiness, hyperventilation
Table salt	Sodium chloride NaCl	LD_{50} 3 g/kg (rat, oral) 12357 mg/kg (human, oral)	White cubic crystal	Eye irritant, elevated blood pressure
Bleach (fumes)	Chlorine CI_2	LD_{50} 850 mg/kg (rat, inhaled)	Greenish colored gas, amber liquid, pungent odor	Corrosive to eyes, skin, respiratory tract, nausea, vomiting, pulmonary edema
Helium	Helium He	Not established	Odorless colorless gas	Dizziness, nausea, simple asphyxiant
Lorchel mushroom	Gyromitrin $C_4H_8N_2O$	LD_{50} 200 mg/kg (rat, oral)		Nausea, vomiting, severe liver damage, coma, convulsions
Arsenic	Arsenic, arsenic trioxide As, As_4O_6	LD_{50} 15mg/kg (rat, oral)	Grey, metallic crystals	Acute- irritates the yes, skin, respiratory tract, and nausea. Chronic convulsions, tissue legions, hemorrhage, kidney impairment
Sugar	Glucose $C_6H_{12}O_6$	LD_{50} 30 g/kg (rat, oral)	Sweet white powder	Depressed activity, gastrointestinal disturbances. If diabetic- heart disease, blindness, nerve damage, kidney damage
Iron tablets	Iron sulfate $FeSO_4$	~5 adult tablets toxic for a 3 year old	Grayish white powder	Nausea, vomiting, diarrhea, black stool, liver damage, coma
Lead	Lead Pb	Lowest published dose 450 (human, oral)	Bluish or silvery solid	Acute –headache, insomnia, joint pain. Chronic-anemia, kidney disease, reproductive and developmental toxin.
Snake venom	α-bungarotoxin $C_{338}H_{529}N_{97}O_{105}S_{11}$	Not available	Large protein molecule	Paralysis, suffocation, loss of consciousness, seizures, hemorrhaging into tissues
Cola	Caffeine $C_8H_{10}N_4O_2$	LD_{50} 140 mg/kg (dog, oral)	White odorless powder or crystals	Acute renal failure, nausea, psychosis, hemorrhage, increased pulse, convulsions
Alcohol	Ethanol C_2H_6O	LD_{50} 7060 mg/kg (rat, oral)	Colorless liquid, pleasant odor	Nausea, headache, vomiting, dizziness, nervous system depression, confusion, loss of consciousness
Vitamin A	Retinol $C_{20}H_{30}O$	LD_{50} 2000 mg/kg (rat, oral)	Yellow crystals, orange solid	Convulsions, unconsciousness, reproductive toxin



DRUG TOXICITY ON LIVER

Dr. Muhammed Malik Al-Ani



Objectives:

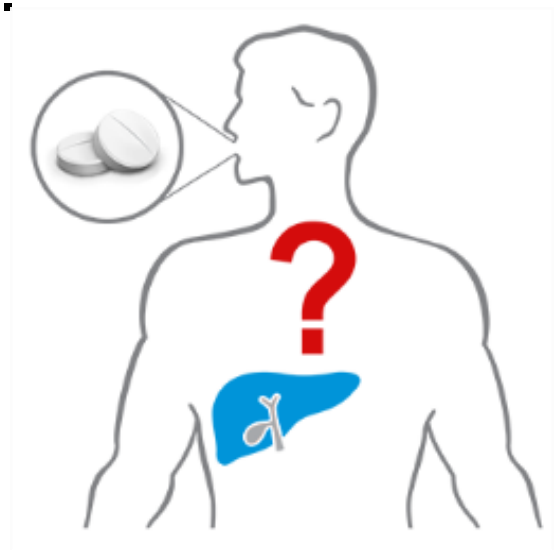
- Liver is a major biotransforming and elimination organ
- Drug-drug interactions occur in liver
  - May increase toxicity or reduce effect
- Drugs cause liver damage
  - Mechanism and can it be predicted?
- Liver disease that alters drug disposal (remember renal disease and drug excretion)

Hepatic Clearance of Drugs

- Liver removal of drugs/xenobiotics from blood called (Cl_H)
- Hepatic clearance is actually a very complex process due to many steps
- Can be simplified to three factors:
  - Liver blood flow.
  - Liver intrinsic clearance.
  - Fraction of drug not bound to albumin.

- **Liver Biotransformation of Drugs steps:**

Firstly, transport of drugs from blood to liver which consider a unique organ access to blood.



1. Phases of Biotransformation:
    a. Phase I (cytochromes P450)
    b. Phase II (conjugation).
    c. In some cases phase III.
2. Efflux to blood for last renal excretion.

Note: These processes exist for endogenous compounds, not just for drugs and xenobiotics

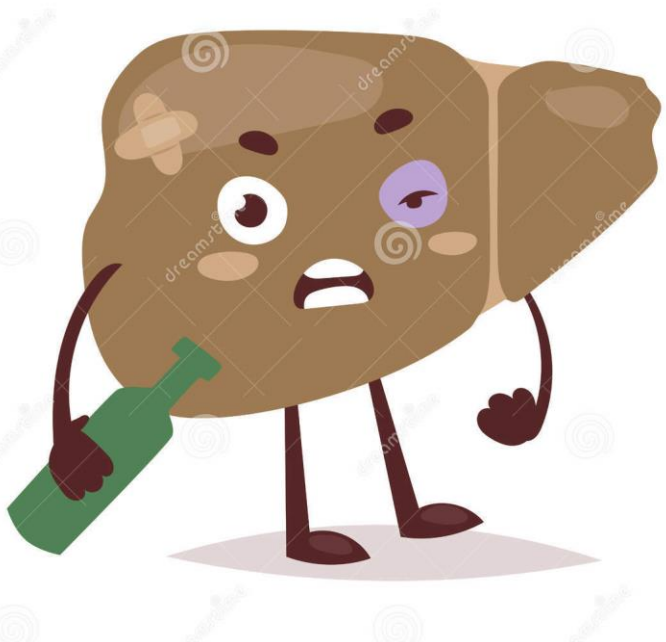
• Conjugation of drugs

- Often follow Phase I biotransformation reactions which catalyze covalent binding of drugs to polar ligands ("transferases"):
  - glucuronic acid, sulfate, glutathione, amino acids
- Endogenous examples:
  - Conjugation of bilirubin to glucuronide
  - Conjugation of bile acids to glycine/taurine

Drug Elimination

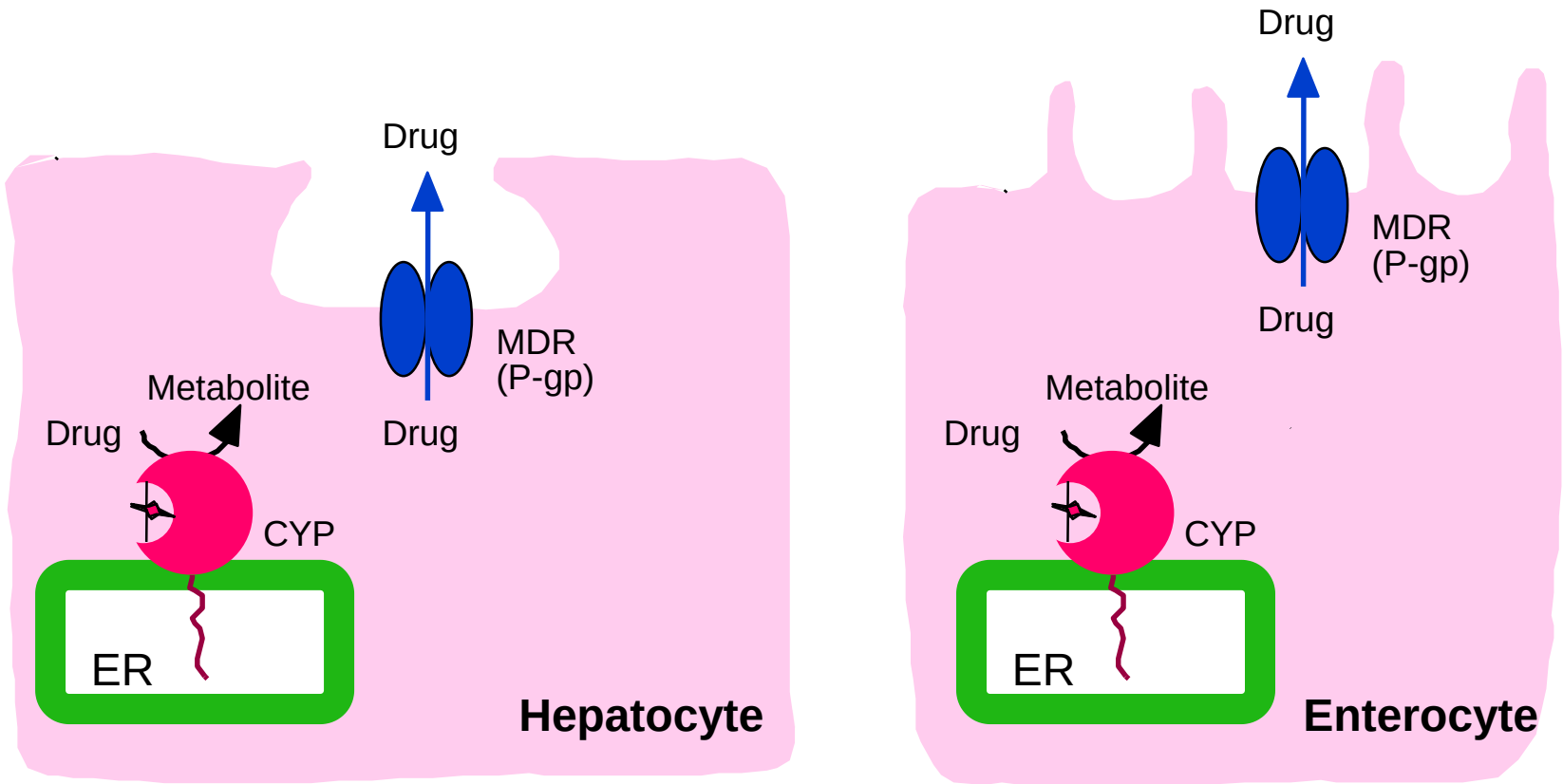
- Once drugs have been altered by Phase I and Phase II enzymes, they may be excreted by:

- Biliary Excretion
- Renal Excretion



Liver and Intestine Handling of Drugs/Xenobiotics

Not exclusive to liver: Gut may also handle drugs/xenobiotics

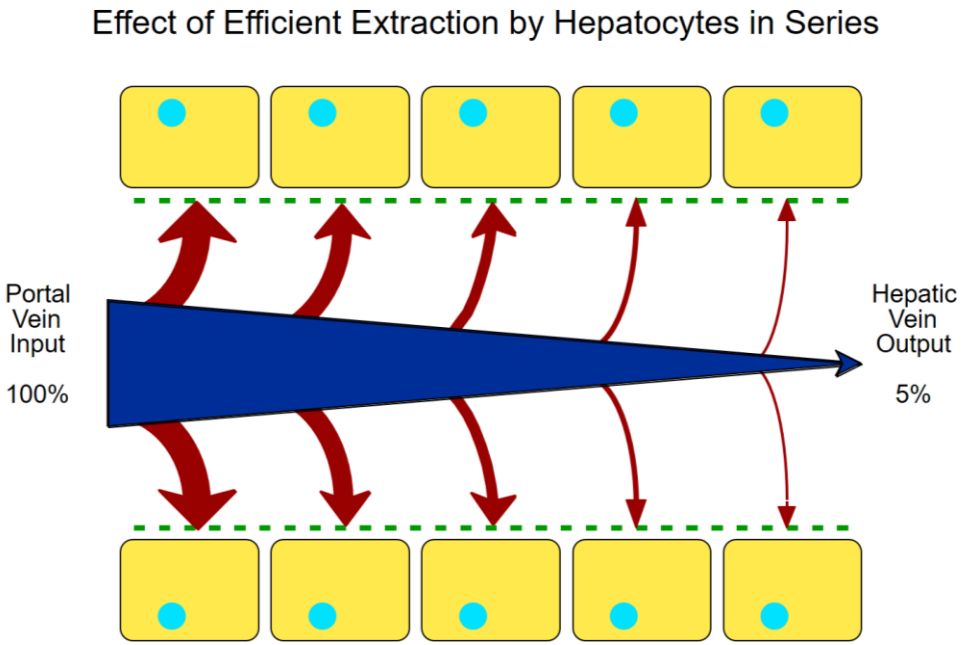


Both liver and gut can eliminate drugs by metabolism and/or apical excretion.

Reduce any or all and blood concentration will rise.

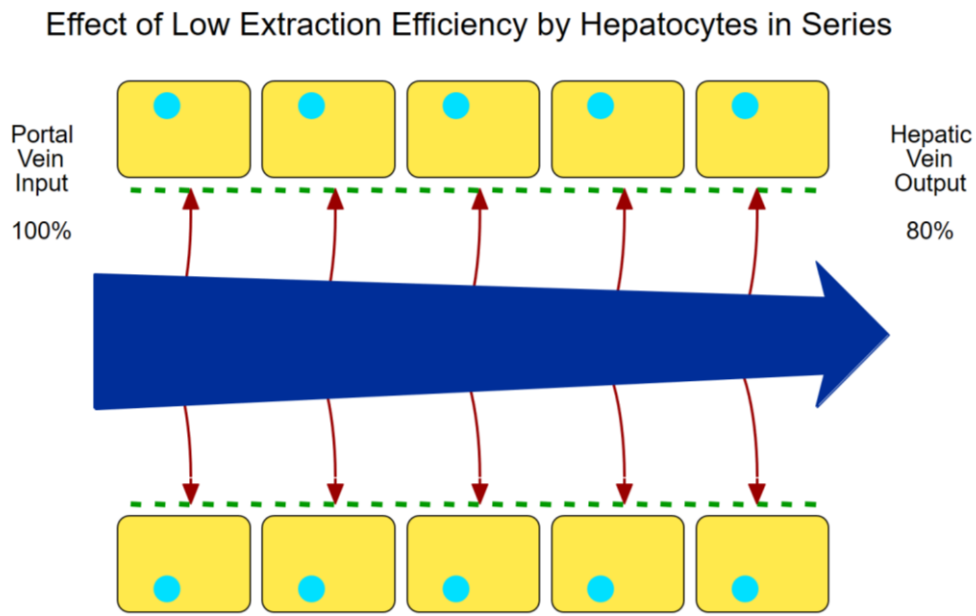
- **Type of extraction:**

A



- Nitroglycerine
- Lidocaine
- Propranolol
- Bile Acids

B

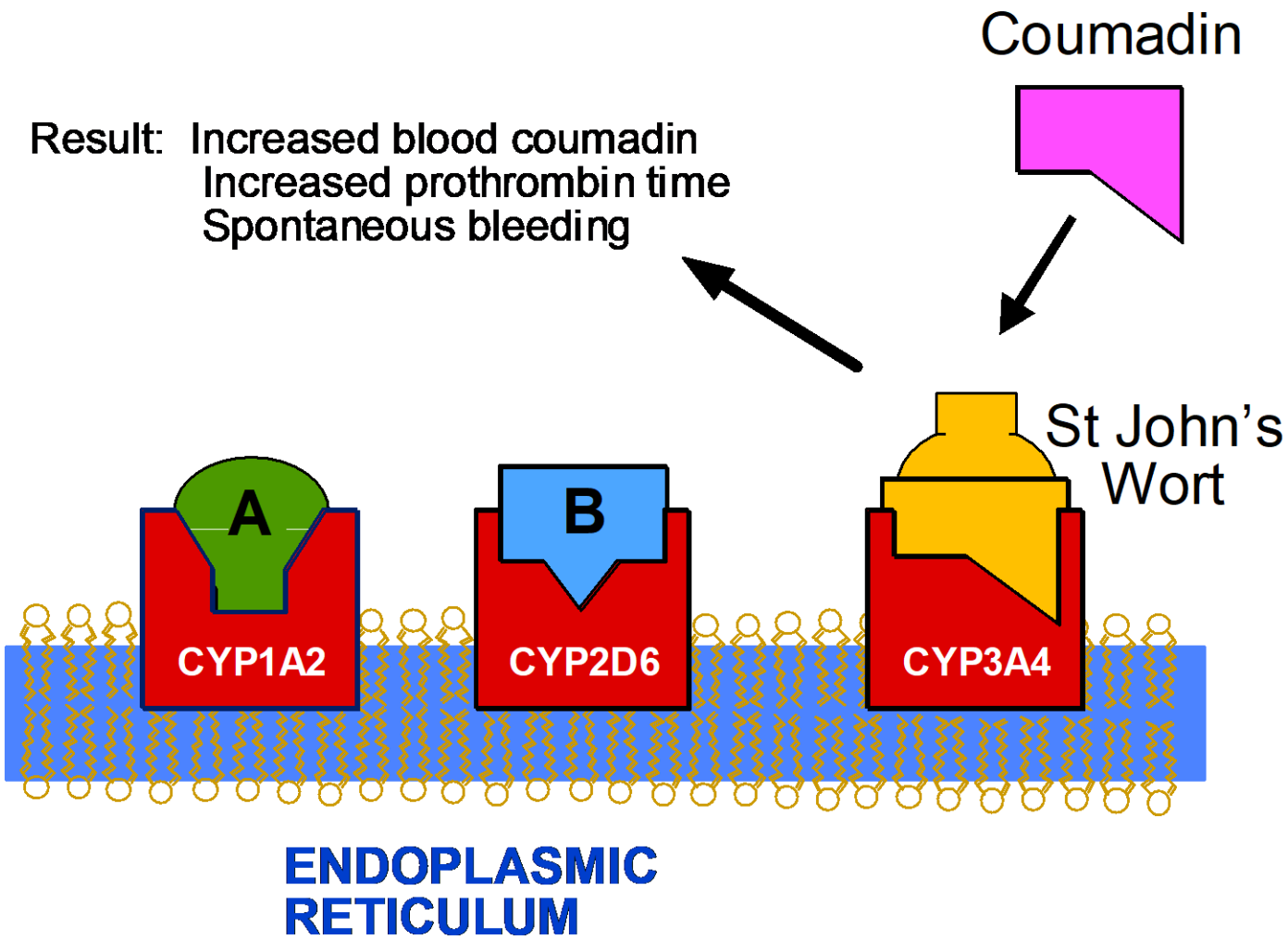


- Diazepam
- Phenytoin
- Theophylline
- Bilirubin

- **Drug-Drug Interactions:**

- Competitive inhibition of CYP
  - drug A increases toxicity of drug B
- Induction of CYP lead to:
  - increased elimination of drug
  - increased production of toxic metabolites

Drug-Drug Interactions Leading to Toxicity



• Approach to Drug-Drug Interactions

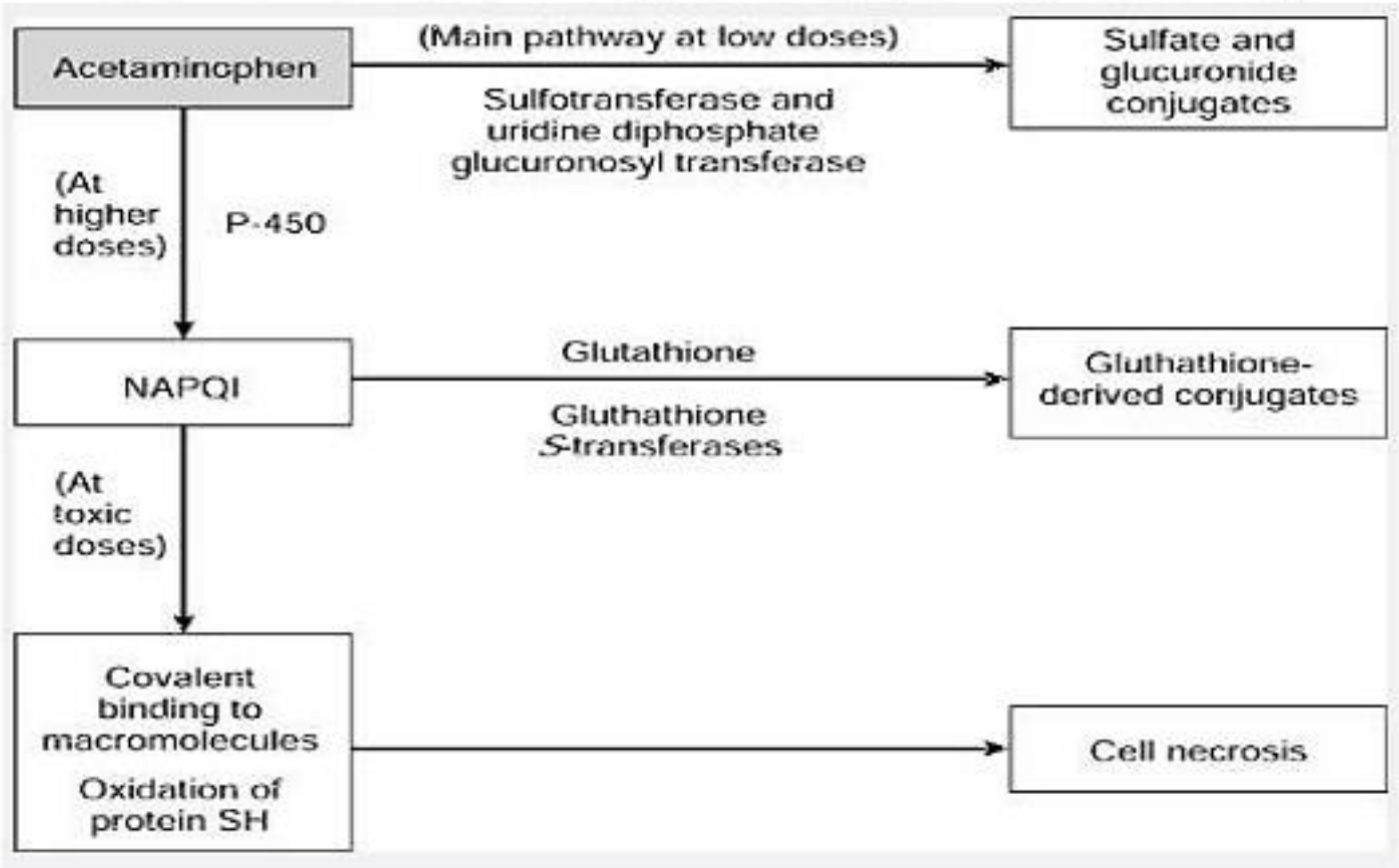
1. Be aware of the problem
2. Look up potential interactions
   - computer databases
3. Monitor blood levels of drug
4. Monitor biologic action
5. Monitor for known toxicities

• Drug-Induced Liver Disease

Type of Reaction	Effect on Cells	Examples of Drugs
Hepatocellular	Direct effect or production by enzyme–drug adduct leads to cell dysfunction, membrane dysfunction, cytotoxic T-cell response	Isoniazid, trazodone, diclofenac, nefazodone, venlafaxine, lovastatin
Cholestasis	Injury to canalicular membrane and transporters	Chlorpromazine, estrogen, erythromycin and its derivatives
Immunoallergic	Enzyme–drug adducts on cell surface induce IgE response	Halothane, phenytoin, sulfamethoxazole
Granulomatous	Macrophages, lymphocytes infiltrate hepatic lobule	Diltiazem, sulfa drugs, quinidine
Microvesicular fat	Altered mitochondrial respiration, β-oxidation leads to lactic acidosis and triglyceride accumulation	Didanosine, tetracycline, acetylsalicylic acid, valproic acid
Steatohepatitis	Multifactorial	Amiodarone, tamoxifen
Autoimmune	Cytotoxic lymphocyte response directed at hepatocyte membrane components	Nitrofurantoin, methyldopa, lovastatin, minocycline
Fibrosis	Activation of stellate cells	Methotrexate, excess vitamin A
Vascular collapse	Causes ischemic or hypoxic injury	Nicotinic acid, cocaine, methylenedioxymethamphetamine
Oncogenesis	Encourages tumor formation	Oral contraceptives, androgens
Mixed	Cytoplasmic and canalicular injury, direct damage to bile ducts	Amoxicillin–clavulanate, carbamazepine, herbs, cyclosporine, methimazole, troglitazone

- Safe, useful and widely available
- However, a little may be **good**.
- a lot may be **bad**.

Mechanism of Acetaminophen-induced Hepatotoxicty



At usual therapeutic dosages, acetaminophen is metabolized → conjugation reactions. The capacity becomes saturated at higher dosages → diversion of the drug to the P-450-mediated pathway → generates reactive electrophile N-acetyl-p-benzoquinone imine (NAPQI) → undergoes phase 2 conjugation with glutathione → glutathione depletion → allowing the electrophile to exert damaging effects within the cell via covalent binding.

Therapeutic Misadventure

- Patient uses a drug at a “safe” dose.
- But the presence of an environmental change lad to toxicity develops.
- Example: acetaminophen and alcohol

Approach to Prevention of Drug-Induced Liver Disease

Effect of Liver Failure on Drug Disposition

- Drug elimination may be reduced in patients with significant liver dysfunction - thus blood levels may be higher for longer (toxicity vs effectiveness?)
- Low clearance drugs often relatively little effect until end stage liver failure as drug metabolism is relatively well preserved

- **Approach to Drug Use in Patients with Significant Liver Dysfunction**

1. Reduce oral doses of high extraction drugs such as propranolol.
2. Monitor the biologic effect of the drug (heart rate…)
3. Monitor drug blood levels (if possible)
4. Start with low dose and titrate up to biologic effect.


Thank you

HEAVY METALS

DR. MUHAMMED MALIK

Definition

Heavy Metals: are natural components of the Earth's crust.

The term **heavy metal** refers to any metallic chemical element that has a relatively high density and is toxic or poisonous **at low concentrations**.

Some charactrastics:

- They cannot be degraded or destroyed.
- Its enter our bodies via food, drinking water and air.
- As trace elements, some heavy metals (e.g. copper,selenium, zinc) are essential to maintain the metabolism of the human body
- heavy metal poisoning could result, for instance, from drinking-water contamination (e.g. lead pipes), high ambient air concentrations near emission sources, or intake via the food chain.

Mercury - Hg

- Is the only common metal which is **liquid at ordinary temperatures**.
- It rarely occurs free in nature and is found mainly in **cinnabar** or (HgS) in Spain and Italy.
- It alloys easily with many metals, such as gold, silver, and tin - these alloys are called amalgams. Its ease in amalgamating with gold is used in the recovery of gold from its ores.

Health effects of mercury

- Disruption of the nervous system
- Damage to brain functions
- DNA damage and chromosomal damage
- Allergic reactions, resulting in skin rashes, tiredness and headaches
- Negative reproductive effects, such as sperm damage, birth defects and miscarriages

Air pollution

- Fossil fuel combustion
- Mining
- Smelting
- Solid waste combustion

Water pollution

- The application of agricultural fertilizers.
- Industrial waste water disposal

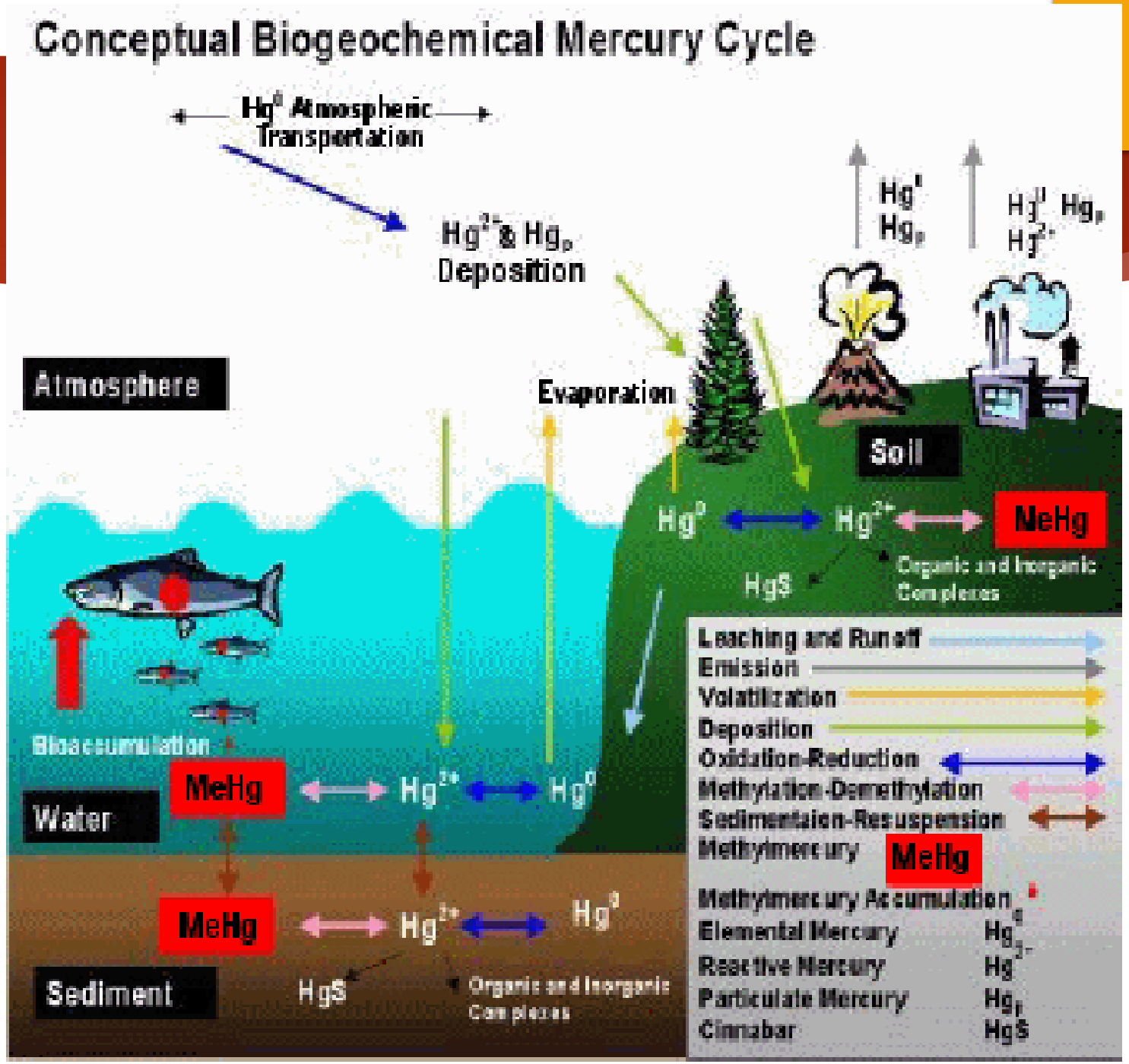
Environmental effects of mercury

- Acidic surface waters can contain significant amounts of mercury
- When the pH values are between five and seven, the mercury concentrations in the water will increase due to mobilisation of mercury in the ground.
- Once mercury has reached surface waters or soils microorganisms **can convert it to methyl mercury**, a substance that can be absorbed quickly by most organisms and is known to cause nerve damage.

Environmental effects of mercury

- **Fish** are organisms that **absorb** great amounts of **methyl mercury** from surface waters every day (**mercury can accumulate** in fish and in the food chains)
- **The effects that mercury has on animals are:** kidneys damage, stomach disruption, damage to intestines, reproductive failure and DNA alteration

Conceptual Biogeochemical Mercury Cycle



Cadmium – Cd

- Human uptake of cadmium takes place mainly through food.
- Food stuffs that are rich in cadmium can greatly increase the cadmium concentration in human bodies (liver, mushrooms, shellfish, mussels, cocoa powder and dried seaweed)

HEALTH EFFECTS OF Cd

- Diarrhoea, stomach pains and severe vomiting
- Bone fracture
- Reproductive failure and possibly even infertility
- Damage to the central nervous system
- Damage to the immune system
- Psychological disorders
- Possibly DNA damage or cancer development

Environmental effects of ca

- Cadmium can be transported over great distances when it is absorbed by sludge
- Sludge riched-Ca pollute surface waters as well as soils.
- Its strongly adsorbs to organic matter in soils.
- Soils that are acidified enhance the cadmium uptake by plants.
- This is a potential danger to the animals that are dependent upon the plants for survival – Cadmium can accumulate in their bodies.

- In aquatic ecosystems cadmium can bioaccumulate in mussels, oysters, shrimps, lobsters and fish
- The susceptibility to cadmium can vary greatly between aquatic organisms
- **Salt-water organisms** are known to be more resistant to cadmium poisoning than freshwater organisms

Chromium - Cr

- Chromium(III) is an **essential nutrient** for humans and shortages may cause heart conditions, disruptions of metabolisms and diabetes
- But the uptake of too much chromium(III) can cause health effects as well, for example: skin rashes.

- Chromium(VI) is a danger to human health, mainly for people who work in the steel and textile industry.
- People who smoke tobacco also have a higher chance of exposure to chromium

- Hexavalent Chromium – Chromium (VI) is a species of chromium that is forbidden to use in electrical & electronic industry.

HEALTH EFFECTS

- When it is a compound in leather.. products, it can cause allergic reactions, such as skin rash
- After breathing it in, chromium(VI) can cause nose irritations and nosebleeds
- Upset stomachs and ulcers
- Respiratory problems
- Weakened immune system
- Kidney and liver damage
- Alteration of genetic material
- **Lung cancer**
- Death

Environmental effects of chromium

- Most of the chromium in air will eventually settle and end up in waters or soils
- Chromium in soils strongly attaches to soil particles and as a result it will not move towards groundwater
- In water chromium will absorb on sediment and become immobile
- Only a small part of the chromium that ends up in water will eventually dissolve

Environmental effects of chromium

- Chromium(III) is an essential element for organisms that can disrupt the sugar metabolism and cause heart conditions, when the daily dose is too low
- Chromium(VI) is mainly toxic to organisms - it can alter genetic materials and cause cancer

Lead - Pb

- Foods such as fruit, vegetables, meats, grains, seafood, soft drinks and wine may contain significant amounts of lead.

- Cigarette smoke also contains small amounts of lead.

Health effects of lead

- Disruption of the biosynthesis of haemoglobin and anemia.
- Kidney damage.
- Miscarriages.
- Disruption of nervous systems
- Brain damage
- Declined fertility of men through sperm damage
- Diminished learning abilities of children
- Behavioural disruptions of children, such as aggression, impulsive behaviour and hyperactivity

- Lead can enter a foetus through the placenta of the mother.
- Because of this it can cause serious damage to the nervous system and the brains of unborn children.

That is why women in pregnancy can not work with lead.

Lead sources

- Application of lead in gasoline
- Fuel combustion
- Industrial processes
- solid waste combustion

Environmental effects of lead

- Lead accumulates in the bodies of water organisms and soil organisms
- Health effects on shellfish can take place even when only very small concentrations of lead are present
- Body functions of phytoplankton can be disturbed when lead interferes. Phytoplankton is an important source of oxygen production in seas and many larger sea-animals eat it
- That is why we now begin to wonder whether lead pollution can influence global balances

Environmental effects of lead

- Soil functions are disturbed by lead intervention, especially near highways and farmlands, where extreme concentrations may be present
- Also soil organisms are suffered from lead poisoning

Thank you

Pesticides Toxicity

Dr. Muhammad Malik Al-Ani

Definition:

- **Pesticides** are substances used to prevent, destroy, repel or mitigate any **pest** ranging from insects, animals and weeds to microorganisms such as fungi, molds, bacteria and viruses.

- Pesticides help to manage and prevent pests that spread disease, that damage crops, buildings, and other property, and that are a public nuisance.

- **Classification of pesticides according to use:**

Target pest group	Type of pesticide
Plant	**Herbicides (Bipyridyls , Chlorophenoxy)**
Algae	**Algicides (Oxyfluorfen)**
Birds	**Avicides (parathion)**
Bacteria	**Bactericides (Vancomycin..etc.)**
Fungi and oomycetes	**Fungicides (Thiocarbamates, Dithiocarbamates)**
Insects	**Insecticides (OPC, Carbamate..)**
Mites	**Miticides or acaricides (Permethrin)**
Snails	**Molluscicides (Metaldehyde)**
Nematodes	**Nematicides (Benomyl)**
Rodents	**Rodenticides (Warfarines, Indanodiones)**
Viruses	**Virucides (Acyclovire)**

- **Classification of pesticides according to toxicity: according to FDA**

Toxicity Class	Toxicity Rating	Signal Word on Label	Example
I A	Extremely dangerous	DANGER-POISON	Parathion, Dieldrin
I B	Highly dangerous	WARNING	Eldrin, Dichlorvos
II	Moderatly hazardous	CAUTION	DDT, Chlordane
III	Slightly hazardous	CAUTION	Malathion

❖ TYPE & ROUTE OF POISONING

Accidental	→	Oral
Suicidal	→	Inhalation
Homicidal	→	Dermal
Occupational	→	Eye contact

❖ BENEFITS of pesticides:

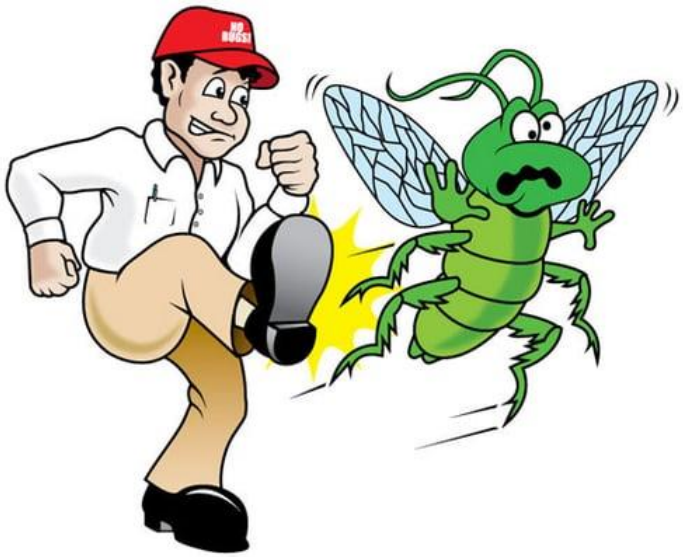
1. Crop protection
2. Food preservation
3. Material preservation
4. Disease control

❖ RISKS

1. Toxic to humans
2. Impact on environment and ecosystems.

- **General modes of action of pesticides:**

1. Disturbance in energy production
2. Inhibition of photosynthesis
3. Free radical generation & SH-group reactivity.
4. Interference with cell division
5. Inhibition of nucleic acid synthesis
6. Inhibition of enzymes: Ergosterol synthesis, Amino acid synthesis, Chitin synthesis, Cholinesterase.
7. behavior-modifying agents



Health effects and toxicity in humans

- exposure to pesticides can cause a variety of adverse health effects, ranging from simple irritation of the **skin** and **eyes** to more severe effects such as affecting the nervous system, reproductive problems, and also causing autism.
- Most studies on leukemia showed positive associations with pesticide exposure.
- There is substantial evidence of associations between organophosphate insecticide exposures and neurobehavioral alterations.

Environmental effects:

- Pesticide use raises a number of environmental concerns. Over **98%** of sprayed insecticides and **95%** of herbicides reach a destination other than their target, including:

1. Non-target species.
2. Air.
3. Water.
4. Soil.

- Pesticide drift occurs when pesticides suspended in the air as particles are **carried by wind** to other areas, potentially contaminating them.
- Pesticides are one of the causes of **water pollution**, and some pesticides are persistent organic pollutants and contribute to **soil contamination**.

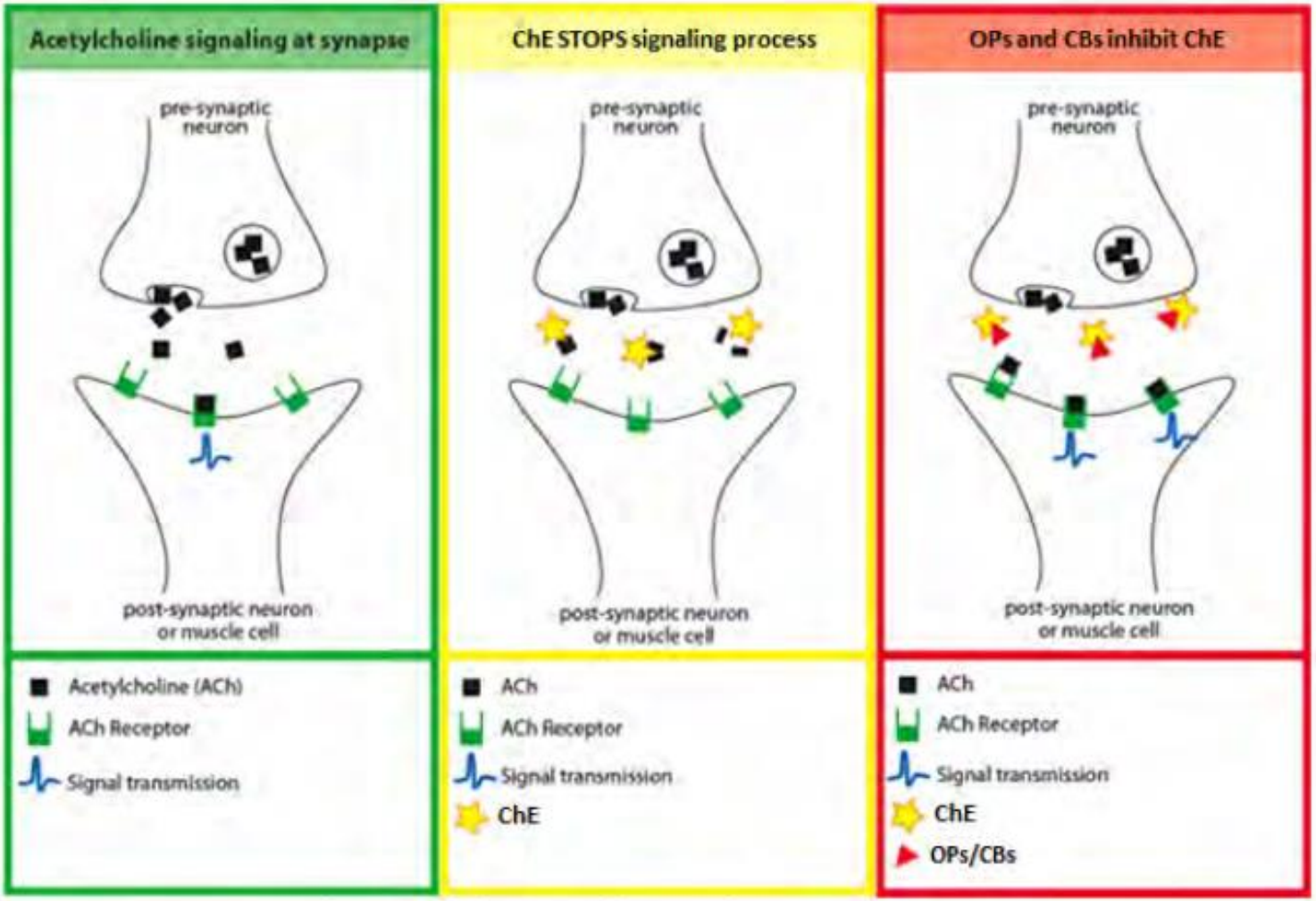
example

Insecticides: Carbamates:

- Is an organic compound derived from carbamic acid (NH2COOH). A carbamate group, carbamate ester (e.g., ethyl carbamate), and **carbamic acids are functional groups** that are inter-related structurally and often are interconverted chemically.
- They have lower dermal toxicities. Mostly absorbed via inhalation, ingestion.
- carbamates can be classified as category 4 (low hazard).

Mode of action:

- Carbamates are designed to inhibit the normal breakdown of Acetylcholine (ACh).
- ACh is nurotranmitter released in the junction between the two nerve cells (synapse) where it binds to its receptor on the target cell, inducing its activation and relaying the signal.
- Acetylcholinesterase (AChE) is an enzyme located in the intercellular space that is responsible for ACh degradation.
- OPs and CBs act by occupying and blocking the site where the neurotransmitter attaches to the ChE enzyme. This leads to the buildup of ACh and continuous stimulation of the receptors on the target cells.


Acetylcholine signaling at synapse
pre-synaptic neuron
post-synaptic neuron or muscle cell
Acetylcholine (ACh)
ACh Receptor
Signal transmission
ChE STOPS signaling process
pre-synaptic neuron
post-synaptic neuron or muscle cell
ACh
ACh Receptor
Signal transmission
ChE
OPs and CBs inhibit ChE
pre-synaptic neuron
post-synaptic neuron or muscle cell
ACh
ACh Receptor
Signal transmission
ChE
OPs/CBs

Toxicity in Rats:

- The oral LD50 of carbamates is 300 to 2000 mg/kg.
- The oral administration of **300 mg/kg** of carbamates can cause following reversible signs:

➢ various levels of immobility.

➢ Muscle tremors.

➢ prostration

➢ salivation.

➢ depression of spontaneous and provoked behavior.

➢ paralysis with extension of hind quarters.

➢ Respiratory distress.

- whereas those that occurred at the **2000 mg/kg** can be more severe and may caused rat death or cause euthanasia statue.

Management Carbamate poisoning:

Atropine:

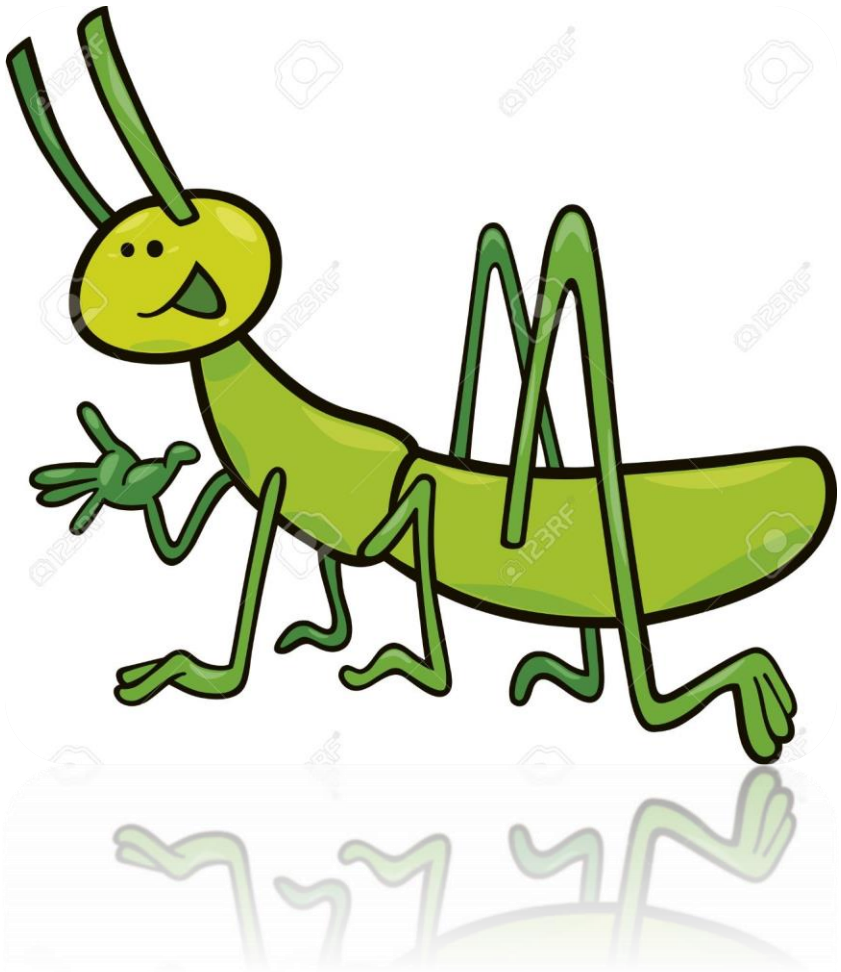
The following features of cholinergic syndrome is an indication for atropine:

1. Poor air entry in to the lungs due to bronchorrhoea and bronchospasm.
2. Excessive sweating
3. Bradycardia
4. Hypotension
5. Miosis

Initial dose: 1.8 – 3 mg, 3-5 of 0.6 mg vials rapidly IV into a fast flowing IV drip depending on the condition.

After 5 min. check the five parameters and if there is no improvement double the dose.

Thank You



General Toxicology

Dr. Muhammed Malik Al-Ani

بسم الله الرحمن الرحيم

﴿وفوق كل ذي علم عليم﴾

صدق الله العظيم

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1. History of toxicology.
2. Definitions
3. Branches of Toxicology
4. Classification of toxic agent
5. Toward and Untoward effect of drugs.
6. Dose-Response Curves for Beneficial Substances.
7. Toxicokinitic.
8. Role of toxicokinitic in the toxicity.
9. Scope of toxic effect.
10. Effect of distribution on toxicity.
11. Steps of clinical study for new substance.
12. Variation in toxic response.

History of toxicology

- Toxicology dates back to the earliest humans, who used animal venom and plant extracts for hunting, warfare. The Ebers papyrus (circa 1500 BC) contains information pertaining to many recognized poisons e.g. opium (used as both a poison and an antidote).
- There is also an indication that plants containing substances similar to digitalis and belladonna alkaloids were known. Hippocrates (circa 400 BC) added a number of poisons and clinical toxicology principles pertaining to bioavailability in therapy and overdosage.

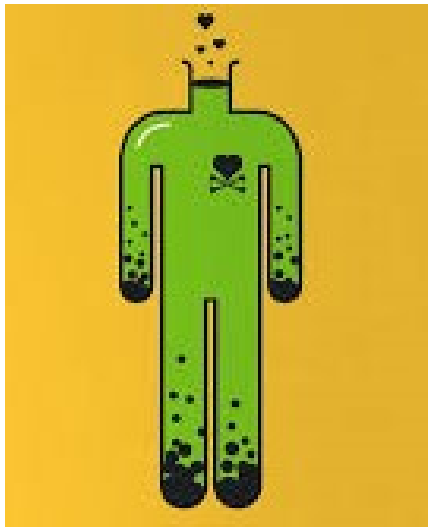
- **General Toxicology**: The science of poison and poisoning, it's the study of undesirable effect of chemical, biological or even radiation on living organism.

- **Hazard:** The likelihood of occurrences of poisoning under specific condition of use or exposure.

- **Toxicosis:** The state of being poisoning.

- **Toxin** – Poison from natural origin e.g. insect fungi.

- **Poison** – Any substance when applied or introduce into living organism at certain dose or rout causes damage to life process, tissue or may deprive life.



Pollutant: A substance which occurs in the environment (air, water, soil) possibly by human activity and adversely effects the living organism who live in this environment.

Xenobiotic: Substance not enter any biological processes or used as a source of energy or nutrition, so they consider as foreign compounds e.g. (drugs, heavy metals and insecticides).

- **Minimum toxic dose (MTD):** The lowest dose that cause detectable toxic effect.
- **No adverse effect level (NOAEL):** The maximum dose that cause no statistical adverse effect in lab animal toxicity study.
- **Low adverse effect level (LOAEL):** The minimum dose that cause significant adverse effect in lab animal toxicity study.

Acceptable daily intake (ADI): Dose in food or water for xenobiotic that cause no adverse effect in whole lab animal life (chronically used).

LD50 (Median lethal dose): The dose of toxic agent that cause death in 50% of the test animals.

ED50 (Effective dose): The dose of substance that give eefctive response in 50 % of test animals

- **Therapeutic index (TI):** It is the ratio of doses required to produce toxic or lethal effect and required to elicit desirable therapeutic effect.

$$TI = \frac{LD50 \text{ or } TD50}{ED50}$$

- The highest ratio, the safest drug.

Branches of Toxicology

Three specialized types of toxicology:

1- Forensic Toxicology:

Mixture of analytical chemistry and fundamental toxicological principles, its concerned with medicological assessment of the effect of toxic agent in human and animal and establish cause of death. and discovering suicidal and kill cases.

2- Environmental toxicology:

Study the effect of pollutant on living organism and to assess the risk to human that live in this environment e.g. factory, fuel, plant combustion, warming smoke…etc.

3- clinical toxicology:

Area of professional of medical science such as doctors, pharmacist, chemists and veterinarian concerned with disease or poisoning by toxic substance or mostly **drugs** overdoses adverse effect and its treatment.

Classification of toxic agent

- Toxic agent are classified in variety of ways:

1- According to target organ (Liver, kidney, brain).

2- According to use (Food additive, pesticides, solvent).

3- According to source (Animal, plant).

4- According to effect (Cancer, mutation, teratogencity).

5- According to state:

a. Physical: (gas, dust, liquid).

b. Chemical: (aromatic amine, acidic or basic)

c. Labeling: (oxidizer, flammable, irritant)

6- According to poisoning potential: (extremely, moderately and slightly toxic)

7- According to mechanism of action: (Enzyme inhibitor, muscle spasm, DNA damage)

Type of toxicity

- The type of potential toxicity can be divided according to the dose and period of exposure as follow:

1- Acute toxicity: sudden violent syndrome caused by single large dose of toxicant with high mortality and sever toxic symptoms.

2- Sub acute toxicity: Repeated large toxic doses for a period less than one month, with sever toxic symptoms and some mortality.

3- Sub chronic toxicity: Repeated moderated to low toxic doses for a period less than three months with moderated toxic symptoms.

4- Chronic toxicity: Long term condition by repeated small doses for a period more than three months with or without any toxicity symptoms, its used to study carcinogenicity and accumulation.

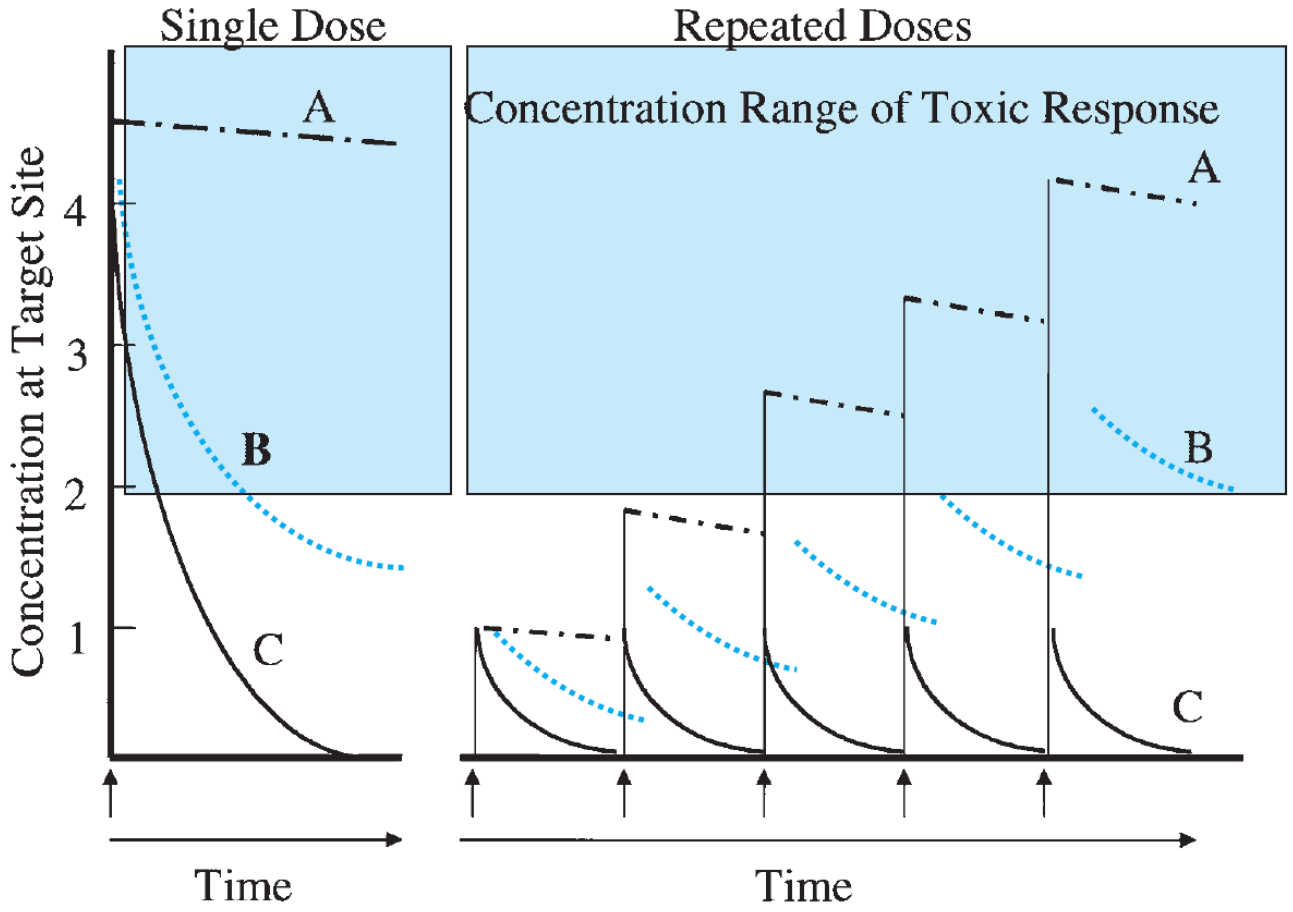


Figure (1) ***Diagrammatic view of the relationship between dose and concentration at the target site under different conditions of dose frequency and elimination rate.***

Line A. A chemical with very slow elimination (e.g., half-life of 1 year). *Line B.* A chemical with a rate of elimination equal to frequency of dosing (e.g., 1 day). *Line C.* Rate of elimination faster than the dosing frequency (e.g., 5 h). Blue-shaded area is representative of the concentration of chemical at the target site necessary to elicit a toxic response.

Toward and Untoward effect of drug

Toward effect of drug:

It's the main therapeutic or pharmacological effect of drug in the body.

Untoward effect of drug:

This is the effect that accompanies therapeutic effect and its may be desirable or undesirable and is include:

a- Secondary effect :

Secondary pharmacological effect that accompanied therapeutic effect and consider some times as desirable effect e.g. (atropine).

b- Side effect :

Secondary predicted undesirable effect that accompanied the therapeutic effect e.g. (Aminoglycosides).

c- Adverse effect:

Unpredicted undesirable effect caused by drug used at recommended dose e.g. Allergy to penicillin.

d-Toxic effect:

Damaged effect to certain biological system or process caused by poison or drug at high doses.

Dose-Response Curves for Beneficial Substances

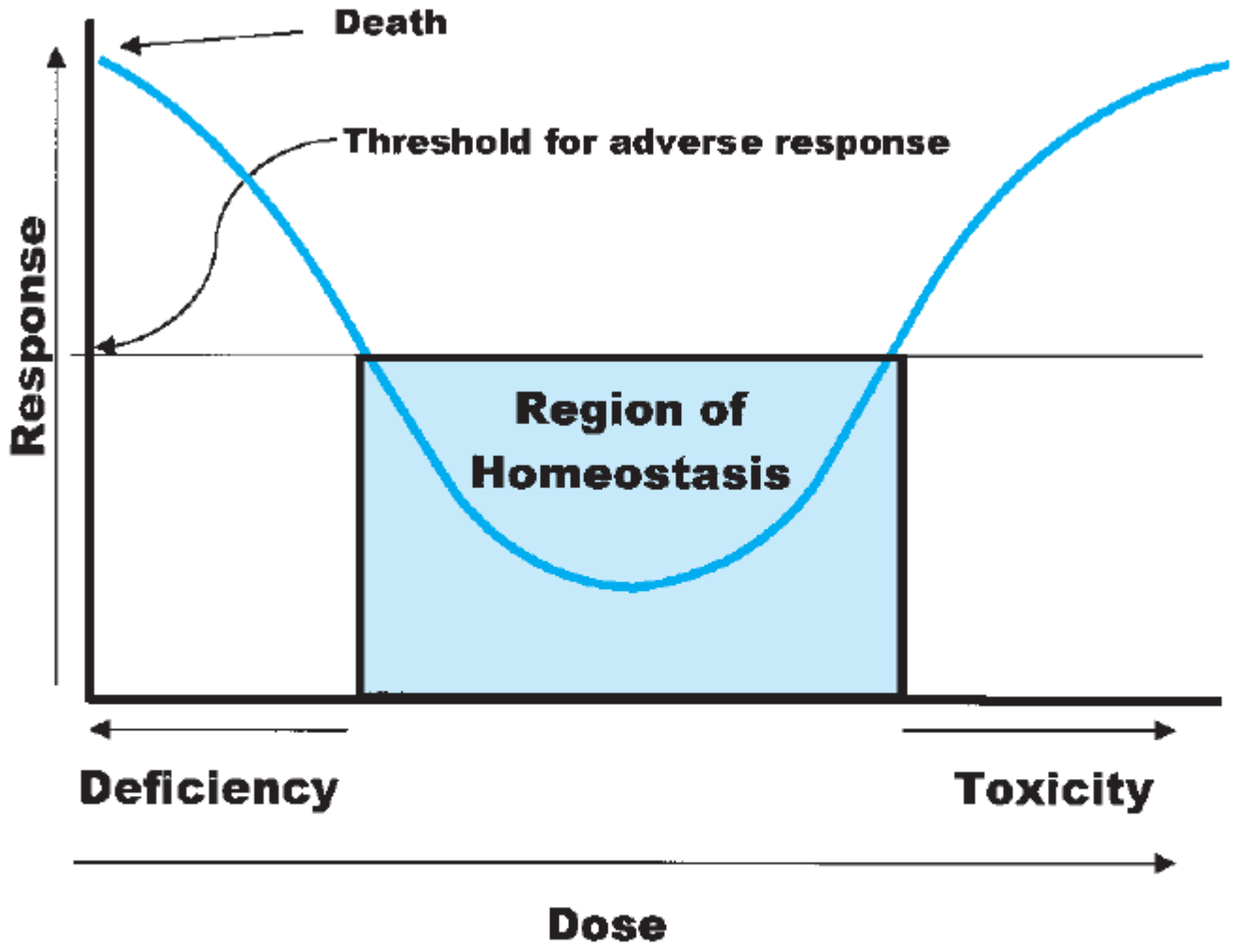


Figure (2) *Individual dose–response relationship for an essential substance such as a vitamin or trace element.*

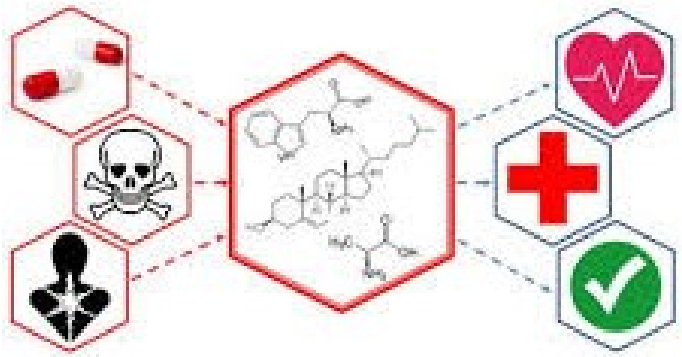
- For substances required for normal physiological function and survival, the dose-response curves will be U-shaped.
- At very low doses, there is an adverse effect (deficiency), which decreases with increasing dose (homeostasis). At very high doses, an adverse response appears from toxicity.
- For example,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

Role of toxicokinitic in the toxicity

The intensity of toxic effect depends on the:

1- Concentration.

2- Persistence of ultimate toxicant at the site of action.



Ultimate toxicant:

- Is chemical species molecules that formed by metabolic activation act to react with endogenous target molecule or critically alter the biological environment initiating structural or functional alteration that result in toxicity.
- The ultimate toxicant can be original chemical to which the organism is exposed, a metabolite (electrophile that react with nucleophile) or Reactive Oxygen or Nitrogen Species (ROS or RNS) generated during the biotransformation of toxicant or endogenous molecule.

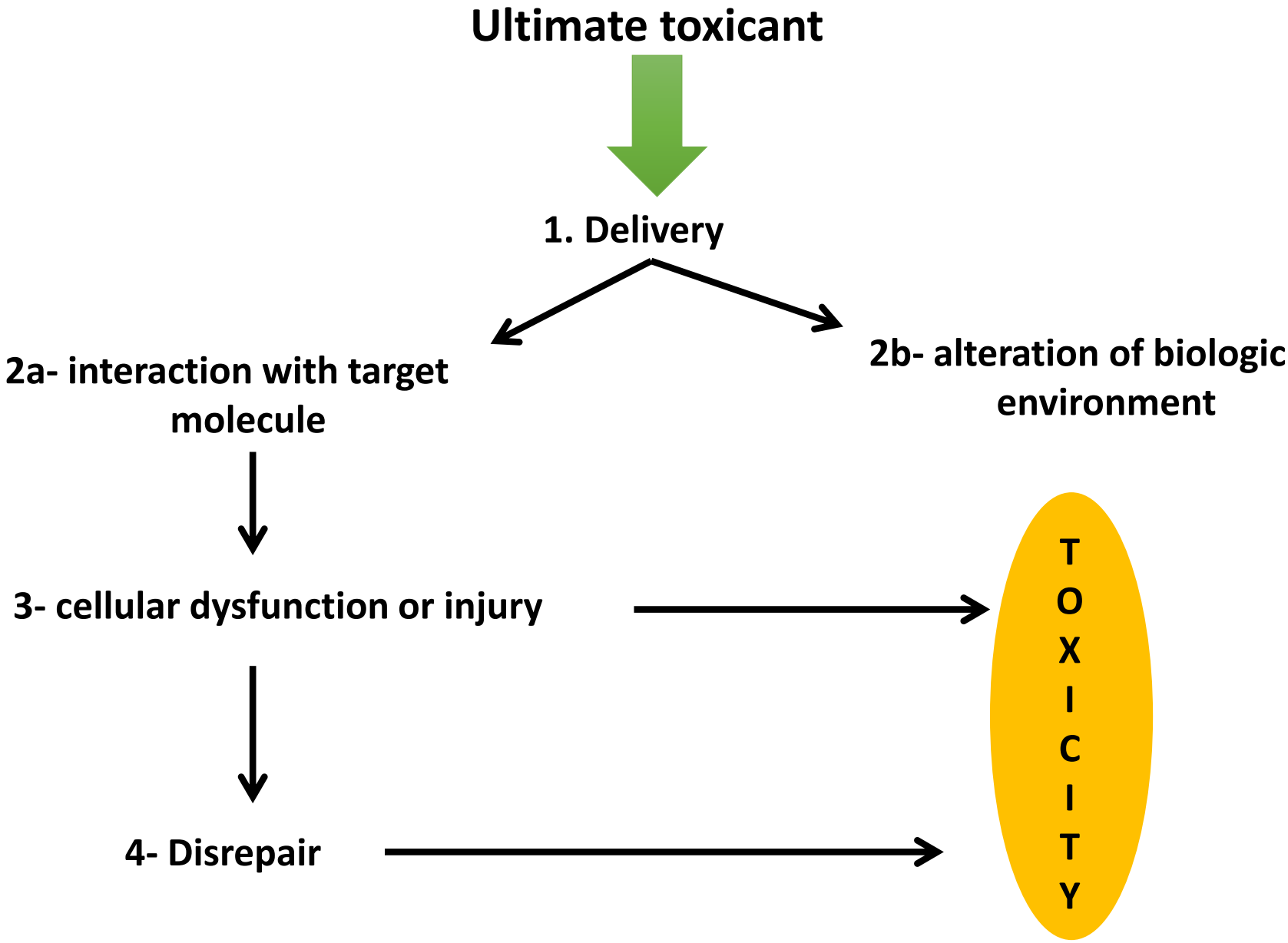


Figure (3): Potential stage in the development of toxicity

Toxicokinitic:

- The concentration of ultimate toxicant at the target molecule depends on the relative effectiveness of the processes the increase or decrease its concentration at the target site (system that showed higher toxic effect).

- The accumulation at its target is facilitated by **(absorption, distribution, reabsorption and toxication or metabolic activation).**

- **(pre systemic elimination, distribution away from the site of action, excretion and detoxication)** oppose these processes and work against the accumulation of the ultimate toxicant at the target molecule.

1-Absorption versus presystemic elimination:

Absorption:

Is transfer of chemical from the site of exposure, usually external or internal body surface, into systemic circulation. Several factors influence absorption

1- concentration

2- surface area of exposure and vasculation.

3- characteristic of epithelial Layer through which the toxicant is being absorbed (skin, GIT).

4- lipid solubility is usually the most important factor because it is the absorbable form.

pre-systemic elimination:

- During transport from the site of the exposure to systemic circulation, toxicant may be eliminated before enter general circulation. This common for chemical absorbed from GIT, because they may pass through GI mucosal cell, liver and lung and eliminated before being distributed to the rest of the body by systemic circulation.
- Pre-systemic or first-pass elimination contribute in reduce concentration of toxicant in general circulation and so reduce their toxic effect at the target site.

2-Excretion versus reabsorption:

Excretion:

The rate and speed of excretion depend largely on physiochemical properties of toxicant. The major excretory organs are (kidney, liver and GIT) for removing highly hydrophilic chemical such as organic acid and bases.

Lung is very important organ for excretion of irritant gases, volatile liquid or aerosol (air pollutant), while excretion in milk is important for public health interest.

Reabsorption:

Mainly occur in renal tubule and contribute in increase the concentration of xenobiotic in blood circulation and so reabsorption will increase substance toxicity.

3-Distribution toward versus away from target site:

Distribution toward target site (tissue or organ):

Occur by crossing their membrane mainly by active transport and binding with target molecule (protein, nucleic acid or cell organelles) either covalently or non covalently (ionic or hydro genic bonding) leading to development of toxicity in the target site.

Distribution away from target site:

To a storage depot (fat or bone) will protect the target site and reduce toxicity of xenobiotic.

4-Toxication versus detoxication:

Toxication:

Biotransformation to harmful product (ultimate toxicant) capable for binding with endogenous molecule (target molecule) causing toxic effect.

Detoxication:

Biotransformation that eliminate the ultimate toxicant or prevent its formation.

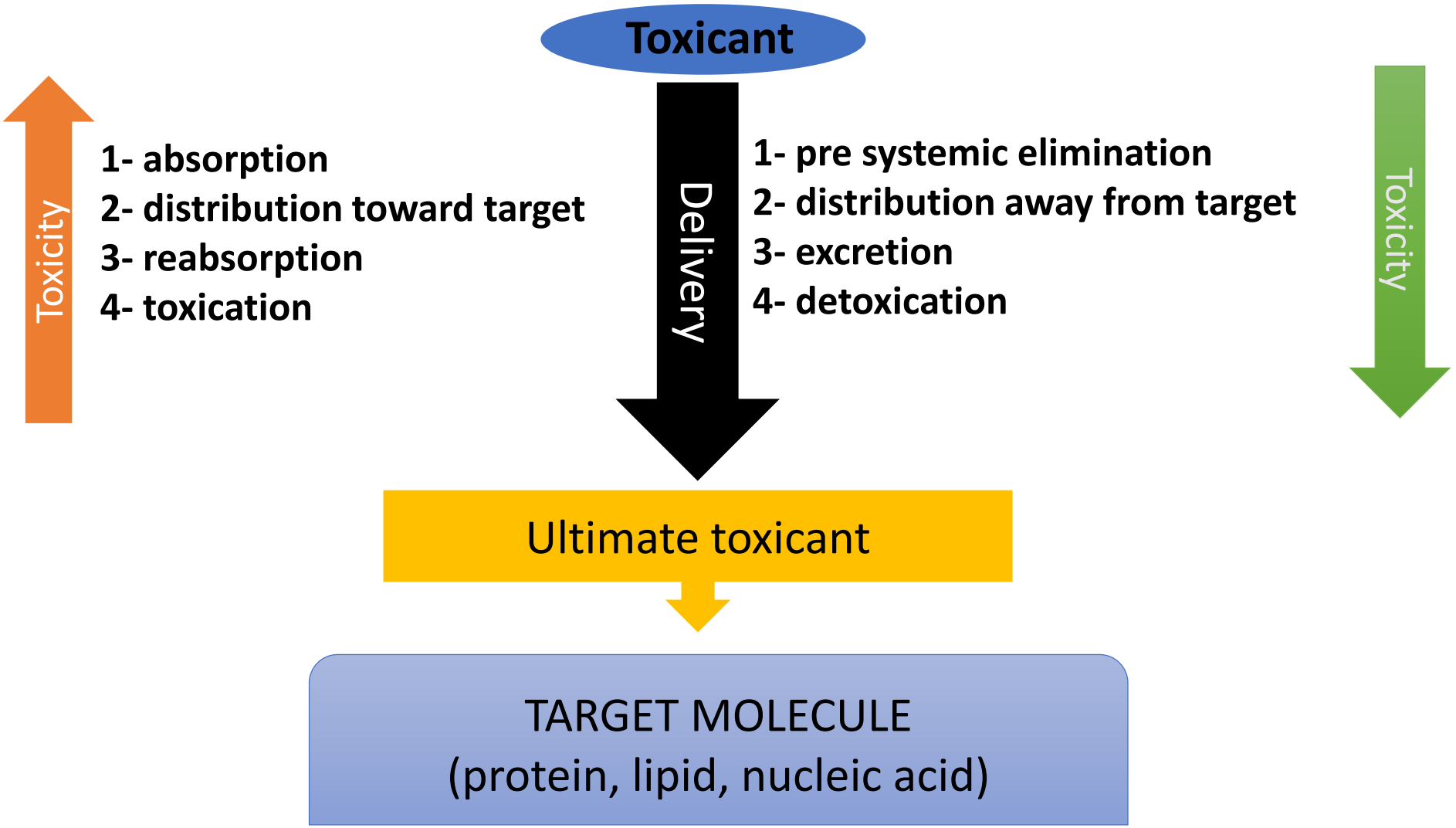


figure (4): Toxicokinitic processes that increase or decrease toxicity

Log dose toxic response effect

Binding of ultimate toxicant with target molecule in the target site will lead to development of toxic response, according to log doses of toxicant which lead either graded or quantal (all or none) toxic response as in the graph.

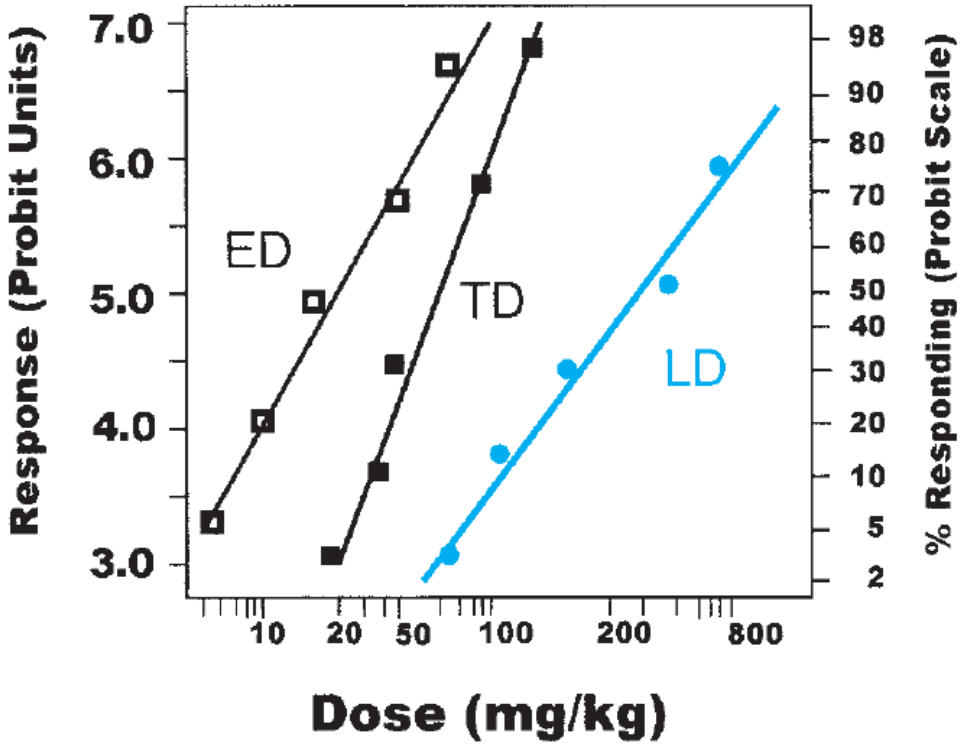


Figure (5) ***Comparison of effective dose (ED), toxic dose (TD), and lethal dose (LD).***

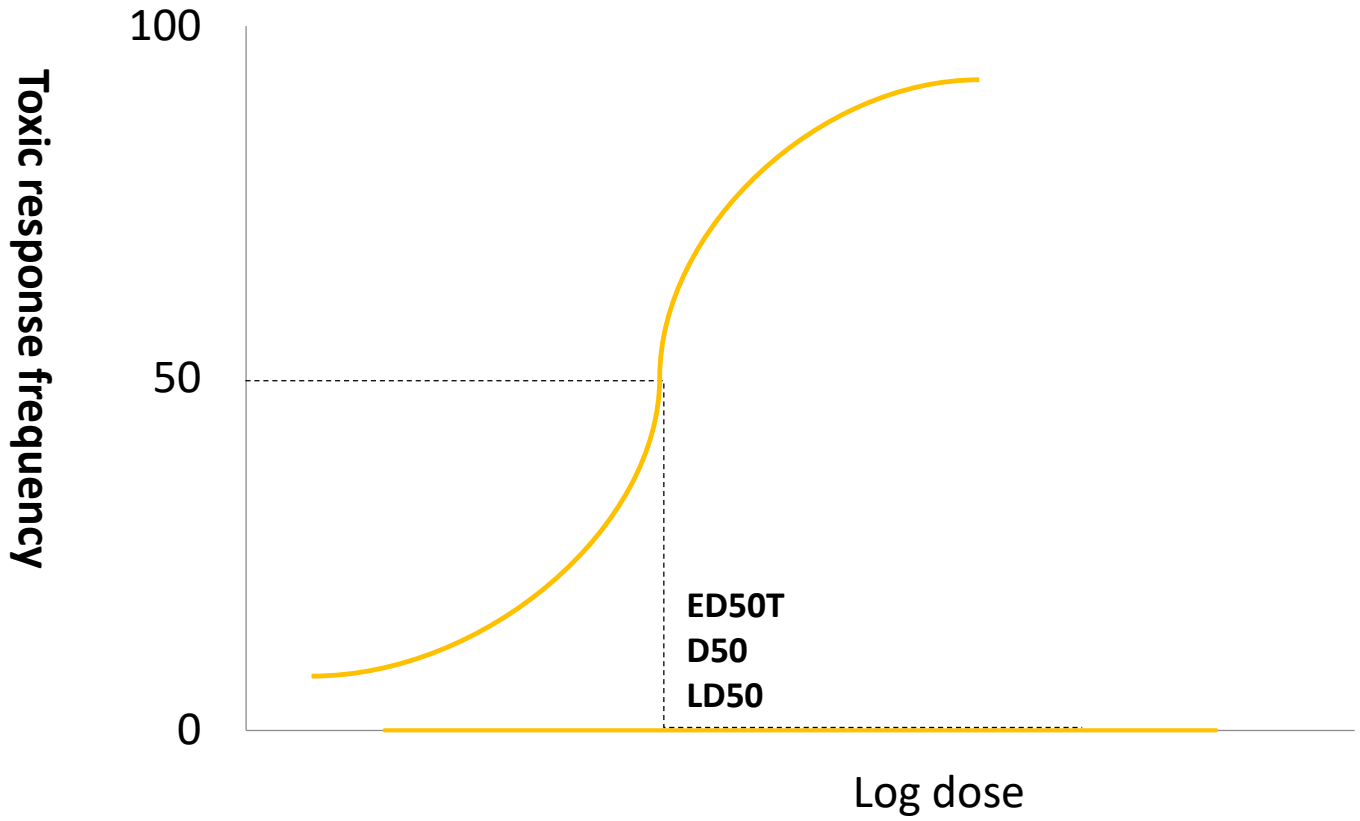


Figure (6) Quantal LDR mainly used for determination of ED50, TD50, LD50 and for estimation of safety of drugs

scope of toxic effect:

1.Local versus systemic effect:

Local effect refer to that occur at the site of application e.g. caustic chemical, inhalation of irritant chemical (riot gas). While systemic effect need absorption and distribution to the organ or sit of toxic effect (target organ) e.g. Hg, Cd. Some toxic agent show both local and systemic effect e.g. snake venom.

2.Reversable versus irreversible effect:

The ability to regenerate will determine whether the effect is reversible (Liver, CNS).

3.Delayed versus immediate effect :

Carcinogen need latent period (years) to exert carcinogenic effect (diethylstilbestrol, this called delayed effect). While most toxic agent showed an immediate toxic effect depending on the dose e.g. CN.

Toxic dose calculation

The volume of distribution (Vd) is the apparent space in which xenobiotic is distributed to the total body water (plasma, intra & extracellular fluids) after absorption.

$$Vd = \frac{Dk}{Cp} \qquad Cp = \frac{D}{Vd} \qquad D = Cp.\ Vd$$

Where Vd= volume of distribution

Dk=dose administered

Cp= plasma concentration at zero time.

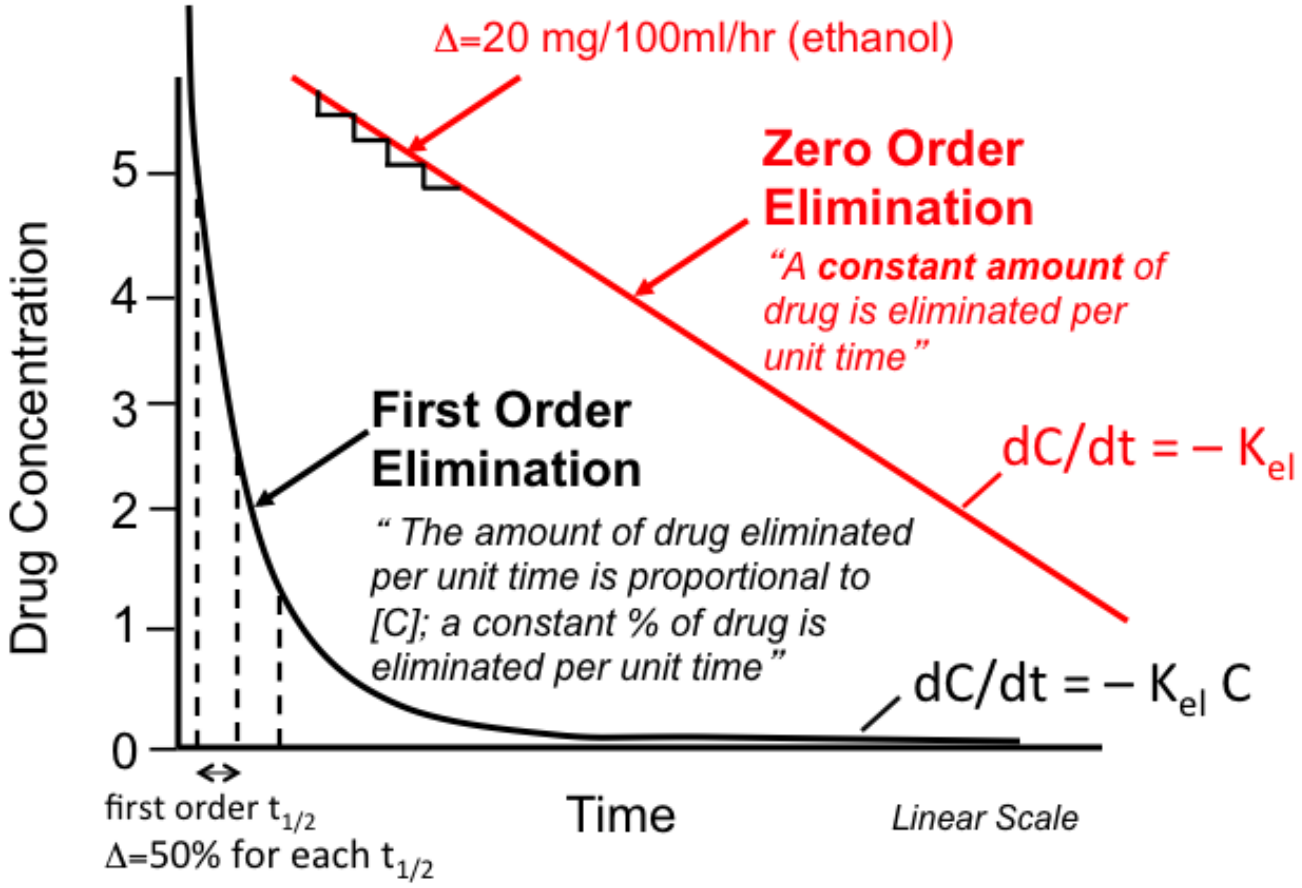
Cl= clearance of drug (ml/min). Is the volume of blood from which xenobiotic is eleminated per unit of time.

Kel= elimination rate constant. Is the ratio of elimination from the body per hour (0.3 - hr = 30% per hr)

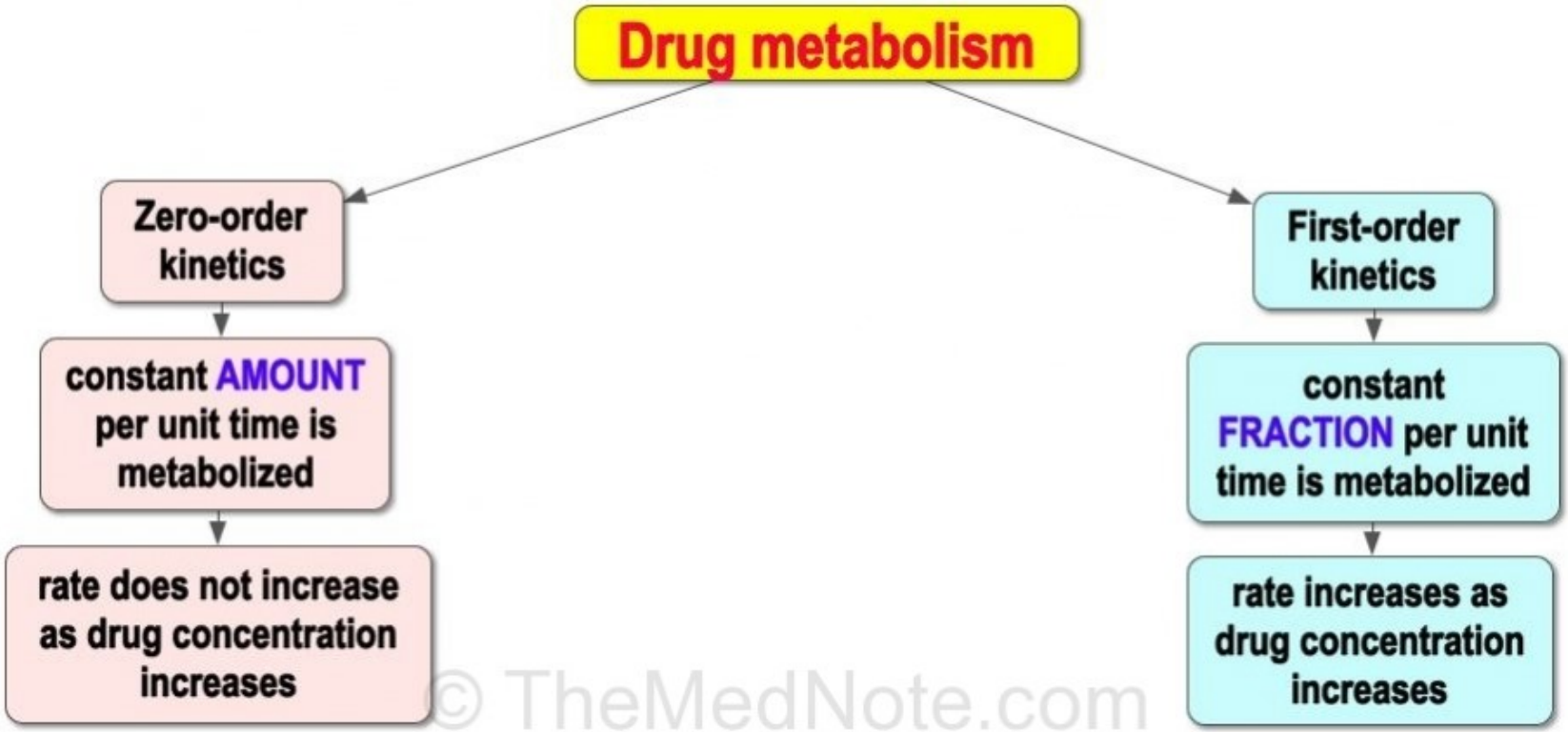
T ½= the time required to half the concentration of xenobiotic in plasma

$$Kel = \frac{0.693}{T\ ½}$$

The most common kinetic in drug toxicity is Zero order kinetic in which all the important vital processes have reach saturation like (protein binding, active transport, metabolism), so elimination will be non linear with non constant values for t ½ or Kel.



Elimination of xenobiotic after I.V administration for one compartment.



VARIATION IN TOXIC RESPONSES

1. Selective Toxicity:

- It means that a chemical produces injury to one kind of living matter without harming another form of life even though the two may exist in intimate contact. They may be related to each other as parasite and host or may be two tissues in one organism.
- This biological diversity interferes with the ability of ecotoxicologists to predict the toxic effects of a chemical in one species (humans) from experiments performed in another species (laboratory animals).

Selective toxicity have benefit, for example:

- There are fungi, insects, and even competitive plants that injure the crop, and thus selective pesticides are needed.

- Animal husbandry and human medicine require chemicals, such as antibiotics, that are selectively toxic to the undesirable form but do not produce damage to the desirable form

2. Species Differences:

- its important to recognize that both quantitative and qualitative differences in response to toxic substances may occur among different species.
- Even among phylogenetically similar species (e.g., rats, mice, guinea pigs, and hamsters), large differences in response may occur.
- The mechanistic basis for this dramatic difference in response appears to be entirely related to species differences in the expression of a particular form of glutathione Stransferase.

- For example, the LD50 for the highly toxic dioxin, differs by more than 1000-fold between guinea pigs and hamsters.
- Large differences in carcinogenic response between experimental animal species are not unusual. For example, mice are highly resistant to the hepatocarcinogenic effects of the fungal toxin aflatoxin B1. Dietary doses as high as 10,000 parts per billion (ppb) failed to produce liver cancer in mice, whereas in rats dietary doses as low as 15 ppb produced a significant increase in liver tumors.

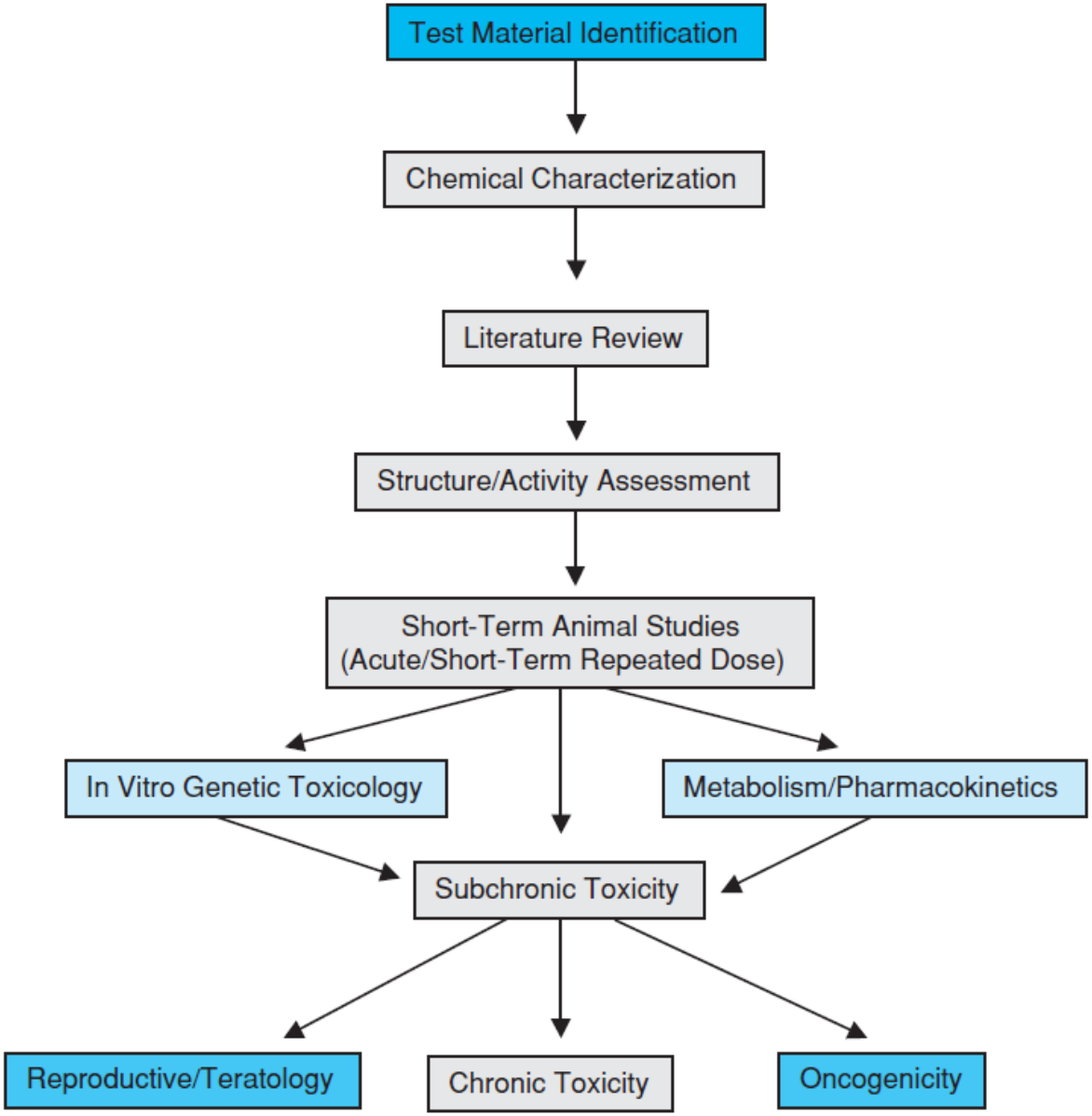
3.Individual Differences in Response

- Even within a species, large interindividual differences in response to a chemical can occur because of subtle genetic differences.
- Hereditary differences in a single gene that occur in more than 1% of the population are referred to as genetic polymorphism and may be responsible for idiosyncratic reactions to chemicals.

- For example, it is recognized that approximately 50% of the Caucasian population has a gene deletion for the enzyme glutathione S-transferase M1.
- This enzyme has no apparent significant physiologic function, and thus homozygotes for the gene deletion (e.g., those who lack both copies of the normal gene) are functionally and physiologically normal.
- Epidemiologic studies have indicated that smokers who are homozygous for the null allele may be at slightly increased risk of developing lung cancer compared with smokers who have one or both copies of the normal gene.

- It is likely that the majority of chronic diseases develop as a result of the complex interplay between multiple genes and the myriad of environmental factors, including diet, lifestyle, and occupational and/or environmental exposures to toxic substances.

Steps of clinical study for new substance



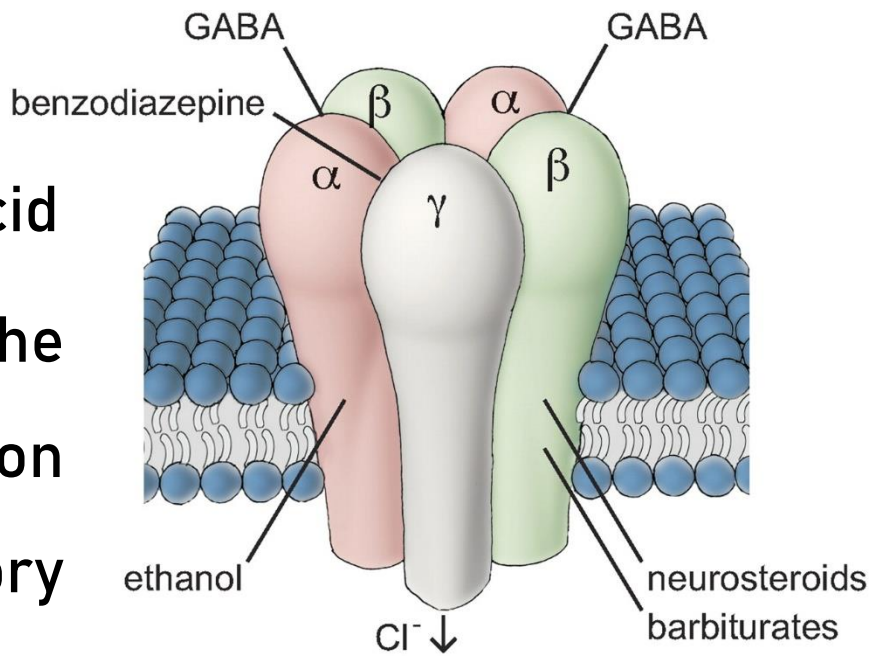
Thank you

PESTICIDES POISONING AND MANEGMENT

Dr. Muhammed Malik Al-Ani

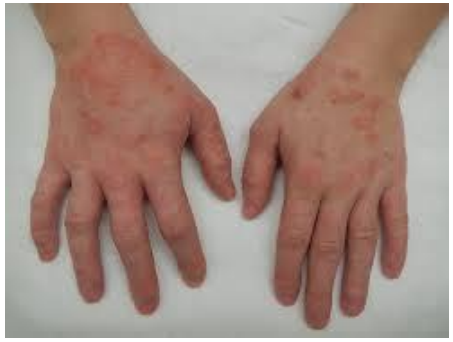
1. ORGANOCHLORINES

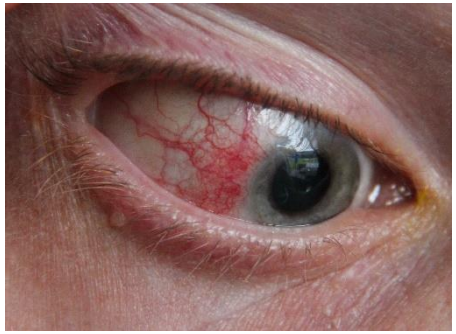
- The mechanism of action is the insecticide binding at the GABAA site chloride ionophore complex, which inhibits chloride flow into the nerve.



- GABA gamma-Aminobutyric acid inhibits chloride flow into the nerve causing hyperpolarization and inhibition of the excitatory impulse.

Clinical signs

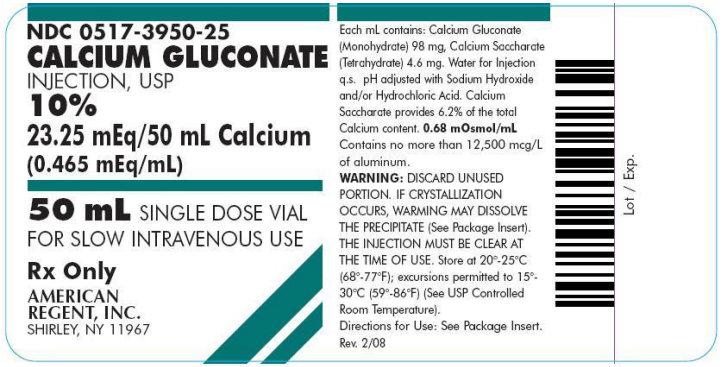




- Skin contact: Dermatitis.
- Inhalation: Inhalation can give rise to irritation of eyes, nose, throat and cough.
- Ingestion: Nausea, vomiting, diarrhea, abdominal pain, headache, dizziness, convulsions and coma.

Management of Organochlorine poisoning

1. For convulsions give diazepam 5-10 mg IV slowly (Paediatric dose 0.2 mg/kg). Repeat if necessary. Up to 40 mg/day can be given orally as maintenance dose.
2. Continue diazepam for 3-4 days after convulsions have been controlled.
3. 10 ml of 10% calcium gluconate IV can also be used to control convulsions.



2. ORGANOPHOSPHATES AND CARBAMATES

- Group of chemicals share a common mechanism of cholinesterase inhibition and hence can cause similar symptoms.
  - Phosphorylation of the acetylcholinesterase (AChE) at nerve endings.
  - Loss of available AChE results accumulation of acetylcholine at receptor sites and effector organ to become over stimulated by the excess acetylcholine.

❖ CLINICAL FEATURES

1. Eye contact: Irritation or pain, lacrymation, swelling, blurring of vision.
2. Inhalation: Cough, difficulty in breathing, bronchitis, pneumonia.
3. Ingestion: Nausea, vomiting, diarrhea, sweating, salivation, small or pin point pupils, muscle twitching and fasciculation.

Management of Organophosphate and Carbamate poiosning by Atropin and Pralidoxime

- Atropine:

  as mention in previous lec.

Target end points for atropine therapy

1. Clear chest on auscultation with no wheeze.
2. Heart rate between 80-100 beats/min.
3. Pupils no longer pinpoint.
4. Dry axillae.

- Excess atropine causes confusion, urinary retention, hyperthermia, bowel ileus and tachycardia.
- In this condition atropine should be ceased and the patient reviewed after 30 min. to see whether the features of toxicity have settled.

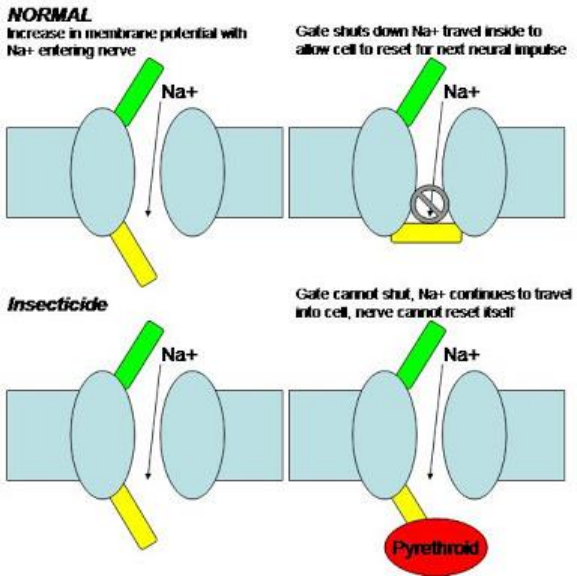
- **Pralidoxime:**

1. Give 30 mg/kg loading dose of pralidoxime over 10-20 min.
2. followed by a continuous infusion of 8-10 mg/kg per hr until clinical recovery.
3. Less severely poisoned patients can be given intermittent doses (1 g/ 6 hrs by slow IV over 10 – 20 mins).

- Oximes are not required for carbamate.
- Pralidoxime reactivates the enzyme cholinesterase by cleaving the phosphate-ester bond formed between the organophosphate and acetylcholinesterase

3.PYRETHROIDS

- Pyrethrum is an insecticide extracted from chrysanthemum flower.
- Active ingredients of pyrethrum are known as pyrethrins.
- It is the active ingredient of Raid.
- It produce repetitive depolarization of axons by inhibiting inactivation of sodium channels.



❖ CLINICAL FEATURES

1. Inhalation: Allergic manifestations such as wheezing.
2. Ingestion: After ingestion pyrethrums have low toxicity, vomiting, epigastric pain and diarrhoea are the common features.
3. Eye contact: Lacrymation, oedema of the eyelids.
4. Skin contact: Allergic dermatitis.

Treatment of pyrethrins toxicity

- Treatment is symptomatic and limited to alleviation of the inflammatory response.
- Oral or topical corticosteroids and H1-antihistamine may be of use.

Corticosteroid Drug	Treatment for	Molecular formula
Betamethasone	Dermatitis	$C_{22}H_{29}FO_5$
Budesonide	Asthma, noninfectious rhinitis, nasal polyposis	$C_{25}H_{34}O_6$
Cortisone	IgE-mediated allergies	$C_{21}H_{28}O_5$
Dexamethasone	Inflammation, rheumatoid arthritis	$C_{22}H_{29}FO_5$
Hydrocortisone	Dermatitis	$C_{21}H_{30}O_5$
Methylprednisolone	Arthritis, Bronchial inflammation	$C_{22}H_{30}O_5$
Prednisolone	Asthma, rheumatoid arthritis, ulcerative colitis, Crohn's disease	$C_{21}H_{28}O_5$
Prednisone	Systemic lupus erythematosus, Bell's palsy, asthma, dermatitis	$C_{21}H_{26}O_5$
Triamcinolone	Eczema, diabetic retinopathy	$C_{21}H_{27}FO_6$

4.PARAQUAT

- Paraquat is a widely used herbicide in SriLanka. It is a safe herbicide because it is inactivated by contact with soil. Paraquat is commonly used as suicidal poison in this country.

- Paraquat has life threatening effects on the gastrointestinal tract, kidney, liver and other organs. The lung is the primary target organ of paraquat poisoning.

- Recently a new paraquat formulation with INTEON technology (containing an alginate that converts to a gel under stomach acid conditions, increased levels of emetic and purgative) was developed in order to reduce oral toxicity. However ingestion of INTEON is still very likely to be lethal.

- # Clinical feature:
- Skin contact: prolonged contact will produce blistering, abrasion and ulceration. Although absorption across intact skin is slow, abraded or eroded skin allows efficient absorption.

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❖ Management of Paraquat poisoning

- An absorbent (Fuller's earth or Activated charcoal) should be given orally or via a nasogastric tube as early as possible.
- The dose of Fuller's earth is 1 litre of 15% aqueous suspension (Paediatric dose 15 ml/kg body weight).
- While activated charcoal 50-100g dissolved in 200 ml of water (Paediatric dose 15 ml/kg body weight).

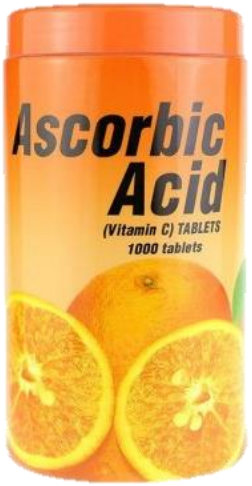
5.PROPANIL & CHLOROPHENOXY COMPOUNDS

- Propanil is a selective herbicide of low toxicity. However, in self poisoning with large doses cause methemoglobinemia, which can be fatal.

- Chlorophenoxy compounds are well absorbed from the gastrointestinal tract. They are less well absorbed from the lung, also cutaneous absorption appears to be minimal.

❖ Management of Propanil poisoning

1. give 1% methylene blue 0.1 ml/kg IV over 5 minutes. The same dose may be repeated within 1 hour if there is no improvement.
2. If IV preparation is not available give methylene blue 300 mg daily orally.
3. If methylene blue is not available give ascorbic acid 1 g IV twice daily.



- methylene blue act by reduces the heme group from methemoglobin to hemoglobin.

7. RODENTICIDES

- Warfarin, Coumarins, indandiones and brodifacoum are used as rodenticides.
- They are fairly safe for human beings due to the low concentration of the active ingredient.
- Their toxicity is due to depression of the synthesis of factors essential for coagulation of blood.

❖ Management of Rodenticide poisoning

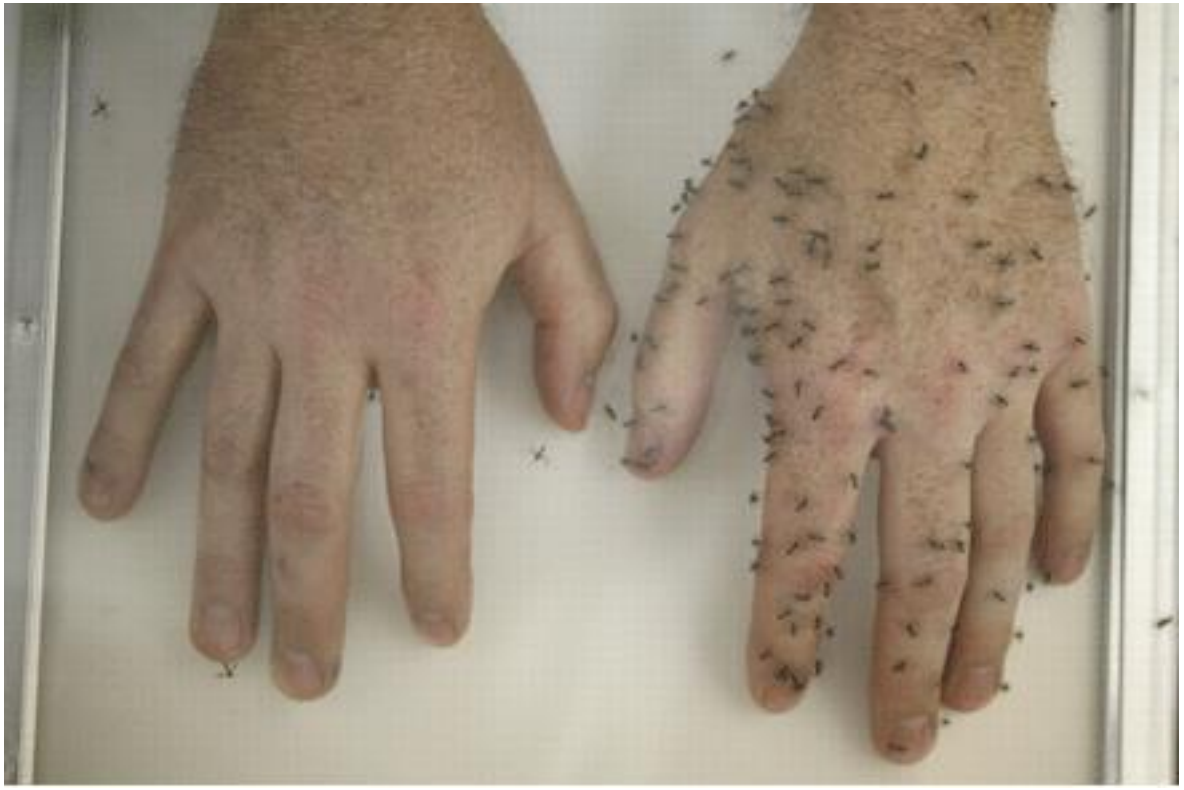
1. If there has been no bleeding, but the PT is prolonged, give vitamin K1 10-50 mg orally two to four times a day (paediatric dose 0.4 mg/kg/dose).
2. For prolonged PT with less severe bleeding, give vitamin K1 10 to 15 mg SC or IM (for a child 1 to 5 mg). Or may be necessary to give fresh frozen plasma or fresh blood

3. In severe haemorrhage with prolonged prothrombin time (PT) give vitamin K1 (phytomenadione) 20 mg by slow IV injection (0.6 mg/kg for children under 12 years).

DIETHYLTOLUAMIDE (DEET)

- DEET *is a popular insect repellant* available in topical preparations at 5 to 10% concentrations (OFF® Insect Repellant).
- About 5 to 10% of a dermal application is absorbed, due to its high lipid solubility, and stored in lipid compartments, resulting in a prolonged plasma half-life (2.5 h).

- It is considered a chemical with low toxicity, dermal reactions reflect excessive topical application of sprays, creams, lotions, or alcohol soaked DEET.



DEET toxicity

- Ocular or dermal irritation is generally limited to allergic reactions and is the most frequent complaint.
- Prolonged dermal contact with significant absorption, or oral ingestion, has precipitated CNS toxicity.
- This is manifested by the development of:
  - headache
  - lethargy
  - confusion
  - tremors
  - *Hypotension, seizures, and coma* are rare.

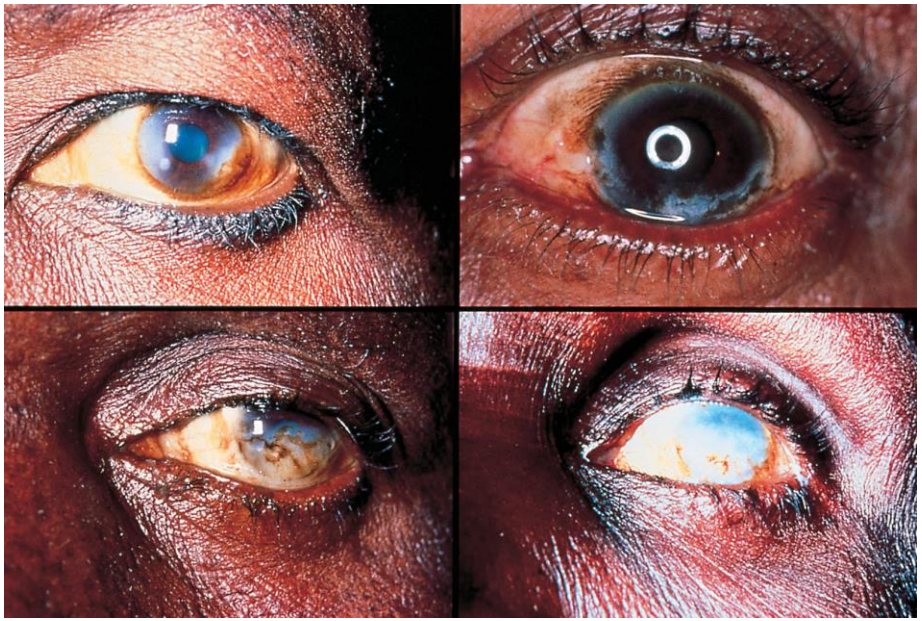
Treatment of Toxicity

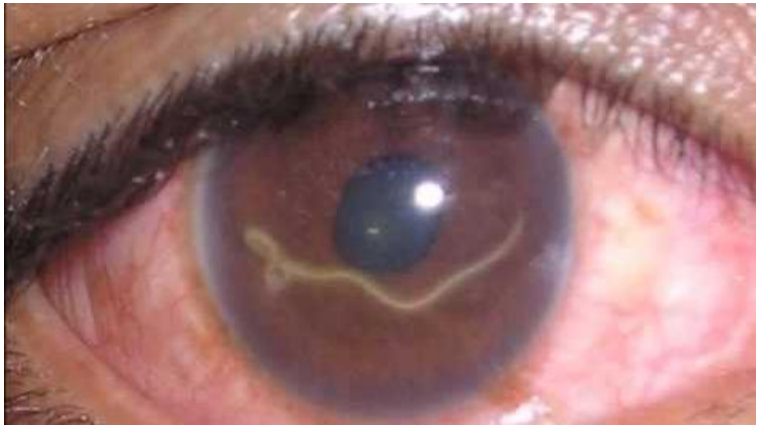
- ✓Treatment is largely **symptomatic** and **supportive** and involves:
  - Decontamination
  - Gastric lavage
  - Maintenance of vital signs
  - Washing the contaminated area with **soap** and **water**
  - Induction of **emesis** is recommended if needed.

Ivermectins

- The avermectins were isolated from a culture of the actinomycete *Streptomyces avermitilis* and may be used for a wide range of ecto- and endoparasites of domestic and wild animals.
- The semisynthetic ivermectins are highly lipid-soluble, although **dermal absorption** accounts for less **than 1.0 %** of the applied dose.
- Avermectins have low water solubility and extensive nonspecific binding.

- **Ivermectin is the drug of choice in treating onchocerciasis (river blindness) in humans.**
- These agents open **GABA-insensitive chloride channels,** reducing membrane resistance and increasing conductance inward.

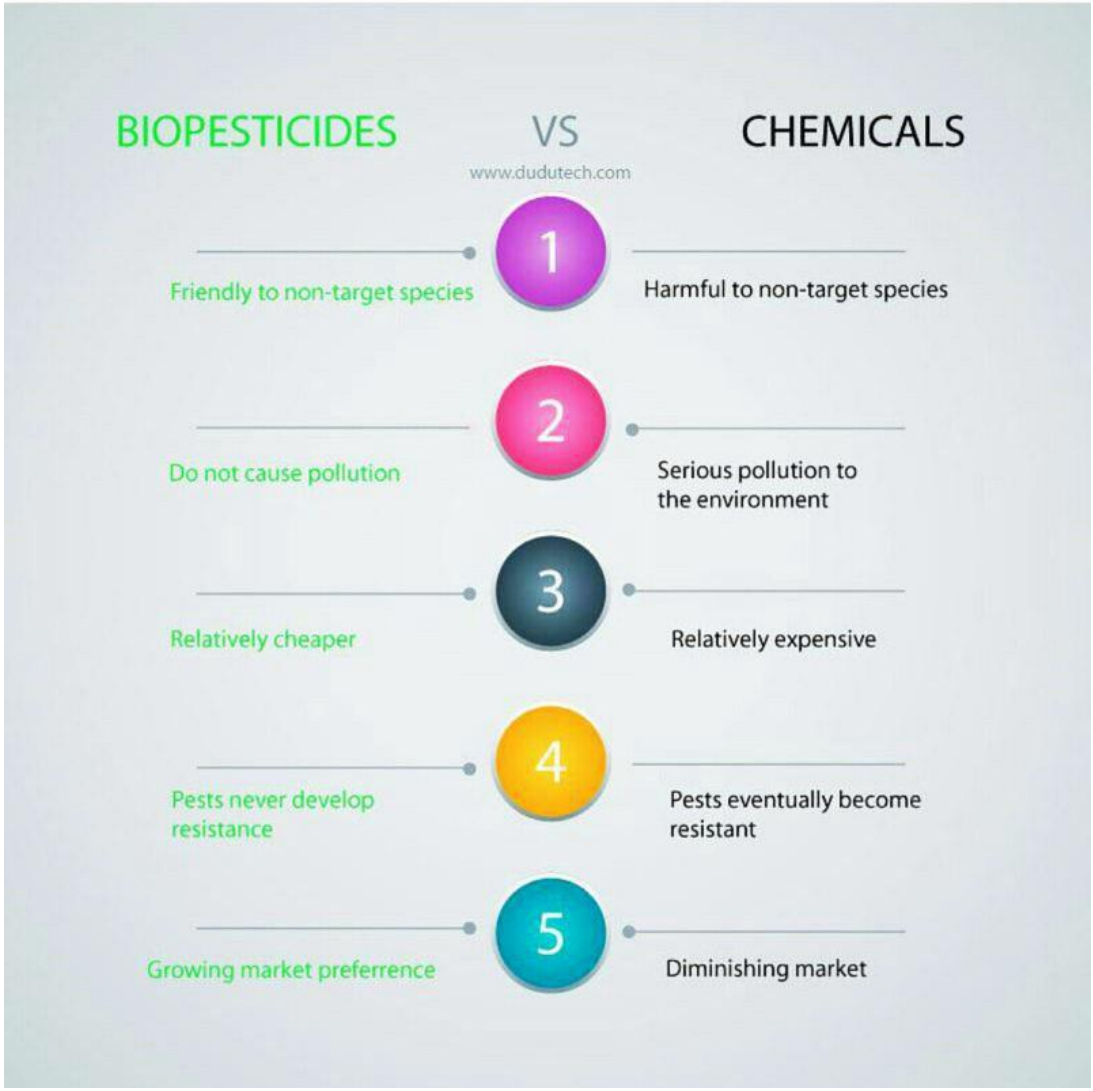




❖ Biopesticide as alternative

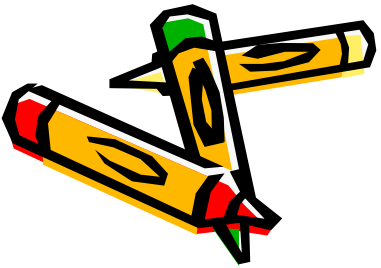
Its naturally occurring substances that control pests (biochemical pesticides), microorganisms that control pests (microbial pesticides), and pesticidal substances produced by plants containing added genetic material (plant-incorporated protectants) or PIPs".

❖ Advantages:


BIOPESTICIDES
VS
CHEMICALS
www.dudutech.com
1
Friendly to non-target species
Harmful to non-target species
2
Do not cause pollution
Serious pollution to the environment
3
Relatively cheaper
Relatively expensive
4
Pests never develop resistance
Pests eventually become resistant
5
Growing market preferrence
Diminishing market

disadvantages:

- Homwork !



FIRST AID

Skin contact:

1. Remove contaminated clothes carefully.
2. Wash the skin with running water for at least 15 minutes.
3. Do not use any local application without seeking medical advice.

Eye contact:

1. Wash eyes with running water for at least 15 minutes.
2. Do not use any eye drops without ensure the type of toxic agent or get medical advice.
3. If there is visual impairment an Ophthalmologist must visit.

❖Inhalation:

Remove the patient away from the source and encourage deep breathing of fresh air.

❖Ingestion:

Do not induce emesis because some pesticides have corrosive effects and some may contain hydrocarbons as solvents.

If patient is semiconscious or unconscious keep the patient in Neck extended position.


many
Thanks!