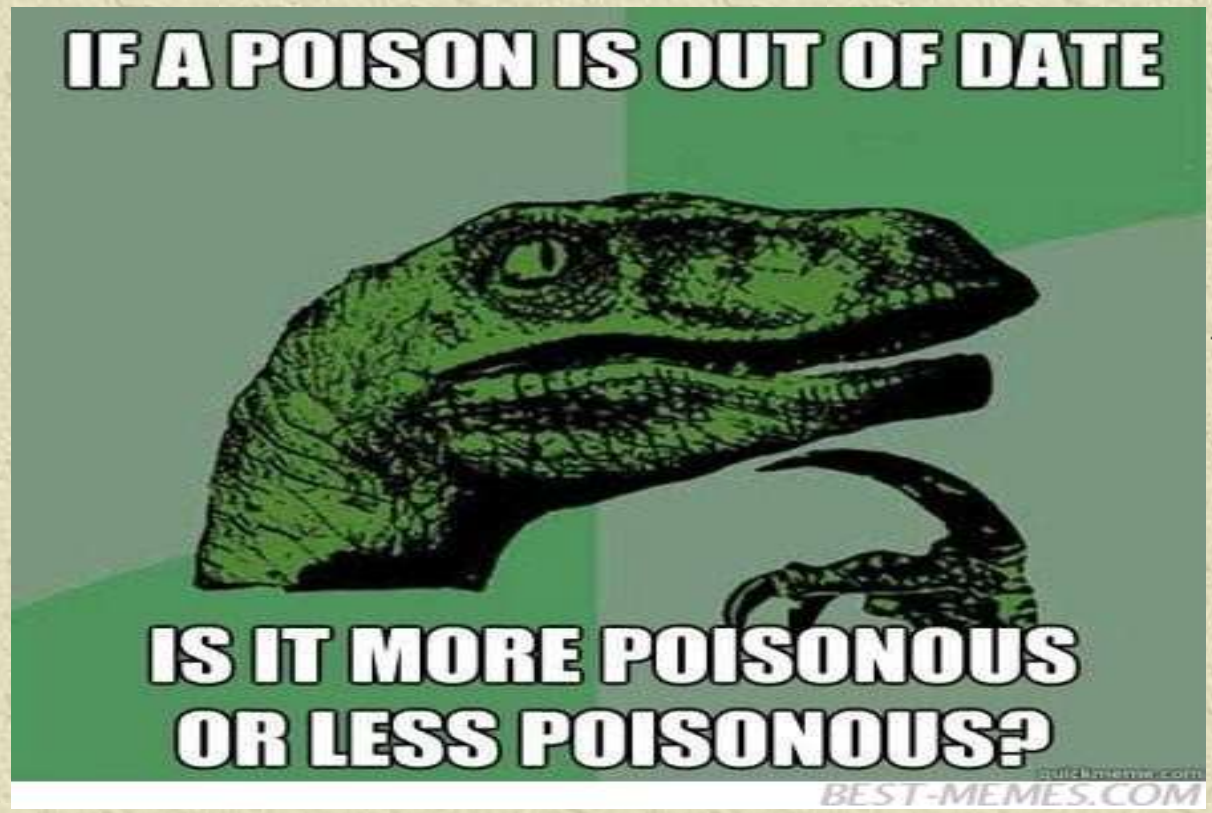
GENERAL

Toxicology



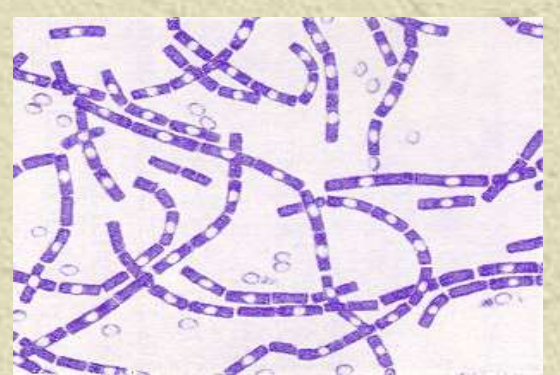
Лектор: доц. д-р В. Данчева, дм

Toxicology is a scientific and medical discipline for the adverse effects of the poisons.

Phytotoxins

Zootoxins

Bacteriotoxins



History

The harmful toxic effects of certain substances - including plants, fruits, insect bites, animal venoms and minerals have been known since prehistoric times.

History

2700 B.C. **Chinese documents**: plant and fish poisons

1900-1200 B.C. - **Egyptian documents** that had directions for collection, preparation, and administration of more than 800 medicinal and poisonous recipes.

800 B.C. - India - **Hindu medicine** includes notes on poisons and antidotes.

50-100 A.D. - **Greek physicians** classified over 600 plant, animal, and mineral poisons.

399 BC Death of Socrates by Hemlock

Socrates was charged with religious heresy and corrupting the morals of local youth.

The active chemical used was the alkaloid coniine which, when ingested causes paralysis, convulsions and potentially death.

History

50- 400 A.D. - **Romans** used poisons for executions and assassinations

Avicenna (A.D. 980-1036) Islamic authority on poisons and antidotes.

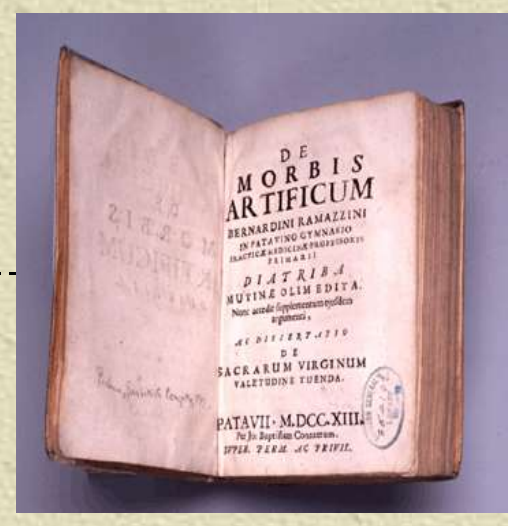
1200 A.D. - Spanish rabbi Maimonides writes first-aid book for poisonings Poisons and Their Antidotes

History

- **Cleopatra** commited suicide through **the bite of an asp**, a poisonous snake.

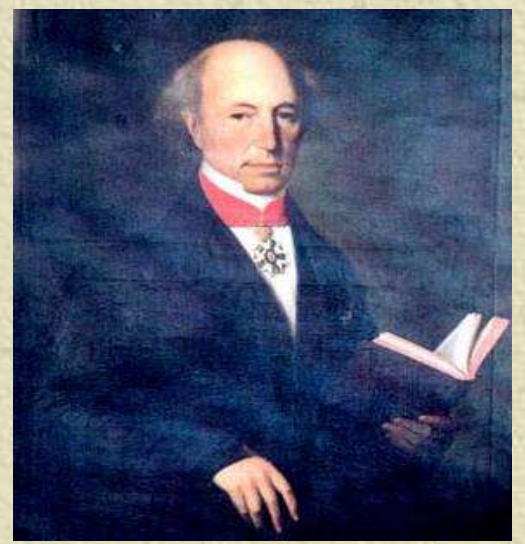
- In 15th century in Italy, **Cesare and Lucrezia Borgia** assassinated many of their political rivals by poisoning with **arsenic, copper** and **phosphorus**.

HISTORY



_Italian physician **Ramazzini** (1713) published **"De Morbis Artificum"** (**Diseases of Workers**) describing **"asthma"** in bakers, miners, farmers, glass-workers, and others. Ramazzini outlined **health hazards** of the **dusts, fumes, or gases that such workers inhaled**. The lung diseases suffered by most of the other workers would now be classified as "pneumoconiosis," a group of **dust-related chronic diseases.**

History

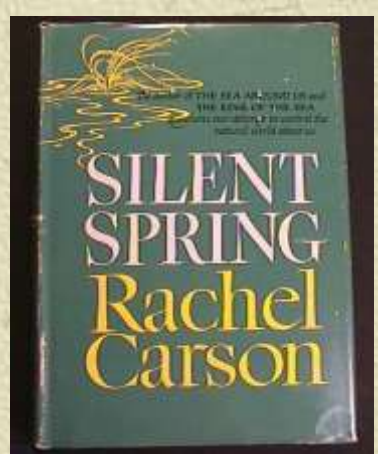


Spanish physician **Orfila** (1815) established **toxicology as a distinct scientific discipline.**

History

20th Century

Rachel Carson – alarmed public about dangers of pesticides in the environment.



BASIC CONCEPTS

- **Poison is any solid, liquid or gas that through either oral or topical routes can interfere with life processes in the organism**.
  - So, as poison could be defined any agent capable to produce a noxious response in a biologic system, seriously injuring function or producing death.
  - In other hand, every known chemical has the potential to produce injury or death if present in a sufficient amount.

Toxicology Terminology

- **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

Paracelsus (1493-1541)
'Grandfather of Toxicology'

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

"The dose makes the poison"

"THE DOSE MAKES THE POISON"

APPLE SEEDS

CONTAIN AMYGDALIN
~0.6g/kg of seeds

PEARS

CONTAIN FORMALDEHYDE
~0.06g/kg

POTATOES

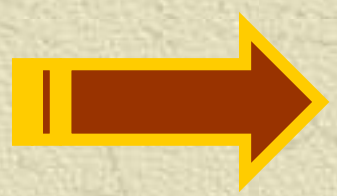
CONTAIN SOLANIN
~0.2g/kg
(higher in green potatoes)

COURGETTES

CONTAIN CUCURBITACIN E
Variable
(higher in bitter courgettes)

ALL OF THE FOOD ITEMS ABOVE CONTAIN NATURAL CHEMICALS THAT ARE TOXIC TO HUMANS. HOWEVER, THEY ARE USUALLY PRESENT IN VERY SMALL AMOUNTS, FAR BELOW THE HARMFUL DOSE.

JUST BECAUSE A CHEMICAL IS PRESENT, DOES NOT MEAN THAT IT IS HARMFUL IN THE *AMOUNT* PRESENT.

Therapeutic effect  **Toxic effect**

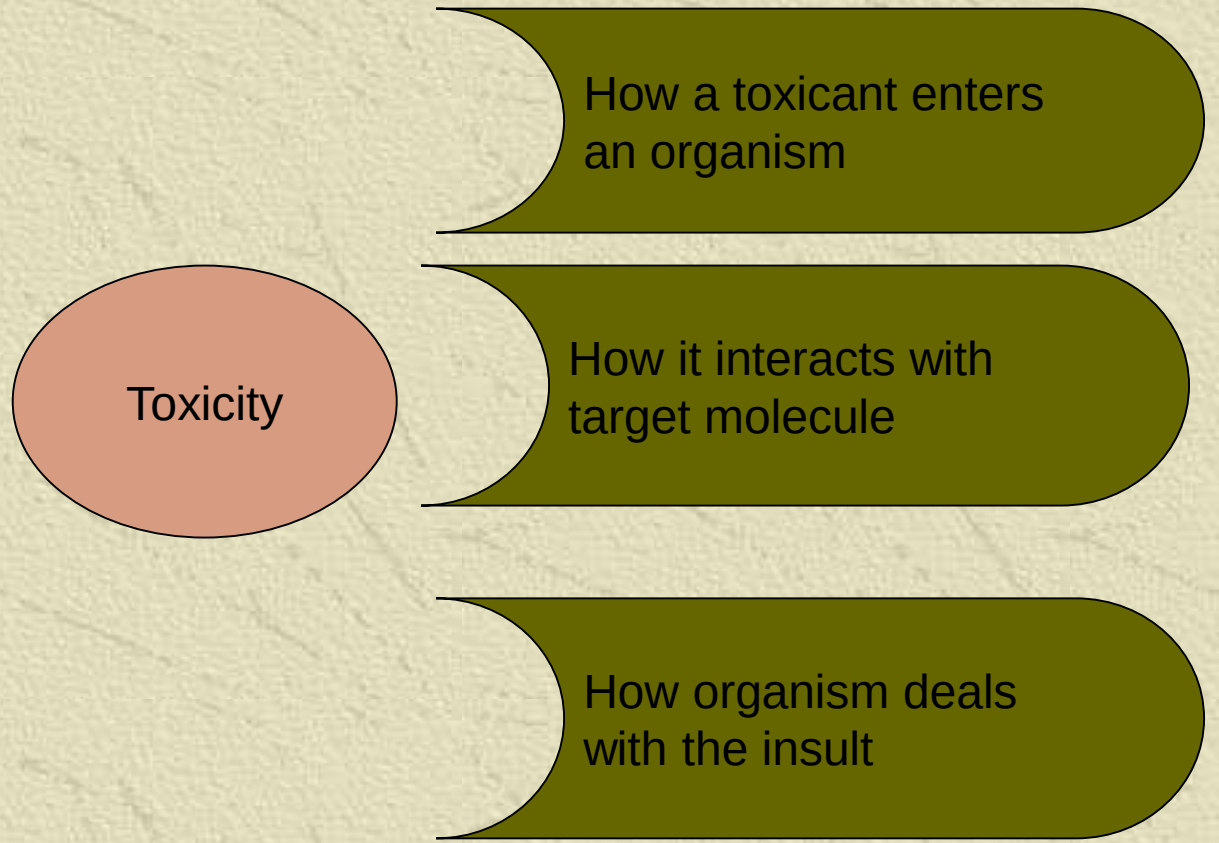
increasing dose

Organic toxins	❖Substances that were originally derived from living organisms ❖Contain carbon and often are large molecules ❖Can be synthesized (that is man-made) as well as be obtained from natural sources
Inorganic toxins	❖Specific chemicals that are not derived from living organisms (minerals) ❖Generally small molecules consisting of only a few atoms (NO_2)

Basic concepts

- **Toxicity is potential for a compound to produce injury in biological system**.
  - Usually, the word **"toxicity"** is used to describe the nature of adverse effects.
  - The toxicity is **usually** expressed **as milligrams (mg) of the substance per kilogram (kg)** of body weight that will produce defined biologic effects.

Toxicity


Toxicity
How a toxicant enters an organism
How it interacts with target molecule
How organism deals with the insult

BASIC CONCEPTS

- **The dose** is the total amount of poison received per organism (person or animal).
- **The lethal dose (LD)** is the lowest dose that causes death in any animal during the period of observation (usually 14 days). Various percentages can be attached to the LD value to indicate doses required to kill **1% (LD_1), 50% (LD_{50})** or **100% (LD_{100})** of test animals.
- **Median lethal dose (LD_{50})** or (MLD) is a commonly used measure of toxicity.
- **The lethal concentration (LC)** is the **lowest concentration** of compound in the air that causes death.
  - It is **expressed as milligrams of compound per meter cubic** of the air.

Types of doses in Toxicology

- **Exposure dose** – the amount of a xenobiotic encountered in the environment
- **Absorbed dose** – the actual amount of the exposed dose that enters the body
- **Administered dose** – the quantity administered usually orally or by injection
- **Total dose** – the sum of all individual doses

Effective dose

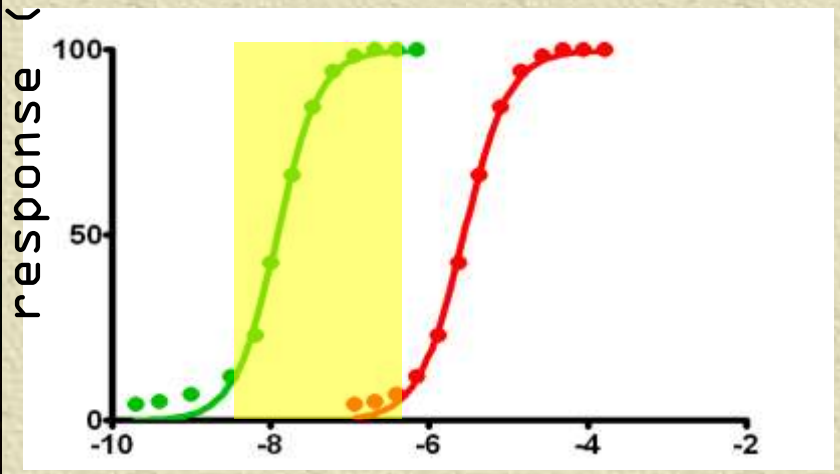
- **Effective doses** (EDs) are used to indicate the **effectiveness** of a substance. Normally, effective dose refers to a **beneficial effect** (**relief of pain**). It might also stand for a **harmful** effect. Thus the specific endpoint must be indicated.

Therapeutic Index/Ratio (TI)

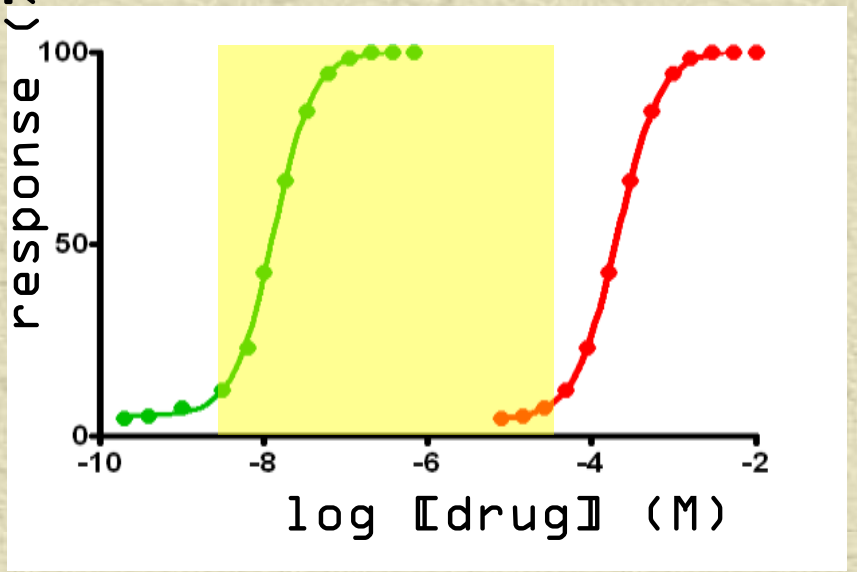
- TI (or Window) measures "**how safe a drug is**" or "**Margin of Safety**".
- **High Therapeutic Index = safe**
- **Low Therapeutic Index = not so safe**
- **The larger the ratio, the safer the drug**

Therapeutic Index (TI)

The ratio of the dose of the drug that produces an unwanted (toxic) effect to that producing a wanted (therapeutic) effect.



Small TI: e.g. warfarin



Large TI: e.g. penicillin, aspirin

Preliminary toxicity testing

- **NOAEL** (no observed adverse effects level)

Highest concentration that does not a toxic response

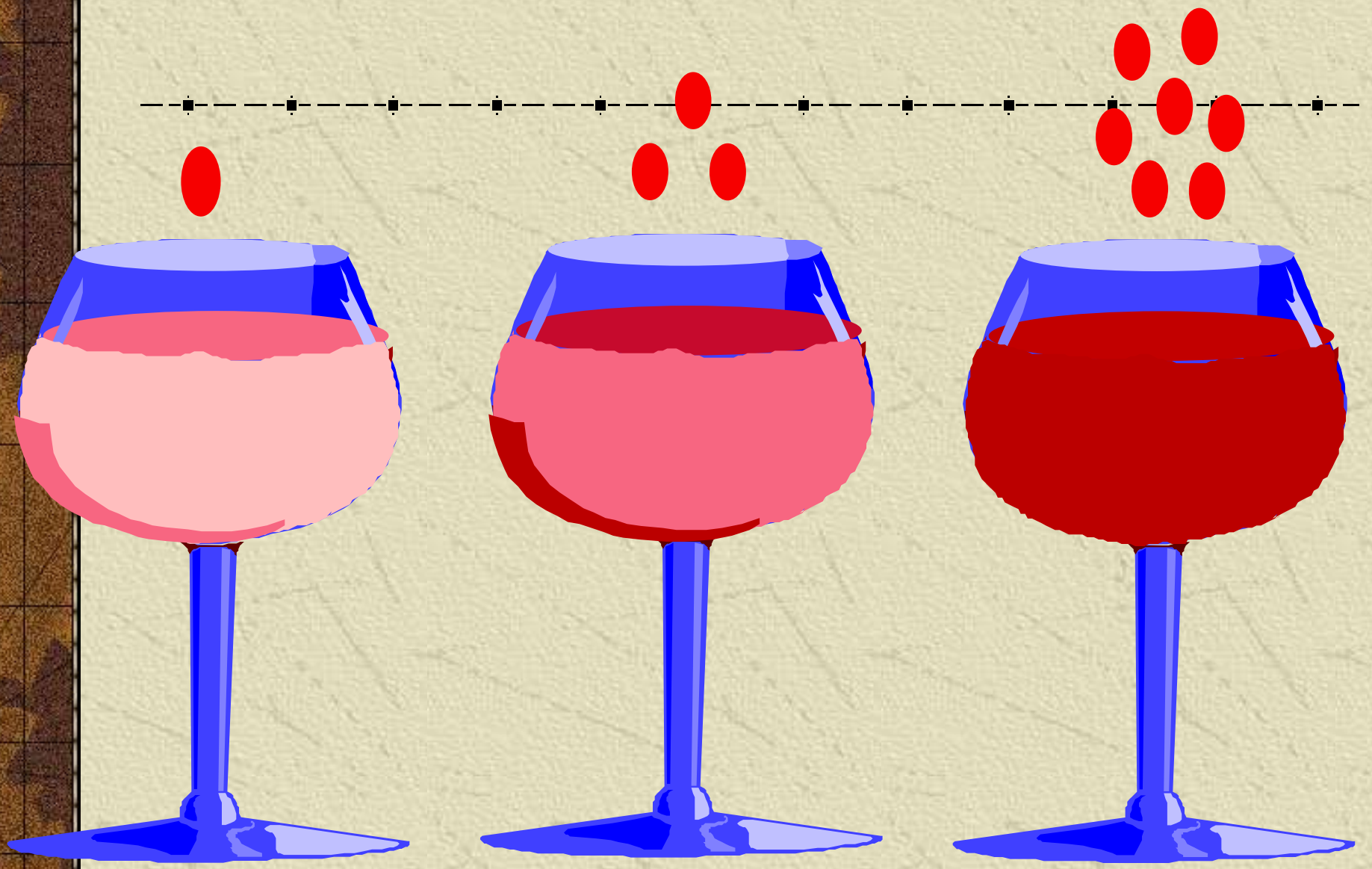
- **LOAEL**- lowest observed adverse effects level

Lowest concentration that produces a toxic response

Dose / Response

$$\text{Risk} = \frac{\text{Hazard X Exposure}}{\text{Individual Sensitivity}}$$

Effects of Amount on Response



Effects of Size on Response

Toxicity of compounds

Classification	Toxicity
Extremely toxic	< 1 mg/kg
Highly toxic	1 - 50 mg/kg
Moderately toxic	50 - 500 mg/kg
Slightly toxic	0.5 - 5 g/kg
Practically nontoxic	5 - 15 g/kg
Relatively harmless	> 15 g/kg

Agent LD_{50} (mg/kg)

Toxicity rating	Example	LD_{50} (mg/kg)
Slightly toxic (5-15 g/kg)	Ethanol	8000
Moderately toxic (0.5-5 g/kg)	Sodium chloride Parathion	4000 1300
Very toxic (50-500 mg/kg)	Aspirin Paracetamol	300 300
Extremely toxic (5-50 mg/kg)	Theophylline Diphenhydramine	50 25
Super Toxic (<5 mg/kg)	Potassium cynanide Digoxin Tetrodotoxin Botulinum toxin	3 0.2 0.01 0.00001 (10 ng/kg !)

Puffer fish

BASIC CONCEPTS

- **Acute poisoning** is a term that describes the biologic effects of a **single high dose** of the poisons or multiple doses during 24-hour period.
- **Sub-acute poisoning –** 1 month repeated doses
- **Fulminant poisoning**
- **Sub-chronic poisoning** – 1-3 months repeated doses
- **Chronic poisoning** (>3 months) - **repeated** (**prolonged**) **exposure** to relatively low doses of the poisons. The ratio of the acute to chronic LD_{50} doses is the **chronicity factor.**

$$Chronicity\ factor = \frac{Acute\ LD_{50}}{90\ day\ LD_{50}}$$

Systemic and organ toxins

- **A systemic toxin** is one that affects the entire body or many organs rather than a specific site
- **An organ toxin** is one that affects only specific tissues or organs

Adverse Drugs Reactions (ADRs)

ADRs are noxious or unintended responses occurring at **therapeutic** doses (WHO definition) ~ 5% of all acute hospital admissions

Type A (**augmented**) ADRs	Effects are: · related to known pharmacology, but undesirable · common, dose-related · predictable	Examples · haemorrhage with anticoagulants · respiratory depression with opioids · sedation with anxiolytic and older antihistamine drugs
Type B (**bizarre**) ADRs	Effects are: · unrelated to known pharmacology · rare · unpredictable · often idiosyncratic	Examples · anaphylaxis with penicillin · allergic liver damage by halothane · bone marrow suppression by chloramphenicol · individual allergy/genetic basis

Factors determining adverse effects

- Intrinsic toxicity
- Dose
- Exposure conditions
- Response of host

Intrinsic toxicity

- **Chemical properties**
  - Molecular structure & functional groups
  - Solubility – Insolubility
  - Volatility
  - Stability (light, water, acids, enzymes….)
  - Reactivity
- **Physical properties**
  - Gas (density….)
  - Liquid (vapour pressure….)
  - Solid (crystal structure, size, shape….)

Routes of Exposure

gastrointestinal tract (ingestion)

lung (inhalation)

skin (topical, percutaneous or dermal)

Injection (s.c., i.v., i.m., i.p. bite, puncture, cut)

- The **nature and magnitude** of **toxic effects** depend **on many factors,** among which are:
  - **Physicochemical properties of the substance**
  - **Biotransformation**
  - **Condition of exposure** (time, temperature etc.)
  - **Presence of bioprotective mechanism** (antioxidant systems etc.)

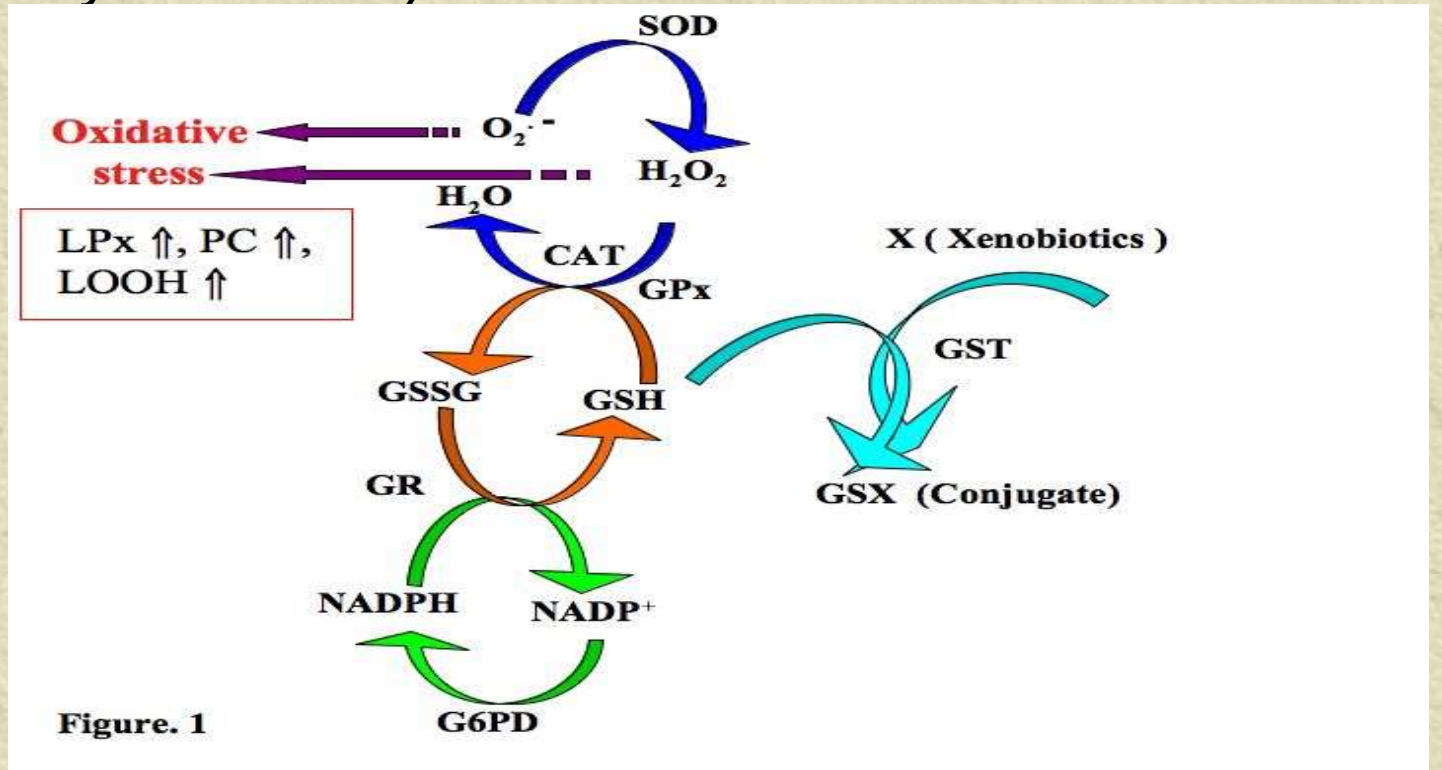
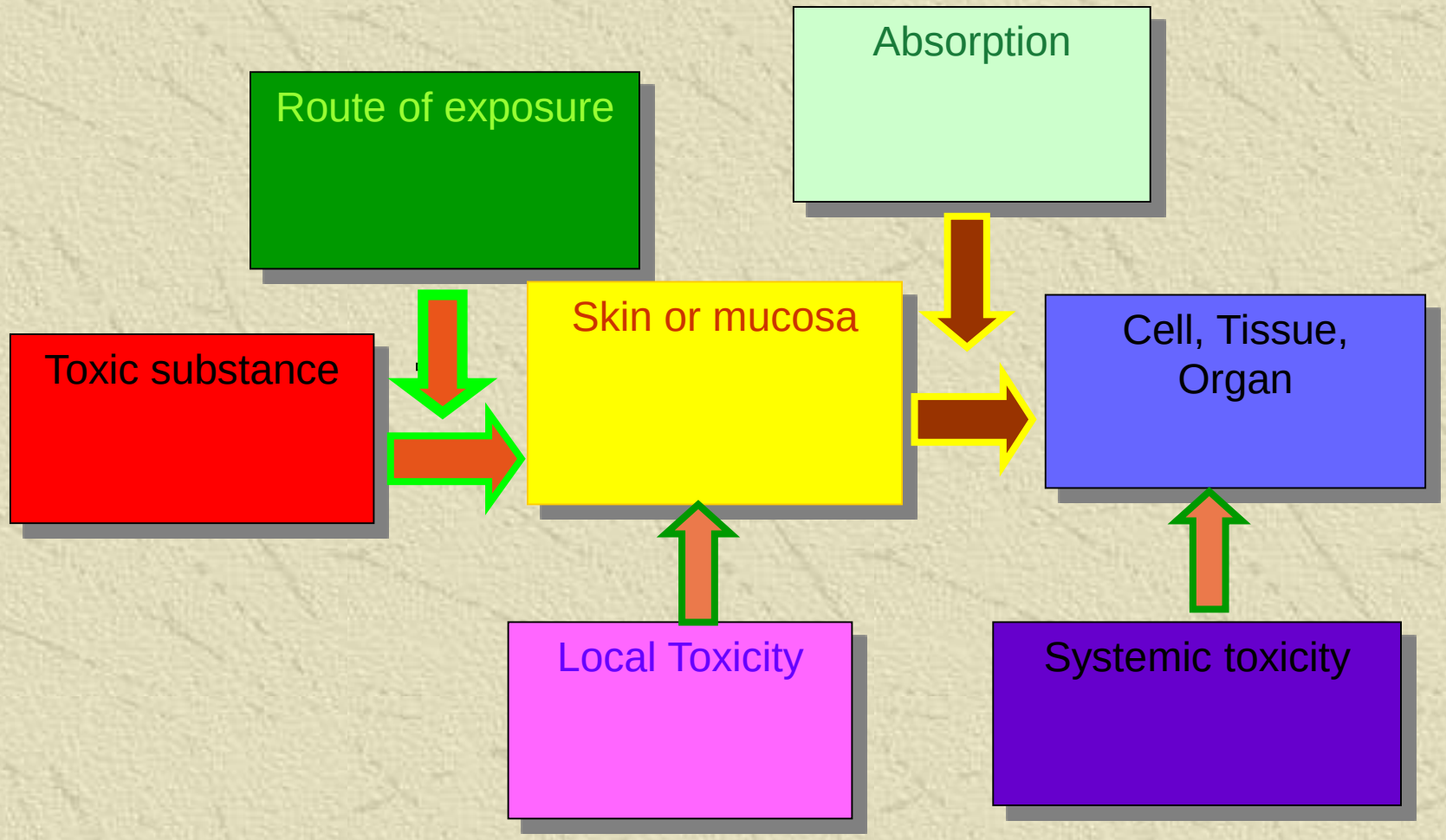


Figure. 1

- Prolonged exposure to a compound may allow people to develop **tolerance** to the poison. In this case the size of the dose producing lethality upon repeated exposure increases.



The induction of toxic effects largely depends on the disposition of the substances concerned.

Interaction of a substance with a living organism

Kinetic Phase

absorption, distribution, metabolism, and excretion → the fate of substance in the body

the body has a number of defense mechanisms at various levels of the kinetic phase, metabolism & excretion

Dynamic Phase

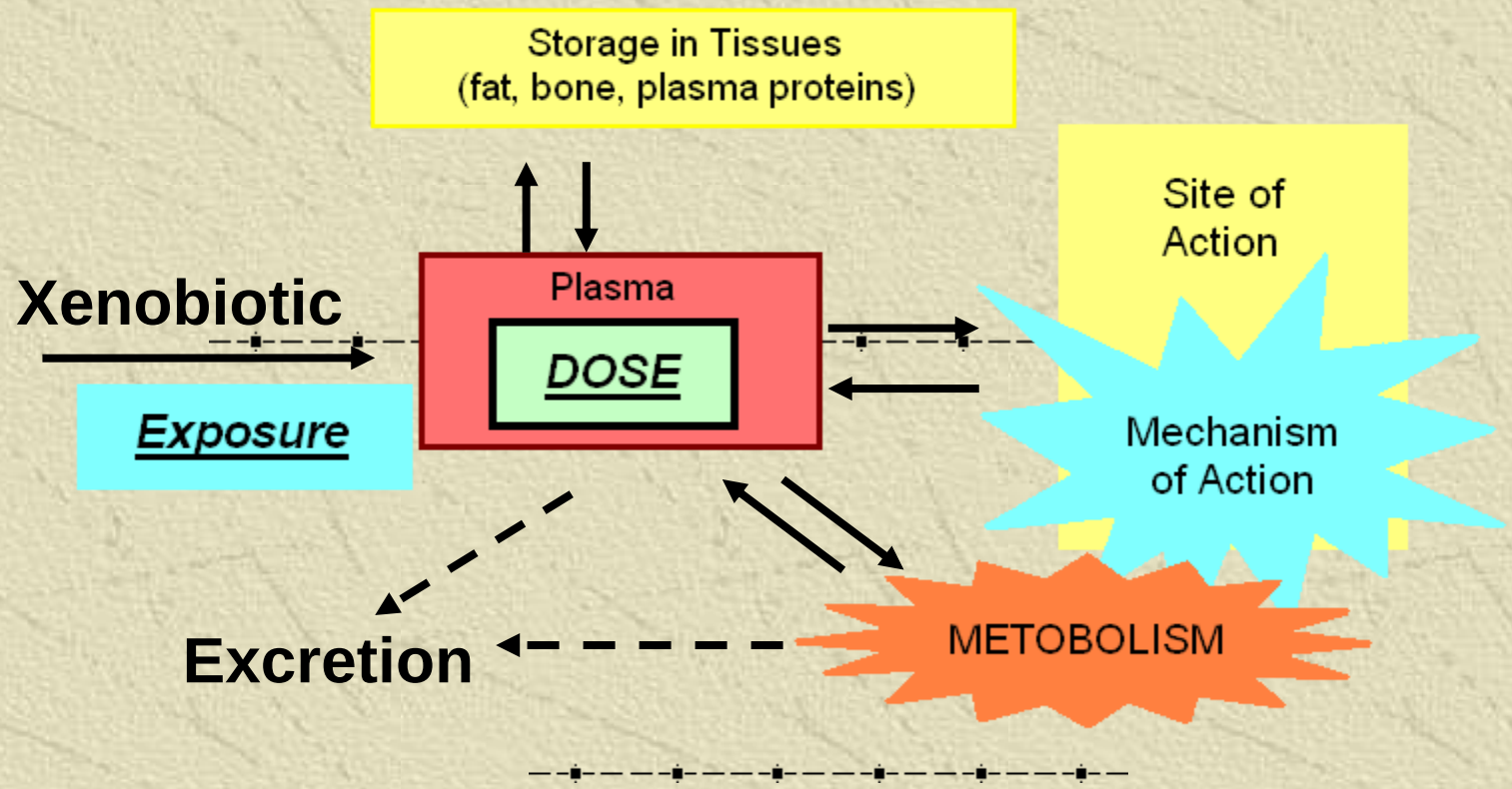
interactions of the toxicant within the organism and describes processes at organ, tissue, cellular, and molecular levels

BASIC CONCEPTS

- **Toxicokinetics is the movement and disposition of poisons in the organism (ADME)**
  - **A**bsorption;
  - **D**istribution of chemical within the body;
  - **M**etabolism (Biotransformation);
  - **E**xcretion;
- A chemical absorbed into the bloodstream is distributed throughout the body, including the site where it produces damage.
  - This site is usually the **target organ** or **target tissue**.
  - A chemical may have **one or several target organs**, and in turn, **several chemicals** may have the **same target structure**.

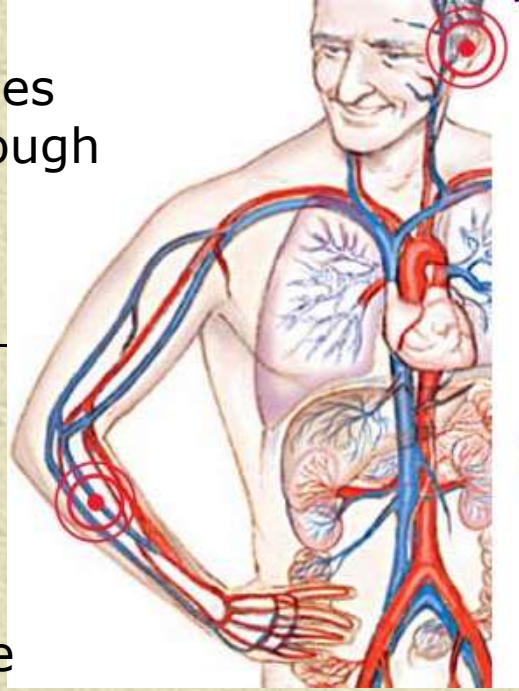
- Toxicants do not affect all organs to the same extent
- A toxicant may have several sites of action and target organs
- Multi-toxicant exposure may target the same organ
- The target organ may not be the site for storage

Toxicokinetics



Background

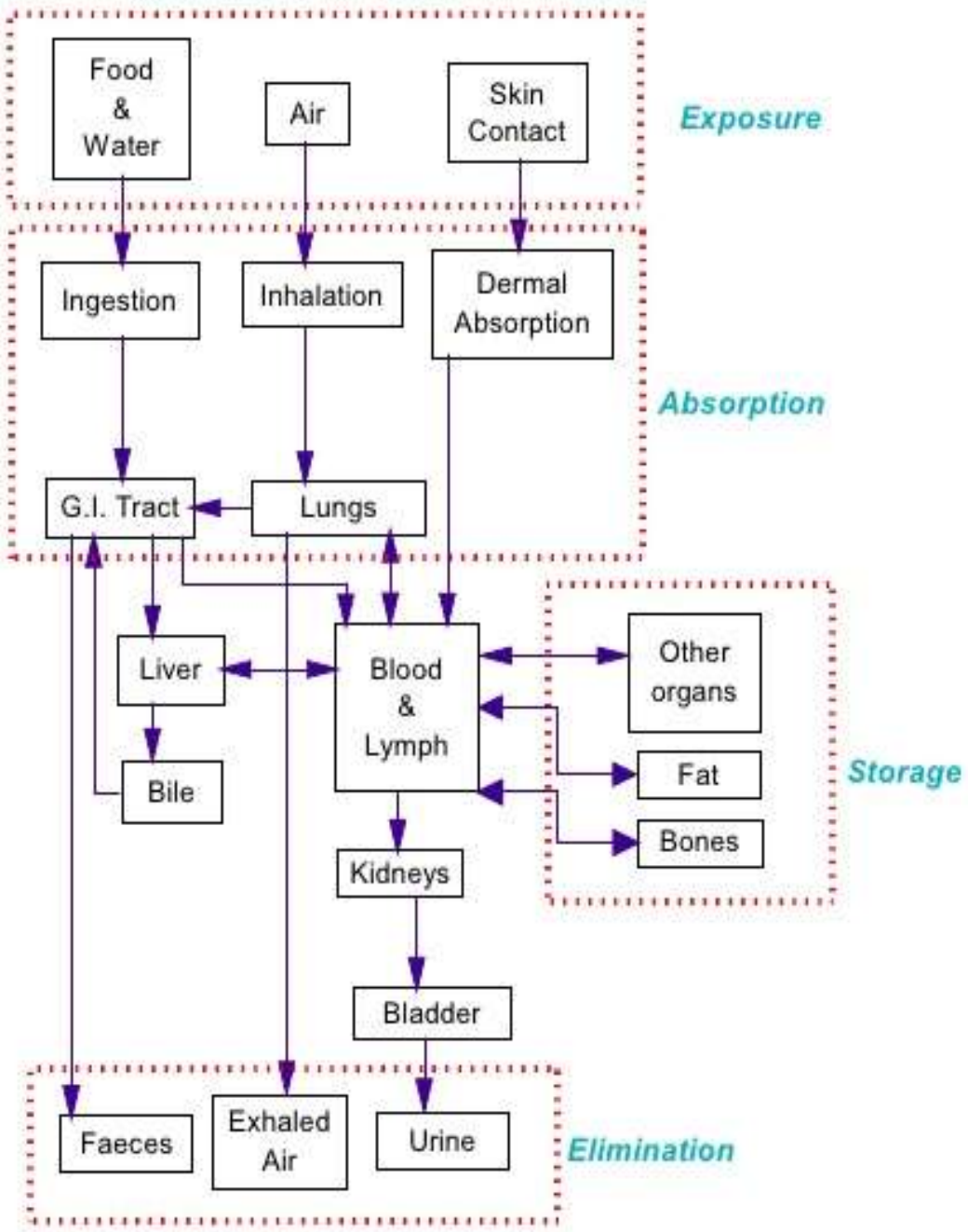
Chemical molecules easily diffuse through membranes



Most substances that enter the body are lipid-soluble

Metabolized in the liver

Reach the target site & produce a toxic response


Food & Water
Air
Skin Contact
Exposure
Ingestion
Inhalation
Dermal Absorption
Absorption
G.I. Tract
Lungs
Liver
Blood & Lymph
Other organs
Fat
Bones
Storage
Bile
Kidneys
Bladder
Faeces
Exhaled Air
Urine
Elimination

NATURE OF TOXIC EFFECTS

- The major mechanisms of action of drugs and chemicals are:

1. **Inflammation** - frequently local response to irritant chemicals or components of systemic tissue injury. - The inflammatory response may be **acute** or **chronic**.
2. **Necrosis** - this is death of tissue or cells, resulting from a variety of pathological processes: **corrosion**, **severe hypoxia**, **membrane damage**, **reactive metabolite binding**, **inhibition of protein synthesis** and **chromosome injury**.
3. **Enzyme inhibition** by chemical, which may **inhibit biologically vital pathway**.

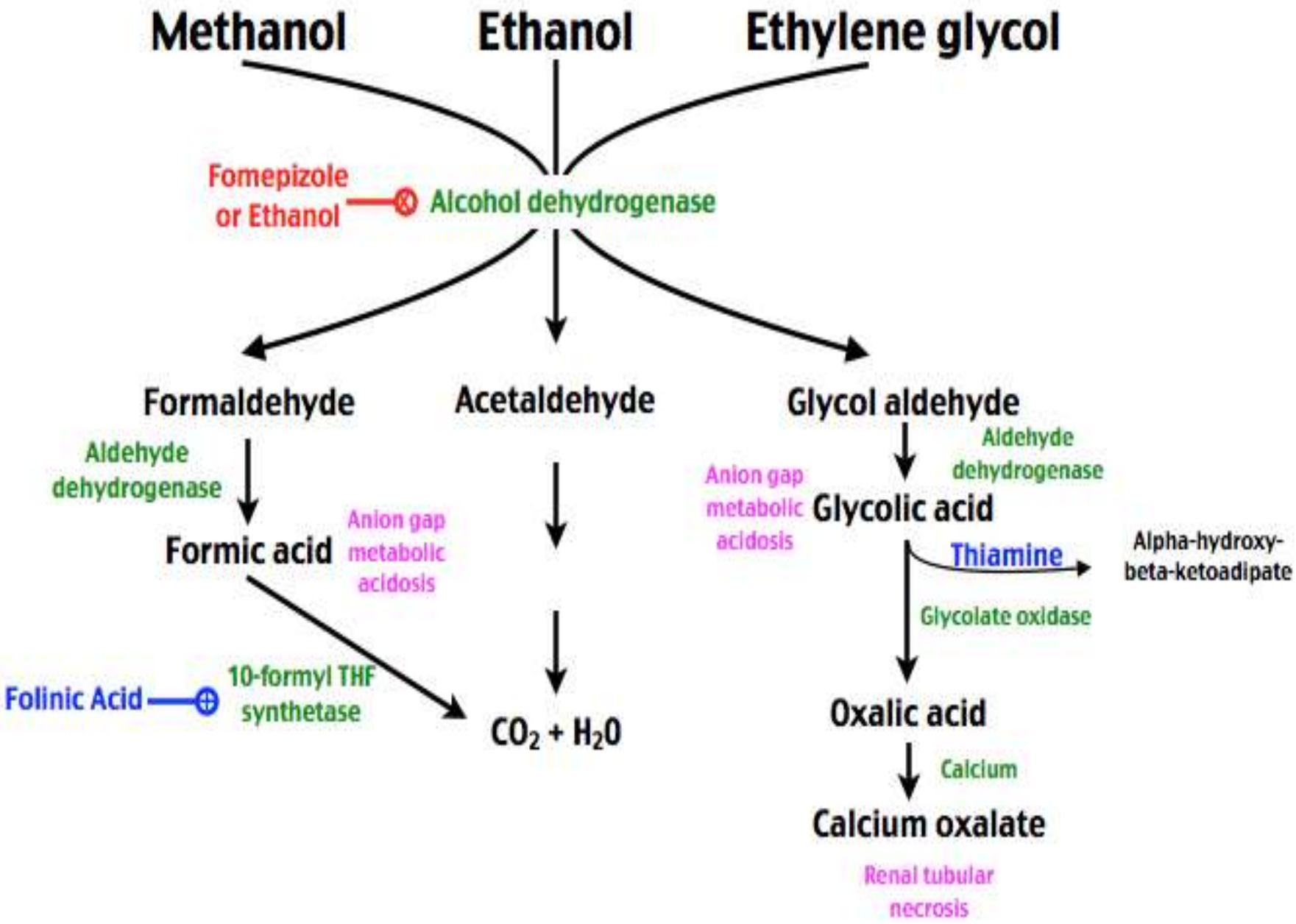
NATURE OF TOXIC EFFECTS

4.Biochemical uncoupling of the synthesis of **high-energy phosphate molecules**.

- In this case the electron transport continues and results **in excess liberation of energy as heat**.

5.Lethal synthesis occurs when foreign substances of close structural similarity to normal biological substances **metabolize** to a **toxic product**.

Toxic Alcohol Metabolism



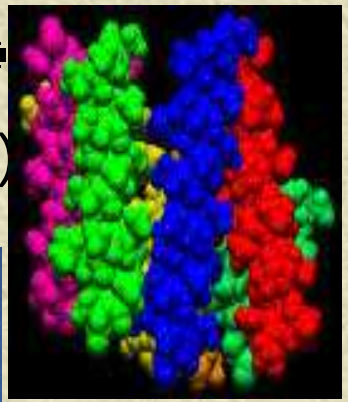
6. **Lipid peroxidation** in biological membrane by free radicals starts a chain of events causing cellular dysfunction and death.

7.**Covalent binding** of electrophylic reactive metabolite to nucleophylic macromolecules (e.g., S, O, and N atoms in cysteine, tyrosine, and histidine, respectively) and nucleic acids (e.g., N and O atoms in purine or pyrimidine).

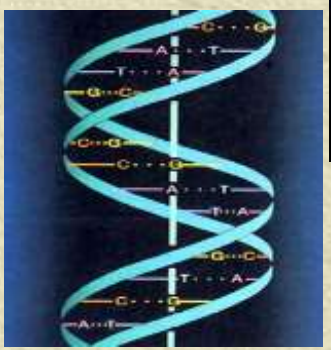
8.**Receptor interaction** at a cellular or macromolecular level with specific chemical structures.

- It may modulate the normal biologic effects, mediated by the receptor.

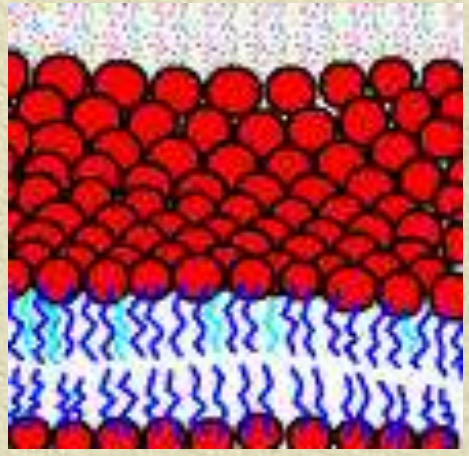
Some xenobiotics cause toxicity by disrupting normal cell functions:



- Bind and damage proteins (structural, enzymes)
- Bind and damage DNA (mutations)



- Bind and damage lipids
- React in the cell with oxygen to form "free radicals" which damage lipid, protein, and DNA

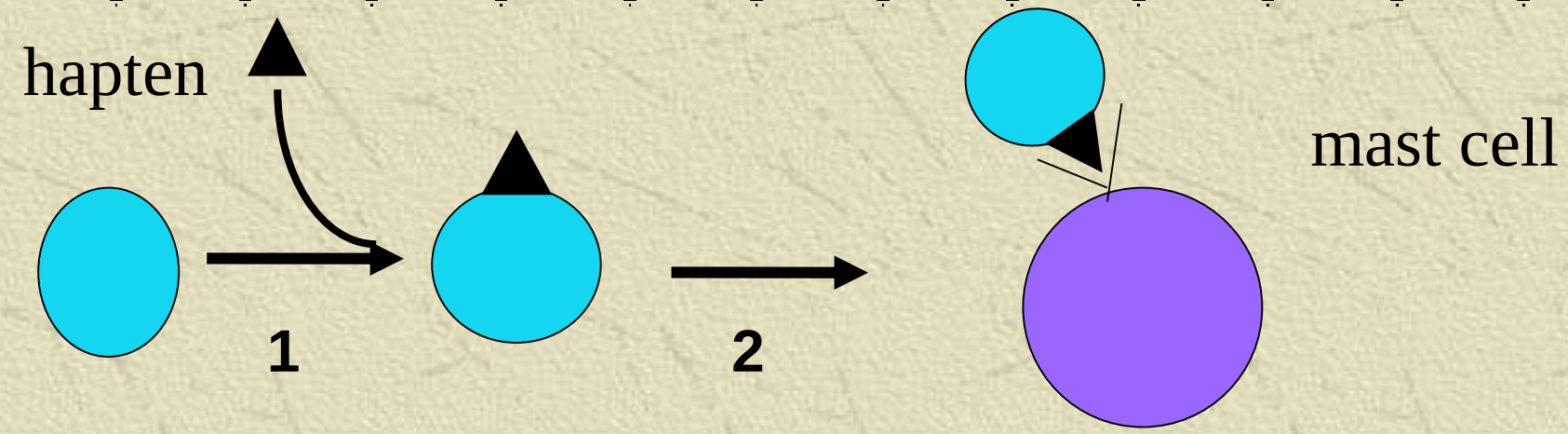


NATURE OF TOXIC EFFECTS

9.Immune-mediated hypersensitivity reaction by antigenic materials, resulting respectively in **allergic contact dermatitis** and **asthma**.

- **Type I hypersensitivity reaction –** IgE-mediated mast cell degranulation
- **Type II antibody-mediated cytotoxic hypersensitivity-** involve haematological reactions i.e. those pertaining to the blood cells and blood-forming organs
- **Type III immune complex-mediated** hypersensitivity
- **Type IV delayed-type** hypersensitivity

Type I hypersensitivity reactions can trigger anaphylactic shock



low MW allergen (eg. bee venom, peanut oil)

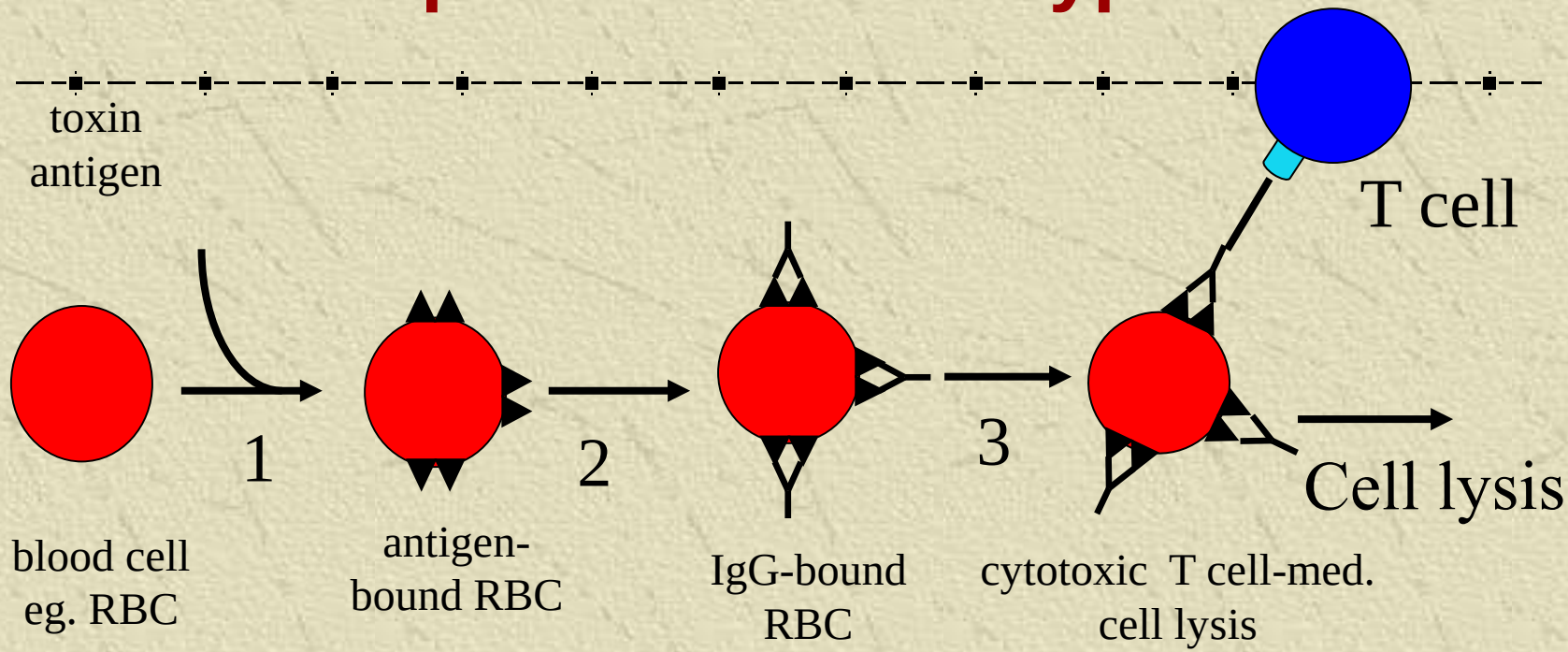
immunogenic conjugate eg. penicillin 75% of all deaths

IgE recognition triggers histamine release

bronchoconstriction
vasodilation
inflammation

treated with adrenaline

Type II hypersensitivity reactions deplete blood cell types



These reactions can deplete:

Red blood cells (haemolytic anaemia) eg. sulfonamides

Neutrophiles (agranulocytosis) eg. certain NSAIDs

Platelets (thrombocytopenia) eg. quinine and heparin

10. **Immunosuppression** by chemicals.

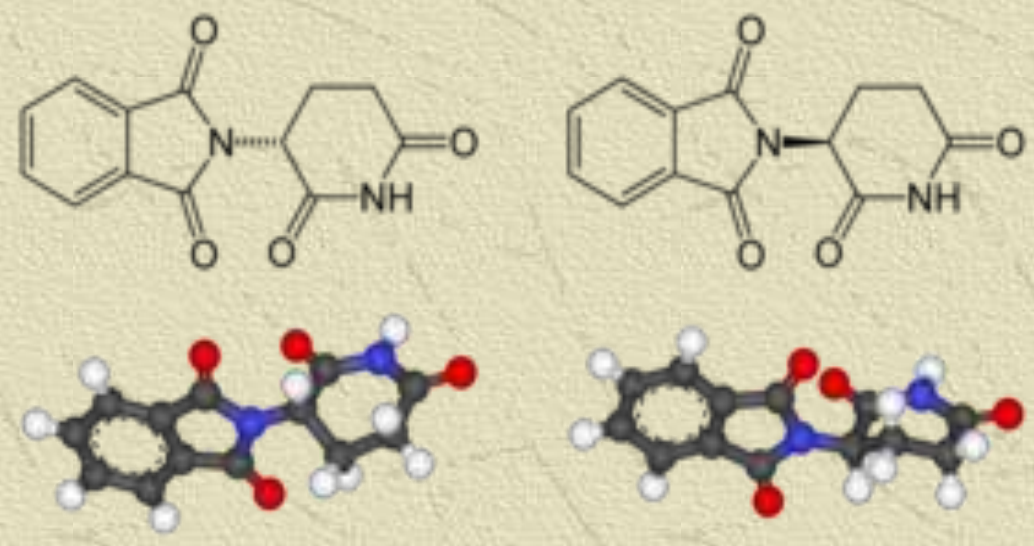
- The adverse effect is manifested as increased susceptibility to ineffective agents.

11. **Neoplasia,** resulting from aberration of tissue growth and control mechanisms of cell division and leading to abnormal proliferation.

12. **Genotoxicity** caused by chemicals, which interact **with DNA** and possibly, lead to **heritable changes**.

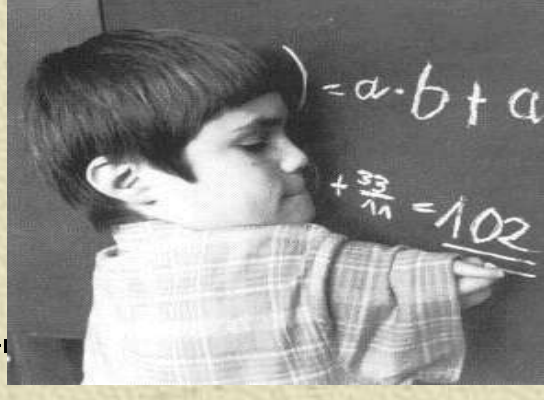
Teratogenesis - the creation of birth defects during fetal development

Teratogens: substances that induce birth defects.



Thalidomide
(R)-enantiomer
sedative

Thalidomide
(S)-enantiomer
teratogen



1950’s- thalidomide was synthesized by the Grünenthal
Non-toxic at high doses in all animals species tested

1957 - marketed throughout Europe as a non-lethal hypnotic and sedative, recommended as an anti-emetic to treat morning sickness in pregnant women

1961 - thalidomide was the best-selling sleeping pill in West Germany and the UK
However, thalidomide produced teratogenic effects in 100% of fetuses exposed between 3-6 weeks gestation

The thalidomide disaster heralded modern teratogenicity testing

- An estimated 8-12,000 infants were born with deformities caused by thalidomide, and only about 5,000 of these survived beyond childhood.
- In fact, thalidomide is a useful drug, used today to treat **leprosy** and **multiple myeloma** (probably due to inhibitory activity on tumour necrosis factor (TNF-α production).

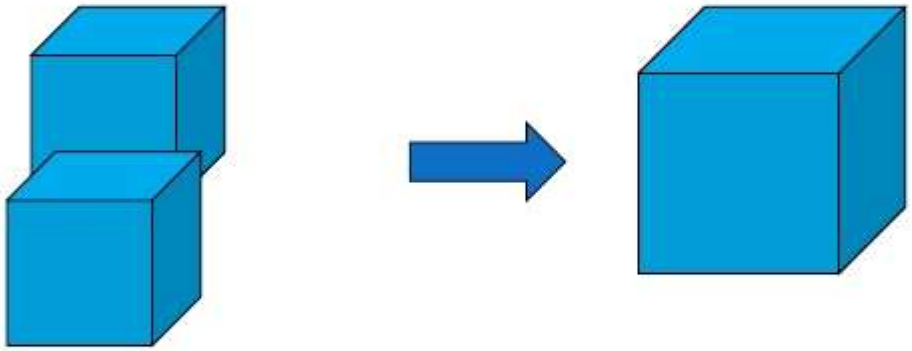
Interactions

- Additive
- Antagonistic
- Synergistic
- Potentiation

Interactions - Independent

No interaction

Interactions - Additive

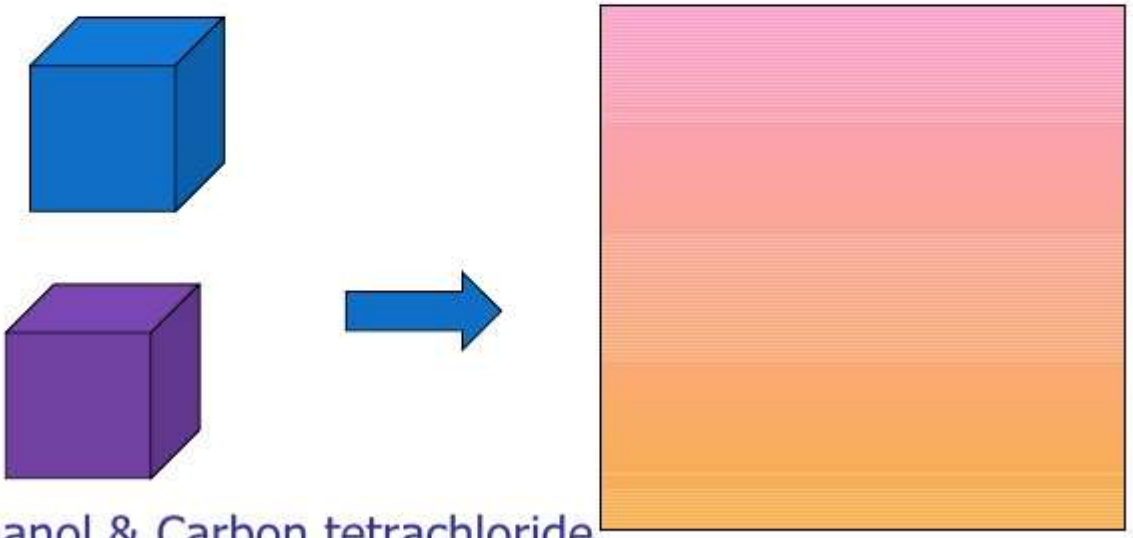


The combined effect is equal to the individual sum of the effects

Example – Narcotics, usually same target organ same mechanism

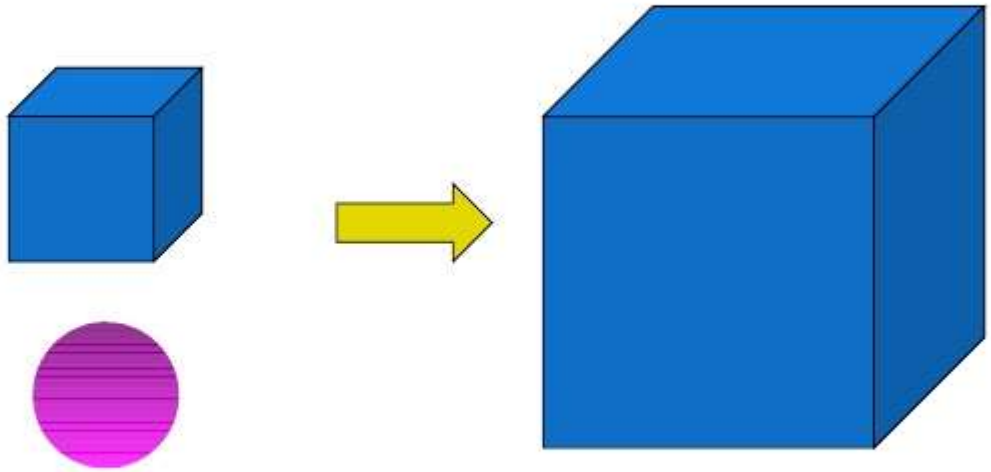
Interactions - Synergistic

Combined effect is greater than sum of individuals



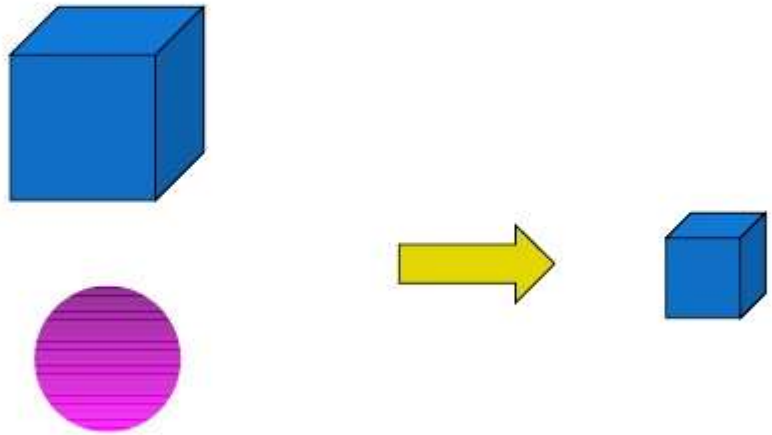
e.g. Ethanol & Carbon tetrachloride

Interactions - Potentiation



Substance increases the effect of a hazardous substance
e.g. Isopropanol & carbon tetrachloride,
barbiturates and solvents

Interactions - Antagonistic



Substance reduces effect of another substance
Cd & Zn – less kidney damage

CLASSIFICATION OF TOXIC AGENTS

- The toxic agents are classified in a variety of ways, depending on their **target organ** (liver, kidney, etc.), their **use** (pesticides, solvents, etc.), their **origin** (animal and plant toxins) etc. In our classification the poisons, which cause intoxications in disaster situations are divided **into five groups, according to their mechanism** of the toxic effect:

1. **Anticholinesterase compounds** - organophosphorus esters, carbamate esters.
2. **Cellular asphyxia** - inducing compounds: carbon monoxide, cyanide etc.
3. **Pulmonary edema-** inducing compounds: phosgene, ammonia, chlorine, nitrogen oxides, etc..
4. **Sensory irritant compounds**: mineral acids, modern riot control compounds, etc.
5. **CNS depression** (narcosis) - inducing compounds: aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, carbon disulfide, etc.