Toxicology

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Introduction

WHAT TOXICOLOGISTS DO?

- involved in the recognition, identification and quantitation of hazard
- develops standards and regulations to protect health and the environment
- involved in safety assessment and use of data as basis for regulatory control of hazards
- determines risk associated with use of chemicals/physical agents

So Toxicology is the study of:

- How toxicants enter the organism?
- How toxicants affect the organism?
- How toxicants are eliminated from (leave) the organism?

What is Toxicology ?

Definition of Toxicology

- the basic science of poisons (old)
- the study of the adverse effects of chemical /physical agents on biological systems (new)

- The study of the negative effects of chemical and physical agents on living organisms
- Toxicology is the quantitative and qualitative study of the adverse effects of toxicants on biological system

Toxicology Branch

- **According to object of study:**

  - Animal Toxicology
  - Human Toxicology
  - Plant Toxicology
  - Insect Toxicology
  - Livestock Toxicology

- **According to field of study:**
  - Environmental Toxicology
  - Food Toxicology
  - Occupational Toxicology
  - Clinical Toxicology
  - Forensic Toxicology
  - AnalyticToxicology…..etc.

- **According to target organ of study:**

- Liver Toxicology
- Kidney Toxicology
- Neurotoxicology
- Immunotoxicology
- Hemotoxicolgy
- Reproductive toxicology
- Pulmonary toxicology ….. etc

- **According to mechanism of study:**

- Cellular Toxicology
- Molecular Toxicology
- Membrane Toxicology
- Biochemical Toxicology
- Genetic Toxicology…. etc

Scope of Toxicology

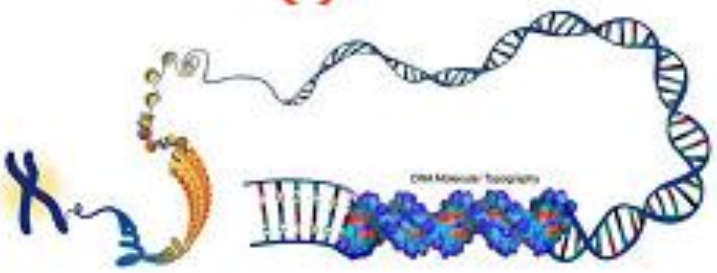
Toxicology is multidisciplinary as it entails:

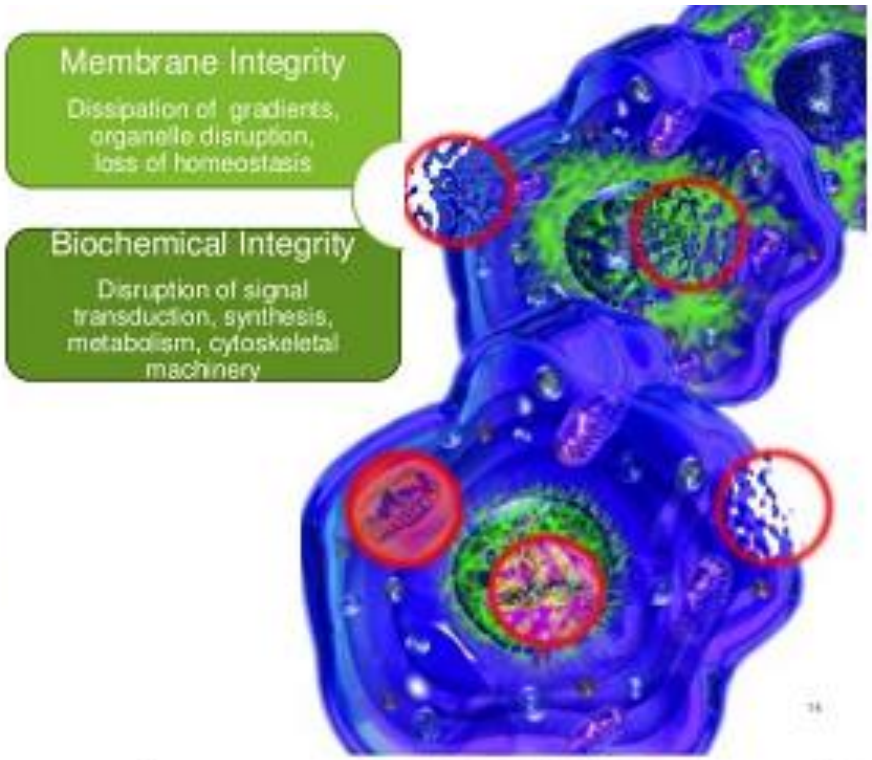
1-Mechanistic Toxicology:

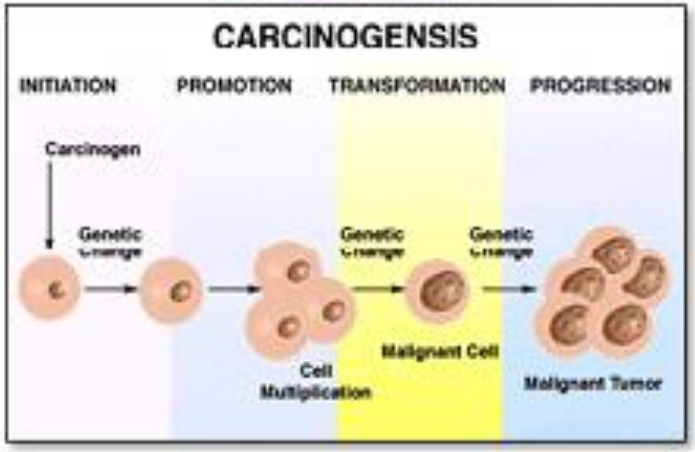
Mechanistic understanding of toxic effects

Example:

Biochemical toxicology,
Behavioral toxicology,
Carcinogenesis,
Teratogenesis,
Mutagenesis







2- Applied Toxicology :

Clinical Toxicology: It deals with emergency cases such as overdoses, poisonings, attempted suicides by:

* Emergency care for patients.

*Management of sign and symptom

*Identification and quantification of the drug, poisons, chemicals…etc

Forensic Toxicology: To aid medical or legal investigation on death, poisoning and drug use

Economic Toxicology: Toxic effect of those chemicals intentionally administered for a specific purpose

a) Therapeutic agents-human and veterinary,
b) food additives & cosmetics
c) Chemicals used for selective elimination of other species – e.g. insecticides

Environmental Toxicology: Study of the harmful effects of various chemical, biological and physical agents on environment & living organisms.

3-Analytical Toxicology:

It is the detection, identification and measurement of foreign compounds (xenobiotics) in biological and other specimens

4-Regulatory Toxicology:

Risk assessment:

It deals with analysis of toxicological data for the determination of:

Safe level of drugs for humans, safe level of heavy metals in water, safe levels pesticides...etc.

Legal aspect:

Concerned with formulation of laws which are intended to minimize the effect of toxic chemicals on humans health & the environment.

Toxicology Subdivisions

- Occupational (Industrial) Toxicology
  - Time weighted average (TWA)
  - Short-term exposure limit (STEL)
  - Threshold limit value-ceiling (TLV-C)
- Environmental Toxicology
  - Detrimental effects of chemicals in the environment
  - Important factors:
    - Persistence
    - Mobility
    - Bioaccumulation
    - Biomagnification

- Ecotoxicology—focus on populations of organisms.
- Other categories:
  - Forensic
  - Clinical
  - Mechanistic
  - Regulatory

Factors Influencing Toxicity

There are many factors which can enhance, increase or decrease toxicity. These factors are divided into

I-Factors related to the host:

species, sex, age, genetics, diet, health

II- Factors releated to the Toxicant /poison:

Dose, **route of exposure**, chemical structure, composition and formulation, innate chemical activity, temperature

I-Factors related to the host:

A-The species.

-Rats cannot vomit and expel toxicants before they cause severe irritation, whereas humans and dogs are capable of vomiting.

Selective toxicity: ***refers to species differences in toxicity response between two species simultaneously exposed*** **- an insecticide is lethal to insects but relatively nontoxic to mammals…???**

Malthion

Oxidation by ME - rapid in insects & slow in mammals

Hydrolysis - Slow in insects & rapid in mammals

Malaoxone - Lethal to insects; Inactive substance to others

Species, strain, individual variations

variations in enzyme allele activities, concentration; some species have enzyme defects, or unique biochemical biotransformation pathway

B) Sex:

Men traditionally weigh more than women.

Therefore, doses of a chemical in a male would be expected to produce lower blood and tissue levels than the same in females, simply because of the male's larger blood volume and greater tissue mass which dilute the chemical.

- **For substances that are injected intramuscularly, lower blood levels can be expected with those drugs in individuals (usually men) with a greater muscle mass.**

- **Also, drugs with a high lipid coefficient that normally partition into fat may produce different toxicological responses in different sexes, based on the individual's ratio of body fat/total weight.**

Sex (includes pregnancy status)

hormone levels affect enzyme concentrations (production) and activities

Examples:

Hexobarbital: higher activity in male vs. female rats.

Parathion: metabolized (and bioactivated) more rapidly in females

C) Age

Some chemicals are more toxic to infants or the elderly than to adults.

Foetus/newborns have undeveloped biotransformational capabilities and deficient blood/brain barrier, **aged people** may have altered enzyme levels and/or decreased blood flow (due to decreased activity levels and reduced capillary beds), impaired excretory function.

Example: young children absorb 4-5 times more Pb and 20 times more Cd than adults

Because these metal ions transport into the body via the children's very efficient Ca++ uptake system needed to support growing bones more susceptible to metal toxicity.

Example: Methyl mercury toxicity to young ones – developing brain

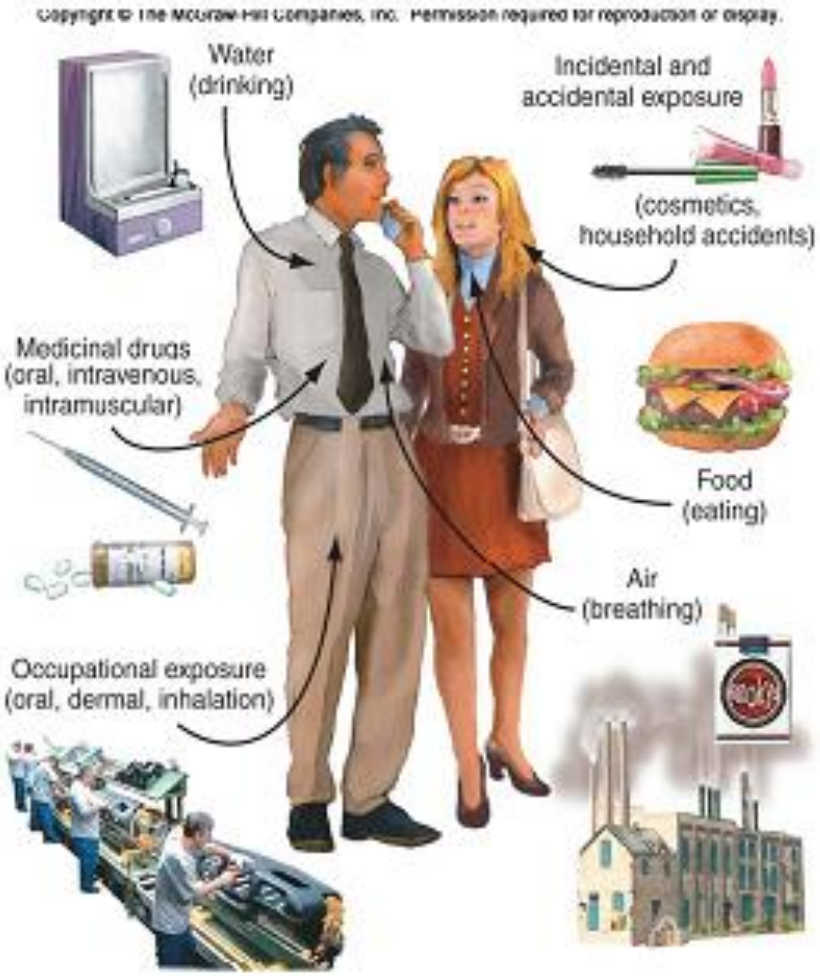
II Factors releated to the Toxicant /poison:

Route of exposure

- Inhalation (mouth or nose to lungs) then into blood(+*)
- Ingestion (mouth to stomach) then into blood(+)
- Injection (cuts, punctures in skin) into blood: intravenous, intramuscular, intraperitoneal
- Dermal absorption (through skin) into blood(+*)

+ Involve membrane transport

* **Greatest threats in industry**



Typical Effectiveness of Route of Exposure: iv > inhale > ip > im > ingest > topical

Biotransformation

It is the biochemical/enzymatic reactions that convert lipophilic compounds to more hydrophilic metabolites generally in preparation for excretion.

(It is the SUM of the processes by which a xenobiotic is subjected to chemical change by living organisms)

Bioactivation

Bioactivation reactions are a subset of biotransformation reactions

It is the biochemical/enzymatic formation of reactive or more toxic intermediates (which may then cause harm).

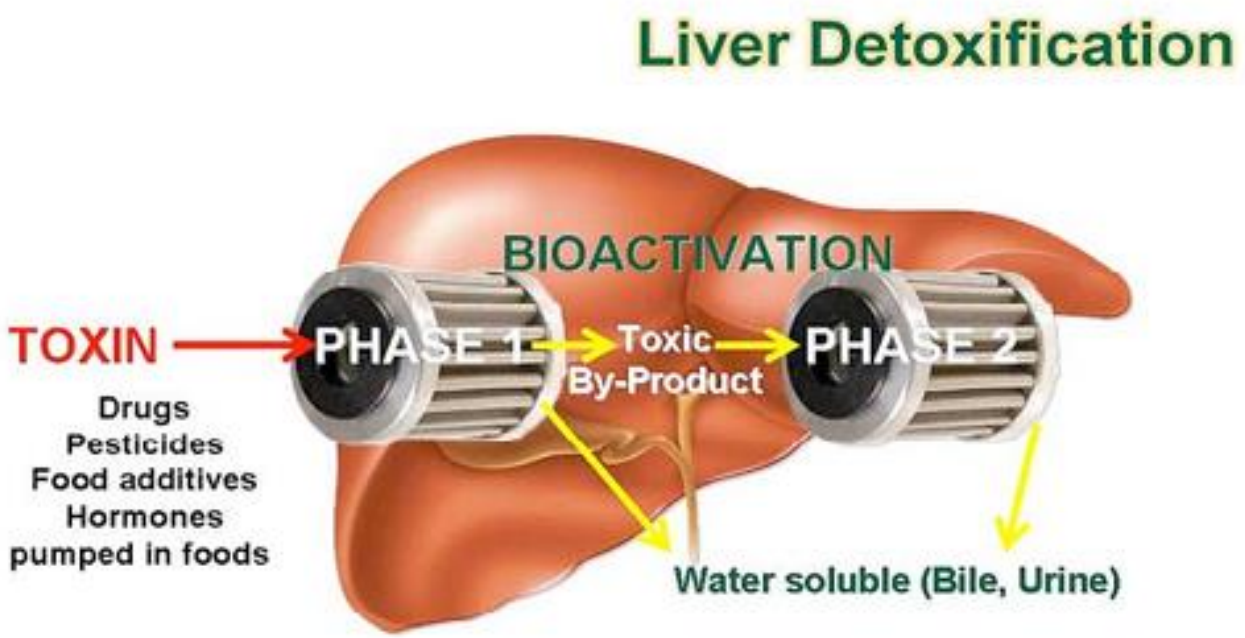
A metabolic process in which a product that is chemically reactive is produced from a relatively inactive precursor .

Bioaccumulation – Agents such as lead, mercury, carbon tetrachloride that build up in organs and have low excretion rate.

- Low exposure over a long time leads to chronic toxic response

Elimination

- Excretion through kidneys, liver and lungs
- **Detoxification** is the biotransformation of chemicals into something less harmful
- Storage in fatty tissue



Chronic vs. Acute Exposure

Health effects caused by exposure to toxic substances are usually differentiated based on whether the adverse effect occurs after **long-term** (chronic) exposure or **short-term** (acute) exposure.

Some substances, such as cyanide, are acutely toxic, which means they cause rapid death after a brief exposure to a lethal (often small) dose.

The effects of other substances, such as asbestos, are more often cumulative, causing measurable damage only after years of exposure.

Systemic Toxicity - Toxicity may occur at multiple sites. This is referred as systemic toxicity.

a) Acute Toxicity:

It occurs almost immediately (hours/days) after an exposure to single dose or a series of doses received within a 24 hour period.

Death is a major concern in cases of acute exposures. Examples are:

-In 1989, 5,000 people died and 30,000 were permanently disabled due to exposure to methyl isocyanate from an industrial accident in Bhopal, India.

-Many people die each year from inhaling carbon monoxide from faulty heaters.

Sub acute: **- one month /repeated doses**

b) Subchronic Toxicity (reversible) - 1-3 months, repeated doses

It results from repeated exposure for several weeks or months.

This is a common human exposure pattern for some pharmaceuticals and environmental agents.

Examples are:

-Ingestion of Coumadin tablets (blood thinners) for several weeks as a treatment for venous thrombosis can cause internal bleeding.

-Workplace exposure to lead over a period of several weeks can result in anemia.

c) Chronic Toxicity (irreversible):

> 3months repeated dose

There is a latency, long period of time before you see effect

It is a cumulative damage to specific organ or system and it takes many months or years to become a recognizable clinical disease.

This damage is so severe that the organ can no longer function normally (irreversible) and a variety of chronic toxic effects may result.

Examples are:

-Cirrhosis in alcoholics who have ingested ethanol for several years

-Chronic bronchitis in long-term cigarette smokers

-Pulmonary fibrosis in coal miners (black lung disease)

Measures of Toxicity

- Toxicity is measured as clinical “endpoints” which include
  - Mortality (death)
  - Teratogenicity (ability to cause birth defects)
  - Carcinogenicity (ability to cause cancer), and,
  - Mutagenicity (ability to cause heritible change in the DNA)
- **2 measures of mortality** – the **LD_{50}** and the **LC_{50}**

The Median Lethal Dose

LD_{50}

The amount (dose) of a chemical which produces death in 50% of a population of test animals to which it is administered by any of a variety of methods

mg/kg

Normally expressed as milligrams of substance per kilogram of animal body weight

- mode of administration

LD_{50}/30 (days)

The Median Lethal Concentration

LC_{50}

The concentration of a chemical in an environment (generally air or water) which produces death in 50% of an exposed population of test animals in a specified time frame

mg/L

Normally expressed as milligrams of substance per liter of air or water (or as ppm)

LCt_{50} .....mg-min/m^3

- Incapacitation than death

TOXICOLOGY OF PESTICIDES

- Pesticides are preparations for the eradication of plant and animal pests, for the protection of plants, animals and man.
- About 800 compounds of active ingredients of pesticides have been registered world-wide.

Classification of pesticides

- fungicides
- zoocides (insecticides, rodenticides, molluscocides)
- herbicides – including desiccants
- plant growth regulators (to shorten the straw of cereals)

Pesticides:

- **Organochlorine pesticides**
- **Organophosphates**
- **Carbamate pesticides**
- **Pyrethroids**
- Phenoxyacetic acid – based pesticides
- Urea – based pesticides
- Diazine and triazine pesticides
- Bipyridil – based pesticides
- Phenylpyrazoles
- Metal – based pesticides

Organochlorine insecticides Chlorinated hydrocarbon

The toxicity of these agents varies according to their molecular size, volatility and effects on the central nervous system (CNS).

In general, they cause either **CNS depression** or **stimulation**, depending upon the agent and dose.

- **Organochlorine Insecticides** were commonly used in the past, but many have been removed from the market due to their health and environmental effects and their persistence (e.g. DDT and chlordane).

Mechanism of toxic action

- DDT
  - Peripheral sensory neurons
  - prolonged negative after potential in neurons
  - K^+ transport, inactivate Na^+ channel closure, inhibit Na^+ /K^+ and Ca^{2+} /Mg^{2+} ATPases, inhibit calmodulin-transport of Ca^{2+}
- Cyclodienes
  - CNS localized
  - $GABA_A$ receptor/channel antagonists, inhibit Cl^--uptake and Na^+ /K^+ and Ca^{2+} /Mg^{2+} ATPases

Organophosphates

- insecticides
- antiparasitics

- **Organophosphate Pesticides** - These pesticides affect the nervous system by disrupting the enzyme that regulates acetylcholine, a neurotransmitter. Most organophosphates are insecticides. However, they usually are not persistent in the environment. (e.g. parathion, malathion, and methyl parathion)

Mechanism of toxic action – irreversible inhibition of enzymes, particularly of **acetylcholinesterase** on nerve synapses (by phosphorylation of hydroxyl group of serine bound in the active centre of ACHE).

- Used as stomach , contact or fumigant poison

Carbamate pesticides

- insecticides
- herbicides
- fungicides

- **Carbamate Pesticides** affect the nervous system by disupting an enzyme that regulates acetylcholine, a neurotransmitter. The enzyme effects are usually reversible. There are several subgroups within the carbamates. (e.g. Bendiocarb, Carbaryl, Methomyl, and Propoxur)

Carbofuran is very up-to-date substance in toxicology. It is used to **control vermin** (foxes) and **is used in baits**. Birds are 10 times more sensitive to carbofuran than mammals (LD50 for mammals 3 – 19 mg/kg body weight). Frequent carbofuran poisoning cases among predatory birds.

Pyrethroids

- insecticides
- antiparasitics

- **Pyrethroid Pesticides** were developed as a synthetic version of the naturally occurring pesticide pyrethrin, which is found in chrysanthemums. They have been modified to increase their stability in the environment. Some synthetic pyrethroids are toxic to the nervous system. (e.g. permethrin, resmethrin, and sumithrin)

Mechanism of the toxic action -

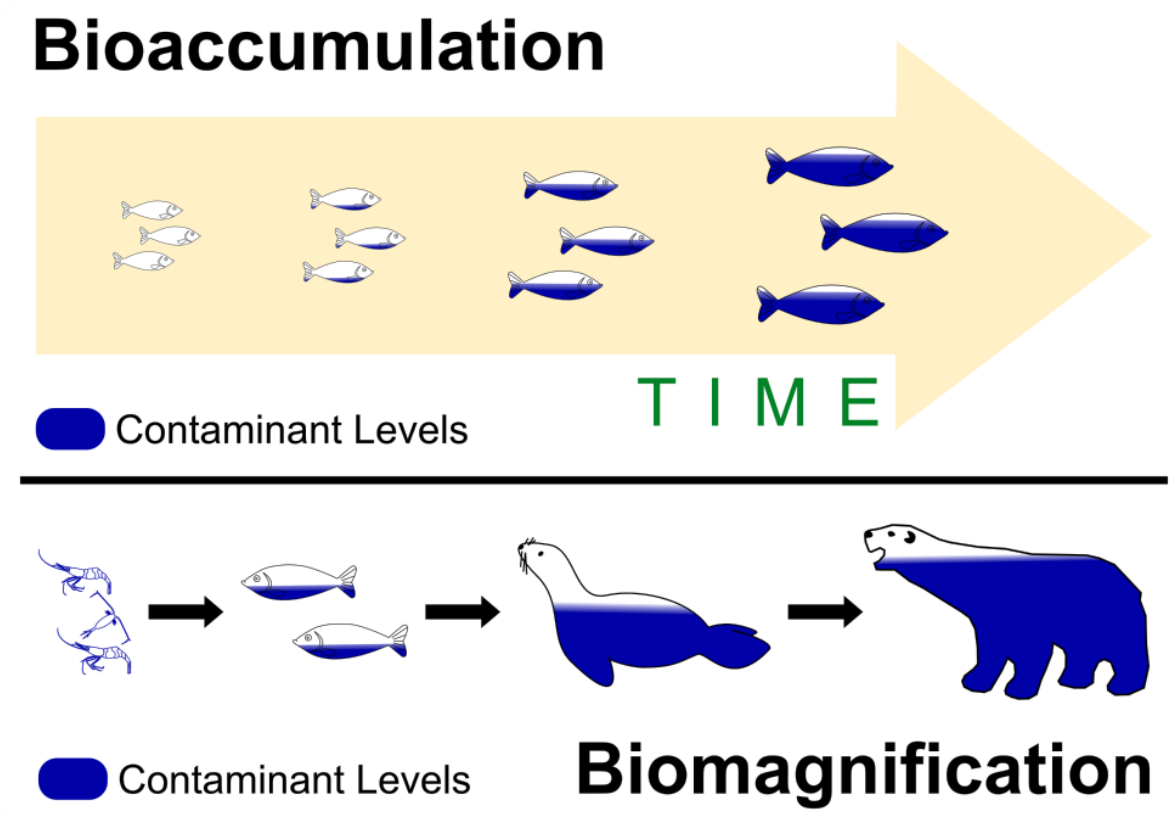
-pyrethroids T (tremor) – contain **no α-cyano group** cause reversible block of sodium channels (e.g. permethrin)

-pyrethroids CS (choreoatetosis, salivation) – contain **α-cyano group** cause reversible block of sodium channels and inhibition of GABA (e.g. deltamethrin)

Pyrethroids are

- highly toxic for fish (LC_{50} below 0,1 mg/l)
- toxic for bees (LD_{50} 2 – 11 µg/bee)
- not very toxic for mammals

Biomagnification



Bioaccumulation:
increase in concentration of a pollutant from the environment to the first organism in a food chain

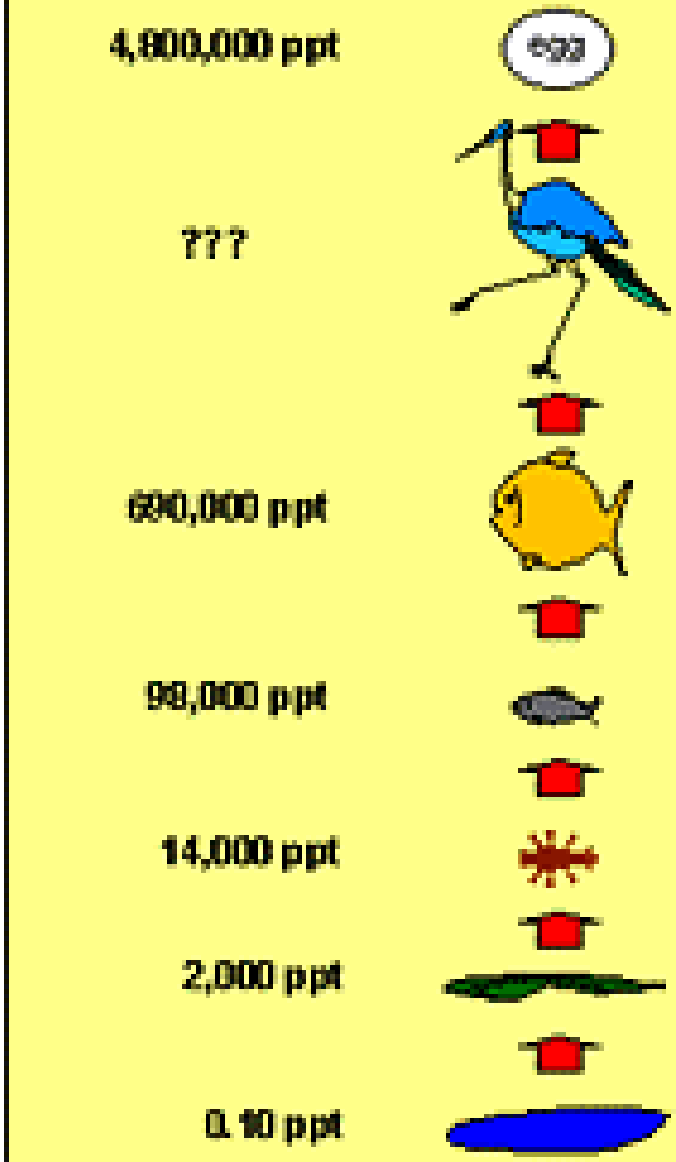
Biomagnification:
increase in concentration of a pollutant from one link in a food chain to another

Biomagnification is the sequence of processes in an ecosystem by which higher concentrations of a particular chemical, such as the pesticide DDT, are reached in organisms higher up the food chain, generally through a series of preypredator relationships. **Oxford University, 2008**

"Result of the process of bioaccumulation and biotransfer by which tissue concentrations of chemicals in organisms at one trophic level exceed tissue concentrations in organisms at the next lower trophic level in a food chain." **Environmental Protection Agency, 2010**

Biomagnification is the process whereby the tissue concentrations of a contaminant increase as it passes up the food chain through two or more trophic levels." **Nowell and others, 1999**

BIOMAGNIFICATION!



ppt = parts per trillion
(mercury concentration)

We are concerned about these phenomena because together they mean that even small concentrations of chemicals in the environment can find their way into organisms in high enough dosages to cause problems.

In order for biomagnification to occur , the pollutant must be:

1. longlived
2. mobile
3. soluble in fats
4. biologically active

If a pollutant is shortlived, it will be broken down before it can become dangerous.

If it is not mobile, it will stay in one place and is unlikely to be taken up by organisms.

If the pollutant is soluble in water it will be excreted by the organism.

Pollutants that dissolve in fats, however , may be retained for a long time.

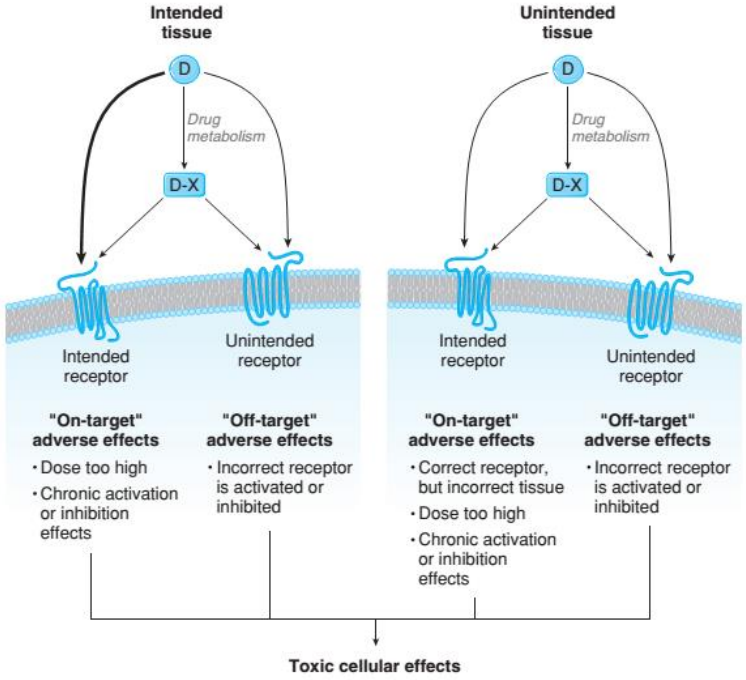
It is traditional to measure the amount of pollutants in fatty tissues of organisms such as fish. In mammals, we often test the milk produced by females, since the milk has a lot of fat in it and because the very young are often more susceptible to damage from toxins (poisons).

If a pollutant is not active biologically, it may biomagnify, but probably won't cause any problems.

Drug toxicity

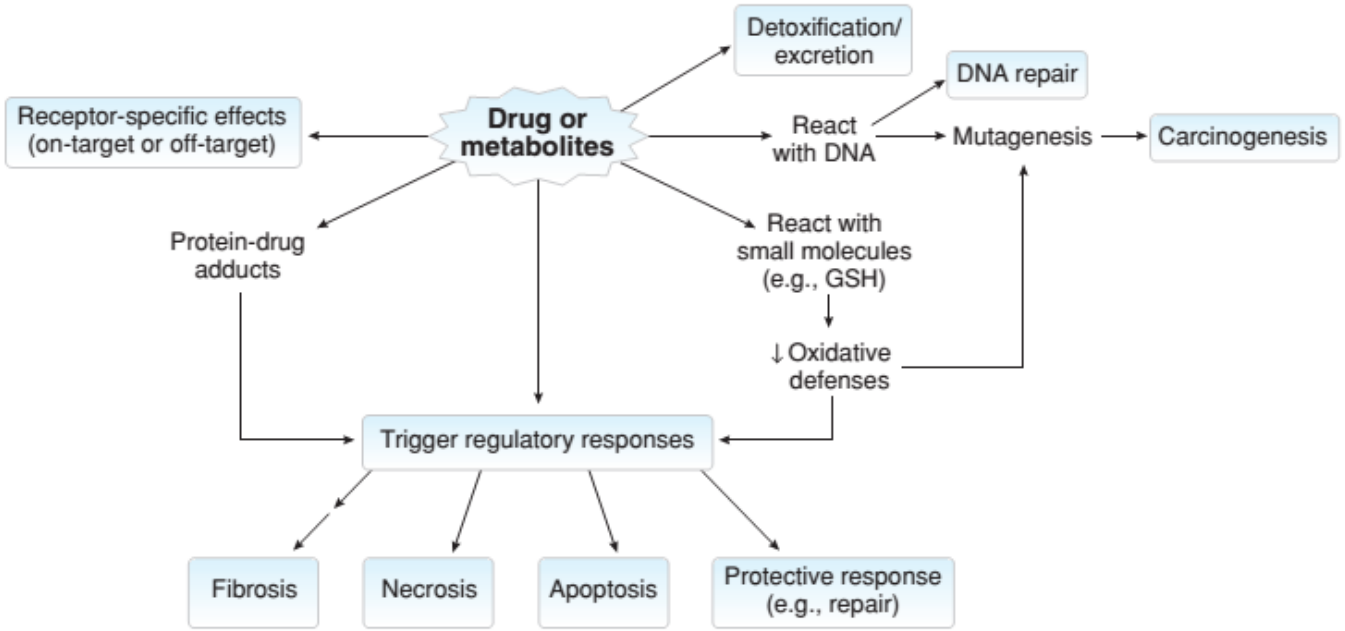
The Swiss physician and chemist **Paracelsus** noted nearly 500 years ago that "**all substances are poison; there is not which is not a poison. The right dose differentiates a poison and a remedy**."

Drugrelated side effects and adverse reactions, also called **adverse drug reaction (ADR), adverse drug event (ADE)** or **drug toxicity**, is defined as the **"manifestations of the adverse effects of drugs administered therapeutically or in the course of diagnostic techniques. It does not include accidental or intentional poisoning..."**



On-target and offtarget adverse drug effects.

Drug Disintended to modulate the function of a specific receptor (Intended receptor)in a particular tissue (Intended tissue). On-target adverse effects in the intended tissue could be caused by a supratherapeutic dose of the drug or by chronic activation or inhibition of the intended receptor by Drug D or its metabolite D–X. The same on-target effects could occur in a second tissue (Unintended tissue); in addition, the intended receptor could mediate an adverse effect because the drug is acting in a tissue for which it was not designed. Off-target effects occur when the drug and/or its metabolites modulate the function of a target (Unintended receptor)for which it was not intended.



Mechanisms of drug toxicity.

A drug or its metabolites or both interact with specific receptors to mediate on-target or offtarget adverse effects. In addition, metabolites can be detoxified and excreted, or can react with a variety of macromolecules including DNA, small antioxidants such as glutathione (GSH), or cellular or plasma proteins. The formation of unrepaired or misrepaired DNA adducts is often mutagenic and may lead to cancer.

The impairment of oxidative defenses can lead to inflammation and cell death (apoptosis or necrosis).

The formation of drug-protein adducts can trigger immune responses that can damage cells and tissues. Regardless of the mechanism of damage, a gradation of acute responses from protective to apoptosis (programmed cell death) and necrosis can result, depending on the extent of damage and the temporal and dose relationships. Chronic inflammation and repair can also lead to tissue fibrosis.

Antidotal therapy

Antidotal therapy is the use of any chemical or physiologic procedure used to **prevent, minimize, or terminate the adverse effects** associated with chemical toxicity or aberrant pathophysiologic processes.

These antidotal procedures may alter the toxicity associated with an exogenous chemical or with endogenous substances.

Antidotes work in any one of a number of ways. Common modes of action are as follows:

1. **Inert complex formation -** Some antidotes interact with the poison to form an inert complex which is then excreted from the body e.g., chelating agents for heavy metals, Prussian Blue for thallium, specific antibody fragments for digoxin, dicobalt edetate for cyanide, etc.
2. **Accelerated detoxification -** Some antidotes accelerate the detoxification of a poison,

   e.g., thiosulfate accelerates the conversion of cyanide to non-toxic thiocyanate, acetylcysteine acts as a glutathione substitute which combines with hepatotoxic paracetamol metabolites and detoxifies them.

3. **Reduced toxic conversion** - e.g., provided by ethanol which inhibits the metabolism of methanol to toxic metabolites by competing for the same enzyme (alcohol dehydrogenase).
4. **Receptor site competition** - Some antidotes displace the poison from specific receptor sites, thereby antagonising the effects completely.

   e.g., naloxone, which antagonizes the effects of opiates at stereo-specific opioid receptor sites.
5. **Receptor site blockage** -

   e.g., atropine which blocks the effects of anticholinesterase agents such as organophosphates at muscarinic receptor sites.
6. **Toxic effect bypass** -

   e.g., by the use of 100% oxygen in cyanide poisoning.

Impact of pesticide pollution on wild animals

Pesticides are applied in **many forms via various delivery methods** to forests, rangeland, aquatic habitats, farmland, urban turf and gardens.

Pesticide poisonings to wildlife may result from acute or chronic exposure.

Additionally, pesticides may impact wildlife via secondary exposure or through indirect effects to the animal or its habitat.

Acute Poisoning

Short exposures to some pesticides may kill or sicken wildlife.

Examples of acute wildlife poisoning include

fish kills that are caused by pesticide residues carried to ponds, streams, or rivers by surface runoff or spray drift, and

bird die-offs caused by foraging on pesticide-treated vegetation or insects, or by consumption of pesticide-treated granules, baits, or seeds.

In general, acute poisoning to wildlife takes place over a relatively short time, impacts a very localized geographical area, and is linked to a single pesticide.

Chronic Poisoning

Exposure of wildlife over an extended period of time.

Example

Organochlorine insecticide DDT have been implicated in **bird mortality / reproduction** in certain birds.

The reduction of these compounds in the 1970s, and early 1980s, has resulted in decreased organochlorine residues in most areas, and reproduction in birds, such as the bald eagle, has greatly improved.

Organochlorine pesticides used in some foreign countries may pose risk to migratory birds which overwinter there.

Secondary Poisoning

when an animal consumes prey species that contain pesticide residues.

Examples

(1) birds of prey becoming sick after feeding on an animal that is dead or dying from acute exposure to a pesticide, and

(2) the accumulation and movement of persistent chemicals in wildlife food chains.

Indirect Effects

Pesticides may impact wildlife indirectly **when a part of its habitat or food supply is modified**.

For instance,

herbicides may reduce food, cover, and nesting sites needed by insect, bird, and mammal populations;

insecticides may diminish insect populations fed on by bird or fish species; insect pollinators may be reduced, thereby affecting plant pollination.

Animal toxins

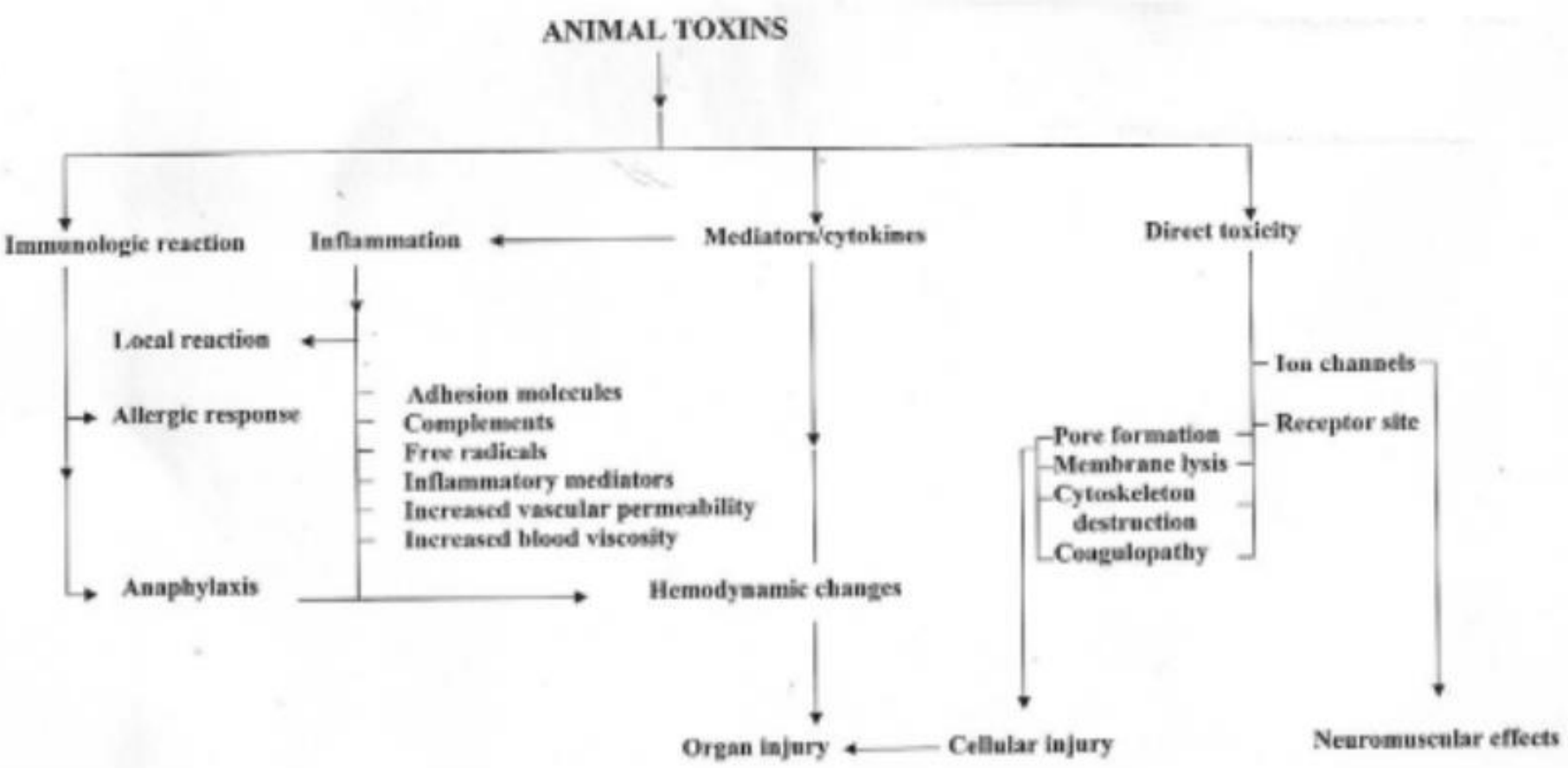
Toxins are proteinaceous susbstances produced from plant and animal origin as well as from micro-organisms

1) They are unstable
2) They are protein in nature
3) Produce antitoxins, against themselves when introduced into the body
4) Tolerance occurs

Table 1. Animal toxin effects on ion channels and pore formation

	Na channel	K channel	Ca channel	Cl channel	Pore formation
Jellyfish	↑		↑		+
Sea anemone	↑	↓	↑		+
μ conotoxin	↓				
δ conotoxin	↓				
ω conotoxin			↓		
Ciguatoxin	↑				
Tetrodotoxin	↓				
Saxitoxin	↓				
Gonyautoxin	↓				
Palytoxin	↑	↓			+
Maitotoxin			↑		
Stonustoxin			↑		
Annelid	↑				
Brevetoxin	↑				
Spider	↑	↓	↑ ↓		
Scorpion	↑	↓	↑	↓	+
Bratachotoxin	↑				
Dendrotoxin	↓	↓			
Bee		↓			+

* ↑ = activation or slow inactivation; ↓ = inactivation


ANIMAL TOXINS
Immunologic reaction
Inflammation
Mediators/cytokines
Direct toxicity
Local reaction
Allergic response
Anaphylaxis
Adhesion molecules
Complements
Free radicals
Inflammatory mediators
Increased vascular permeability
Increased blood viscosity
Hemodynamic changes
Ion channels
Receptor site
Pore formation
Membrane lysis
Cytoskeleton destruction
Coagulopathy
Organ injury
Cellular injury
Neuromuscular effects

- **Arachnids - Scorpions, Spiders, Ticks**
- **Insects**
- **Snakes**
- **Lizards**
- **Fish, and frogs**

Example – Puffer Fish

- **Tetrodotoxin**
- **100 different species of puffer fish**
- **Tetrodotoxin used by fish to discourage consumption by predators**
- **Low dose of tetrodotoxin produces tingling sensations and numbness around the mouth, fingers, and toes**
- **As little as 1 to 4 mg of the toxin can kill an adult**

Arachnids

- **Scorpions, Spiders, Ticks**

- **Scorpions – Stinger – low toxicity**
- **Spider bites**
  - **Widow spiders -– Neurotoxin**
  - **Brown or Violin -– Tissue Damage**
- **Ticks – Neurotoxin – Transmits other diseases**

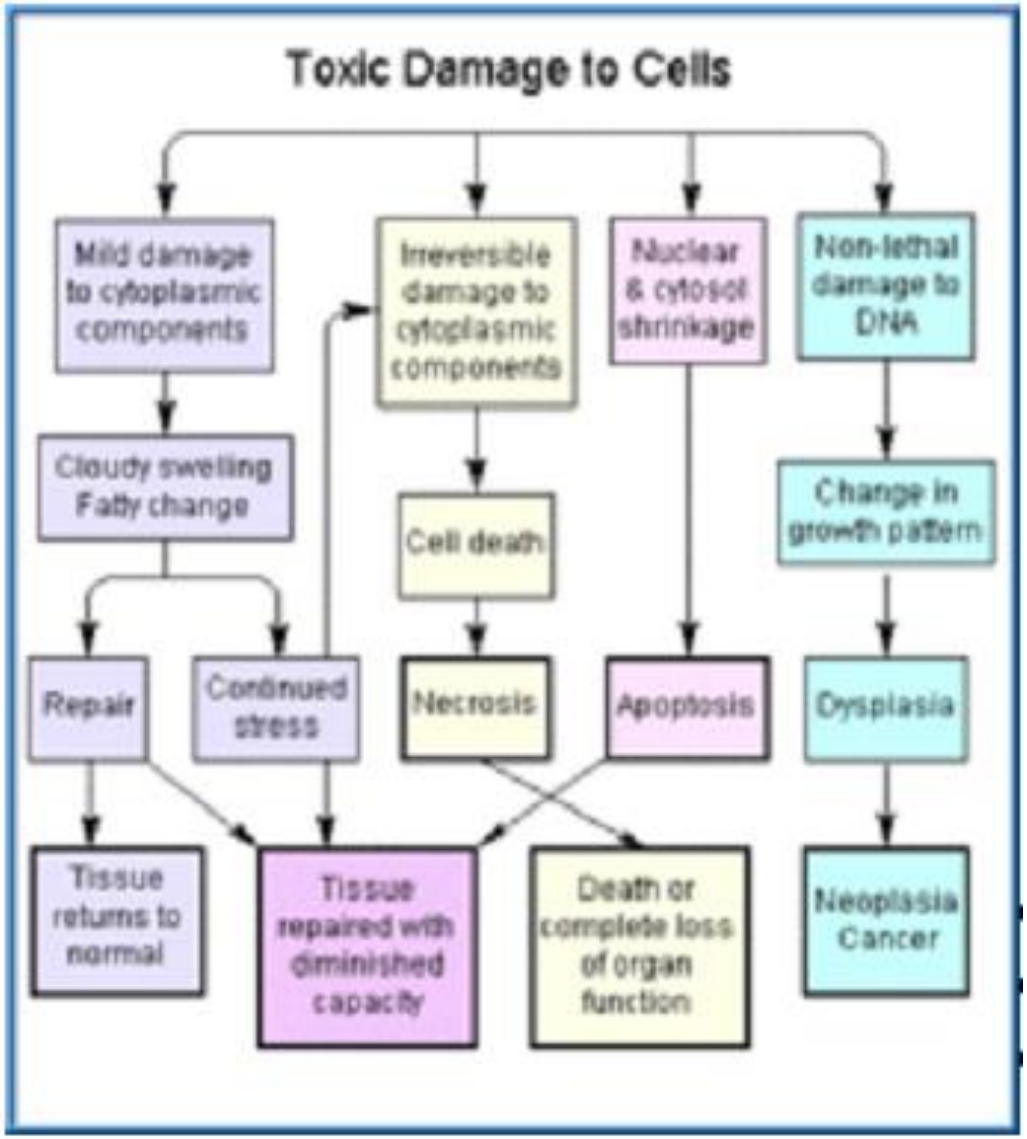
Insects

- Moths and caterpillars – Irritating to eat
- Ants – Proteins, formic acid – Irritation to allergic response
- Honey bees – Proteins – Swelling, allergic response
- Wasps – Formic acid

Reptiles

- **Lizards – Irritating to eat**
- **Snakes**
  - **Vipers – Rattlesnakes, Water moccasins, Copperheads – Complex enzymes – Tissue necrosis, allergic response, shock**
  - **Elapidae Cobras, Kraits, Coral Snakes – Proteins – Neurotoxin, paralysis**

Tissue toxicity



- The tissue may be completely repaired and return to normal
- The tissue may be incompletely repaired but is capable of sustaining its function with reduced capacity
- Death of the organism or the complete loss of a tissue or organ. In some instances, the organism can continue to live with the aid of medical treatment, e.g., replacement of insulin or by organ transplantations.
- Neoplasm or cancers may result, many which will result in death of the organism and some, which may be cured by medical treatment.

Genotoxicity

- **Genotoxicity describes the property of chemical agents that damages the genetic information within a cell causing mutations, which may lead to cancer.**
- The DNA damage can be in the form of **single and doublestrand breaks, loss of excision repair, crosslinking, alkalilabile sites, point mutations and structural and numerical chromosomal aberrations.**

While genotoxicity is often confused with mutagenicity , all mutagens are genotoxic, whereas not all genotoxic substances are mutagenic.

The alteration can have direct or indirect effects on the DNA: the induction of mutations, mistimed event activation, and direct DNA damage leading to mutations.

The permanent, heritable changes can affect either somatic cells of the organism or germ cells to be passed on to future generations.

Cells prevent expression of the genotoxic mutation by either DNA repair or apoptosis; however, the damage may not always be fixed leading to mutagenesis.

Reproductive toxicity

Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring.

Two major classes:

- **Reproductive toxicity**- effects on sexual behavior and fertility in males and non-pregnant females.
- **Developmental toxicity**- abnormal structure or functional development following exposure of pregnant or lactating females.

Toxic effects may cause

- Decrease libido and impotency/infertility.
- Interrupted pregnancy (abortion, fetal death or premature delivery).
- Infant death or childhood morbidity.
- Altered sex ratio and multiple births.
- Chromosome abnormalities and birth defects.
- Childhood cancer.

reproductive toxicity is subdivided under two main headings:

a) Adverse effects on reproductive ability or capacity

- alterations to the female and male reproductive system, adverse effects on onset of puberty,
- gamete production and transport,
- reproductive cycle normality,
- sexual behaviour,
- fertility,
- parturition,
- premature reproductive senescence

b) Adverse effects on development of the offspring

- any effect either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally (to the time of sexual maturation).
- The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.