Toxicology
Lec.2 Carcinogenesis & Mutagenesis

Assist. Lecturer:

Safa Hameed Mohsin

11/2/2024

Introduction

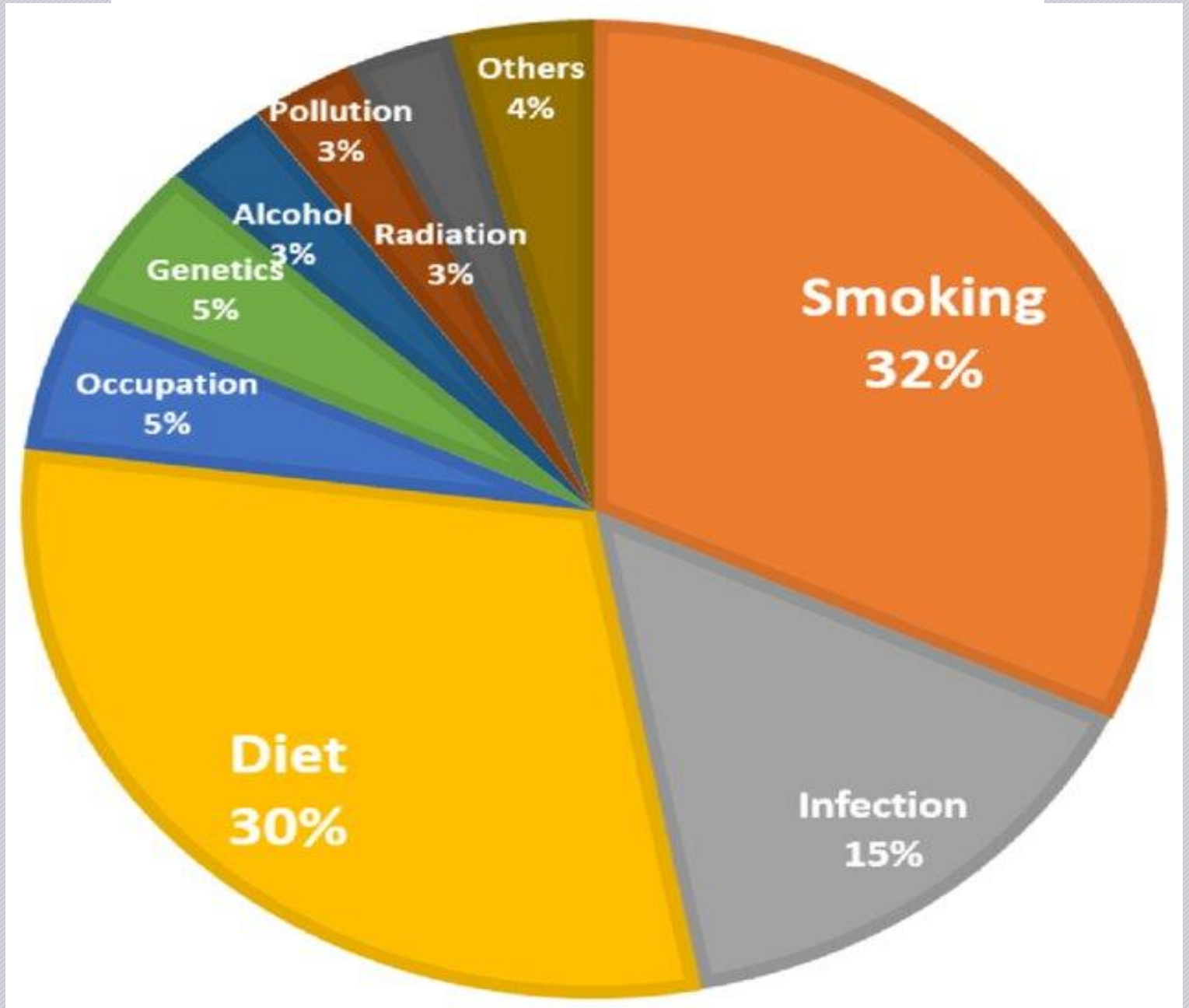
- **Cancer** remains a leading cause of morbidity and mortality in the human population, and the costs to society of this diseases are huge.

- **Cancer** is a disease characterized by mutation, modified gene expression, cell proliferation, and abnormal cell growth.

- Multiple causes of cancer including infectious agents, radiation, and chemicals.

- Estimates suggest that 70% to 90% of all human cancers have a linkage to environmental, dietary, and behavioral factors.

Causes of Cancer



Definition

- **Neoplasia** is a new tissue growth
- **Neoplastic lesion** is a **neoplasm**.

Neoplasm can be either **benign** or **malignant**.

Benign neoplasms: are lesions characterized by:

1. slow rates of proliferation that do not invade surrounding tissue or other organs.

2. impair and damage the normal function of an organ through its growth impeding of blood flow.

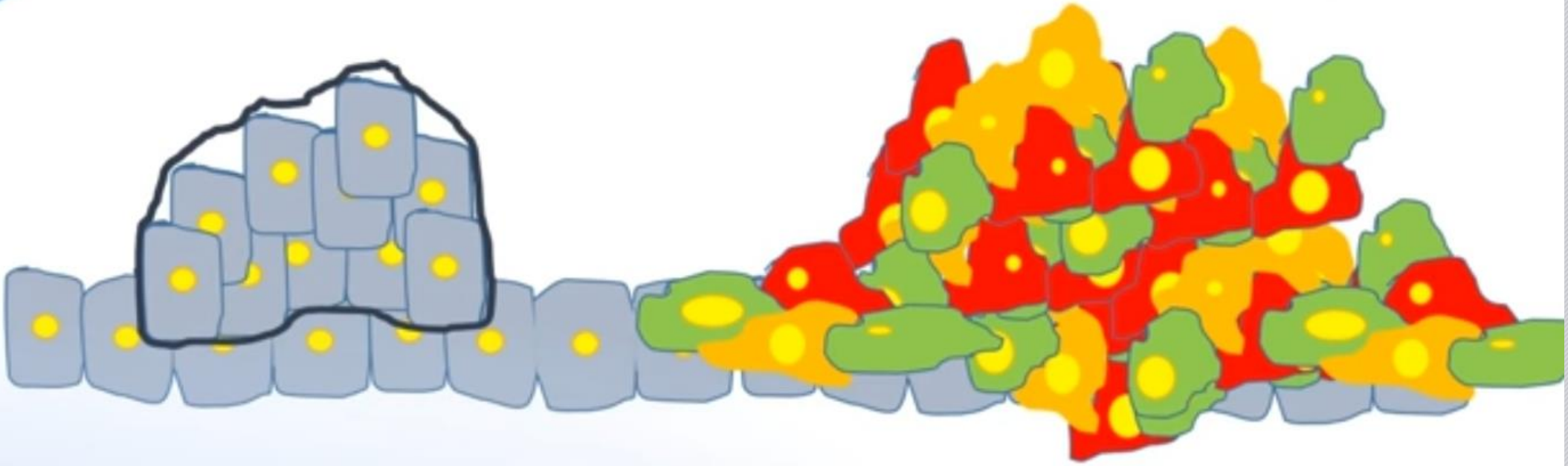
Malignant neoplasm: demonstrates invasive growth characteristics, capable of spreading not only through the organ of origin but via metastasis to other organs.

Metastasis are secondary growths derived from the cells of the primary malignant neoplasm.

Angiogenesis: is the growth of new blood vessels to supply and provide cancer tissue with blood.

Well differentiated
Slow growing
Well contained
Do not metastasise

Poorly differentiated
Fast growing
Invade surrounding tissue
Have potential to metastasise



Benign

Malignant

Nomenclature of tumor

- **Benign neoplasms:** ***Tissue name + oma***

e.g. benign fibrous neoplasm : ***fibroma***

benign glandular epithelium : ***adenoma*** *.*

- **Malignant neoplasms** ***:*** ***Tissue name + carcinoma /sarcoma***

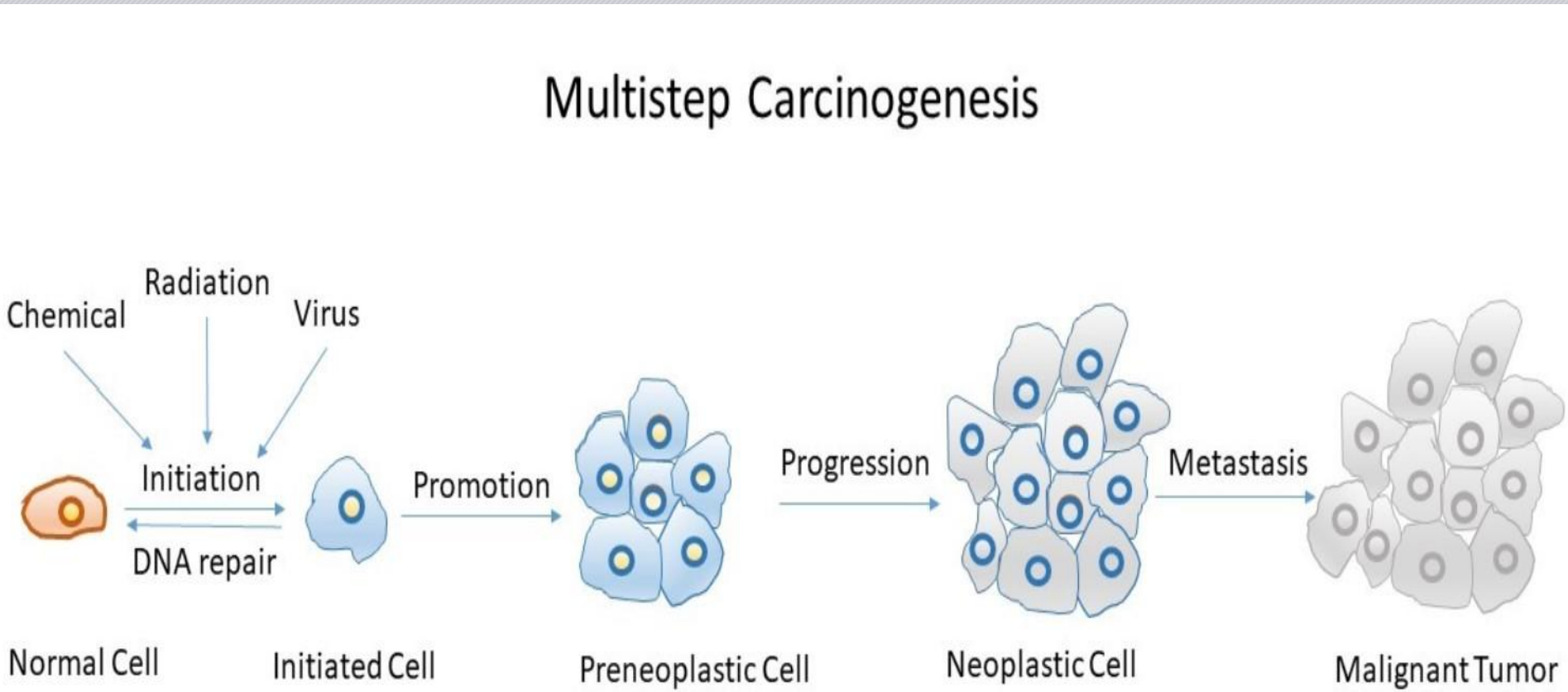
-Epithelial tissue: **tissue name +** ***carcinomas*** e.g. squamous cell carcinoma

-Glandular tissue: ***tissue name + adenocarcinoma***

-Mesenchymal tissue (soft or connective tissue): **tissue name +** ***sarcoma***

e.g. Fibrous tissue : ***fibrosarcoma*** *,* Bone tissue :***osteosarcoma***

Multistage of Carcinogenesis



Stages of Carcinogenesis

1- Initiation

Stable, heritable change, rapid process results in a carcinogen-induced mutational event. (mutation)

• Chemical and physical agents lead to genetic changes including mutations and deletions.

• Chemical carcinogens that covalently bind to DNA and form adducts that result in **mutations** are initiating agents.

2- Promotion

Endogenous/exogenous stimuli of cell growth, involves the selective clonal expansion of initiated cells to produce a pre-neoplastic lesion.

• Both exogenous and endogenous agents is called as tumor promoters.

• **Tumor promoters** are:

- not mutagenic and not able to induce tumors by themselves

- act though several mechanisms involving gene expression changes that result in sustained cell proliferation: either through increases in cell proliferation and/ or the inhibition of apoptosis.

3- progression

The final stage involves the conversion of the benign pre-neoplastic lesions into a neoplastic cancer.

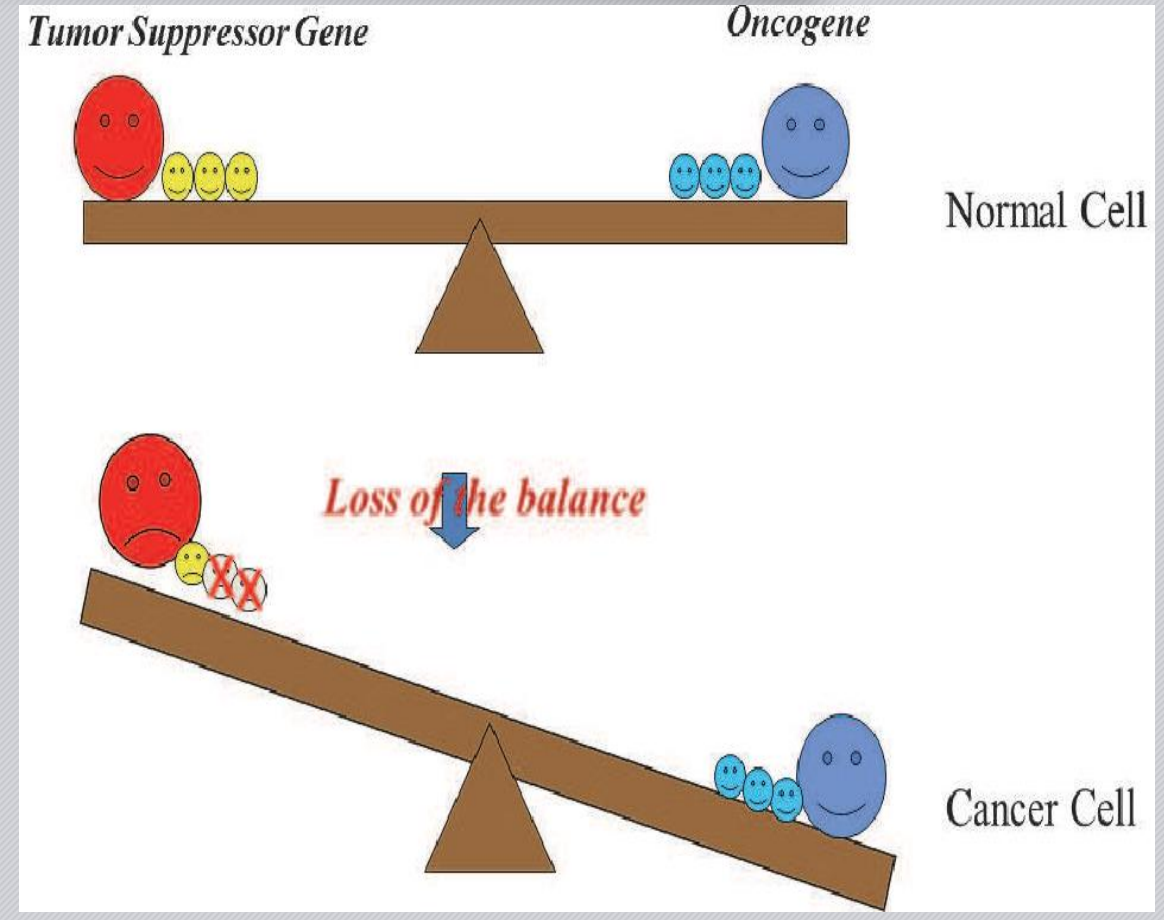
• Due to increase in DNA synthesis in cell proliferation in the pre-neoplastic lesions, additional genotoxic events may occur resulting in additional DNA damage including chromosomal damage such as deviations and translocations.

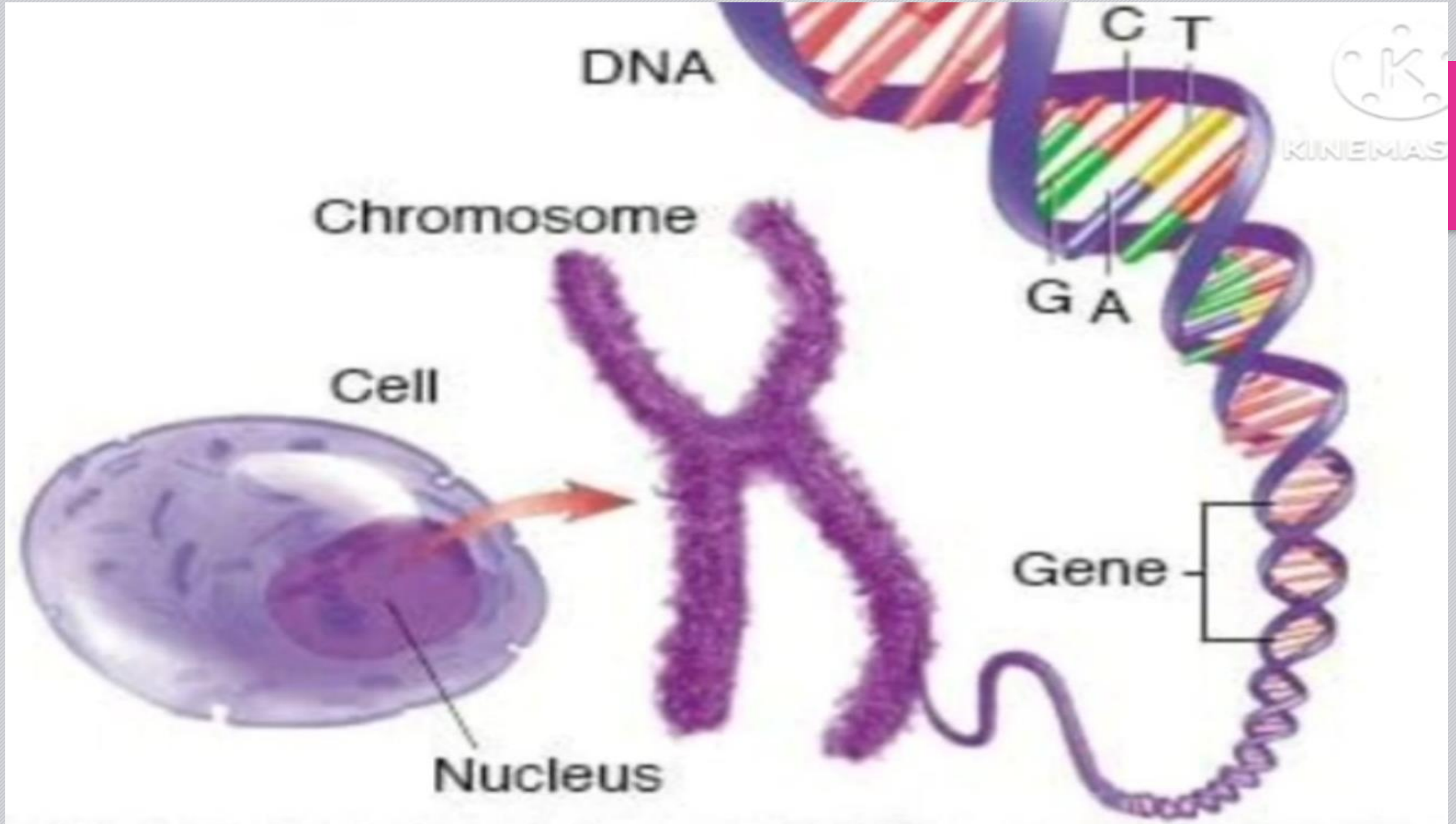
Genes involved in the carcinogenesis

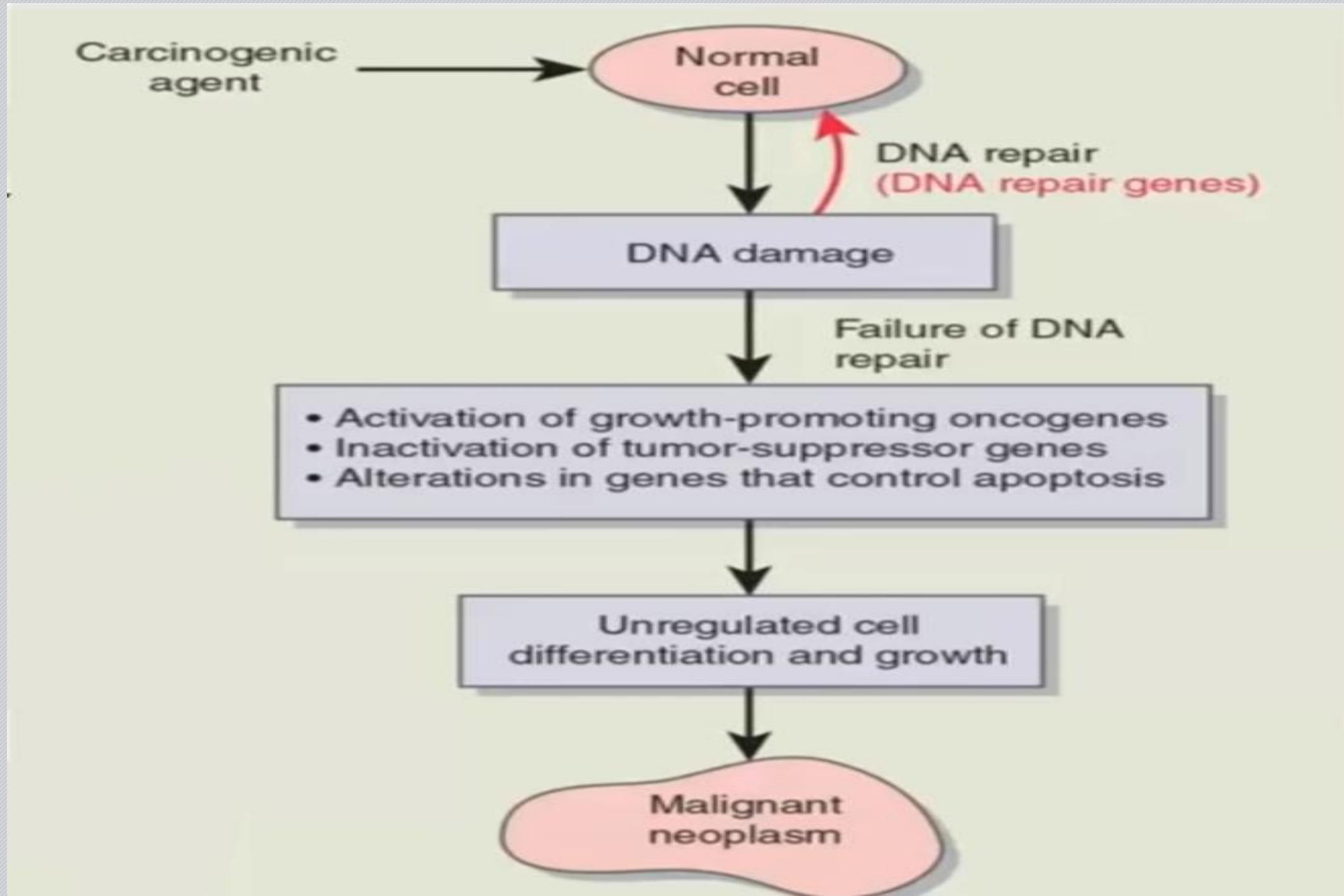
1- Mutator genes: essential for repairing the DNA & protect the genome

2- Oncogenes: regulate cell proliferation and differentiation

3- Tumor suppressor genes: inhibit cell overproliferation by regulating apoptosis, maintain balance of cell growth and cell death




DNA
C
T
G
A
Chromosome
Cell
Gene
Nucleus


Carcinogenic agent
Normal cell
DNA repair
(DNA repair genes)
DNA damage
Failure of DNA repair
• Activation of growth-promoting oncogenes
• Inactivation of tumor-suppressor genes
• Alterations in genes that control apoptosis
Unregulated cell differentiation and growth
Malignant neoplasm

Carcinogen

- ***Carcinogen*** *is chemical or physical agent, that induces* a **cancer**, although it is often also used to describe an agent that produces benign neoplastic lesions in rodent bioassays.

- **Carcinogens** can be chemicals, viruses, hormones, radiation, or solid materials.

- **Carcinogens** either produce new neoplastic growth in a tissue/organ **or** increase the incidence and/or multiplicity of background spontaneous neoplastic formation in the target tissue

Carcinogen Types

• Carcinogens have frequently been divided into two major categories based on their general mode of action: **genotoxic** and **nongenotoxic**.

1- Genotoxic carcinogens are agents that interact with DNA to damage or change its structure.

A- Direct-acting agents that can directly bind to DNA without being metabolized

B- Indirect-acting carcinogens that require metabolic activation (metabolism) in order to react.

- Heavy metals, can directly cause carcinogenesis, whereas many organic chemicals need to first undergo metabolism to form reactive intermediates to induce carcinogenesis

Carcinogen Types

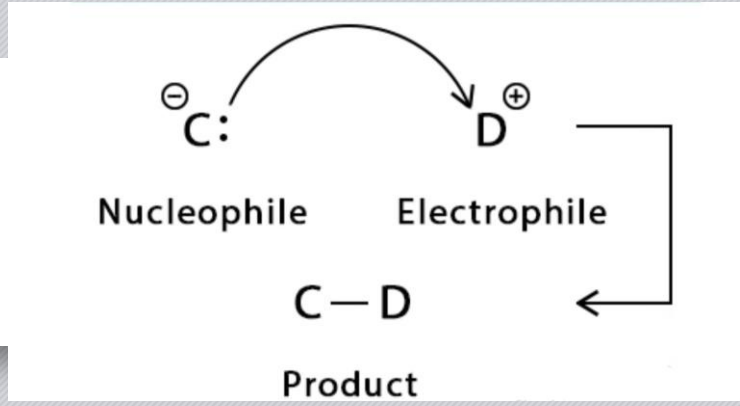
2- Nongenotoxic carcinogens are the agents that do not directly interact with nuclear DNA.

• Nongenotoxic carcinogens may change gene expression, modify normal cell function, bind to or modify cellular receptors, and increase cell growth.

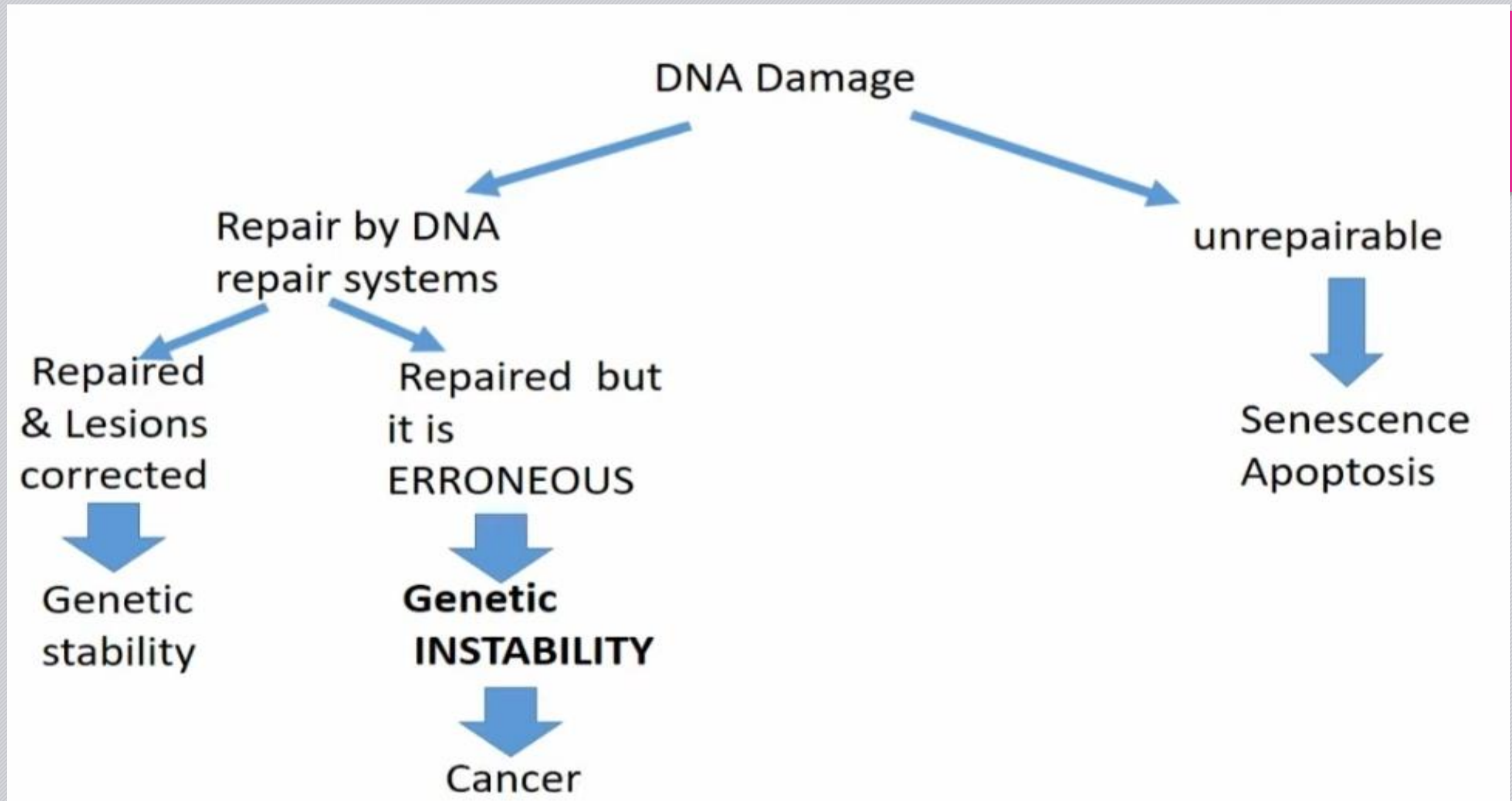
• These agents work through epigenetic mechanisms and change DNA expression without modifying or directly damaging its structure.

• Nongenotoxic chemicals create a situation in a cell or tissue that makes it more susceptible to DNA damage from other source.

Damage by Alkylating Electrophile



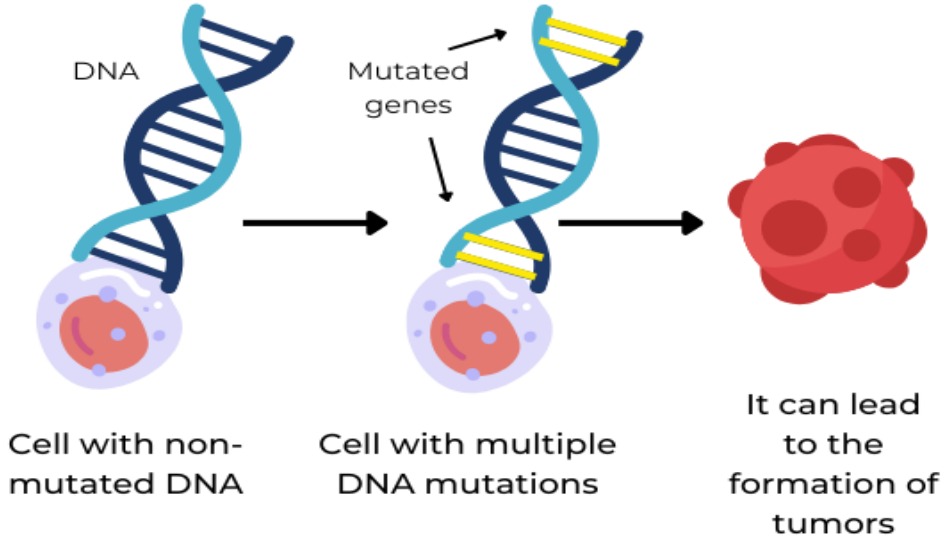
- The most chemical carcinogens require metabolic activation to exert a carcinogenic effect.
- The ultimate carcinogenic forms of these chemicals are frequently **strong electrophiles** that can readily form covalent adducts with nucleophilic targets.
- Because of their unpaired electrons, S:, O:, and N: atoms are nucleophilic targets of many electrophiles.
- In general, the stronger electrophiles display a greater range of nucleophilic targets, whereas weak electrophiles are only capable of alkylating strong nucleophiles (eg, *S: atoms in amino acids).*


DNA Damage
Repair by DNA repair systems
unrepairable
Repaired & Lesions corrected
Repaired but it is ERRONEOUS
Senescence
Apoptosis
Genetic stability
Genetic INSTABILITY
Cancer

Mutagenesis

The reaction of a carcinogen with genomic DNA either directly or indirectly may result in DNA adduct formation or DNA damage, and frequently produces a **mutation**.

Mutations in an oncogene, tumor-suppressor gene or gene that controls the cell cycle, DNA repairing genes can result in a clonal cell population with a proliferative or survival advantage.



DNA damage & Mutation

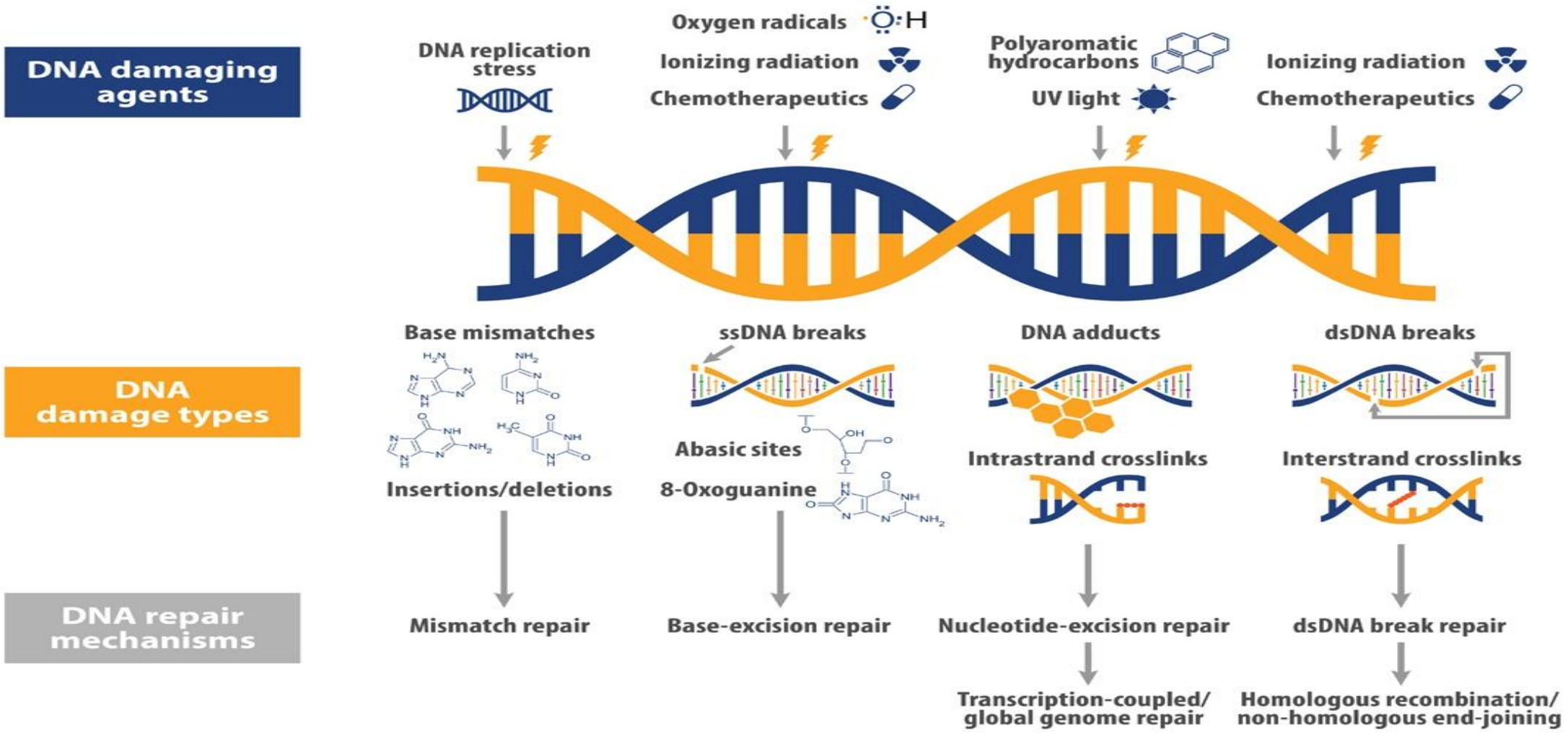
- **DNA damage** is a chemical alteration (can be corrected).
- **Mutation** is a change in the sequence of base pairs (cannot be corrected).

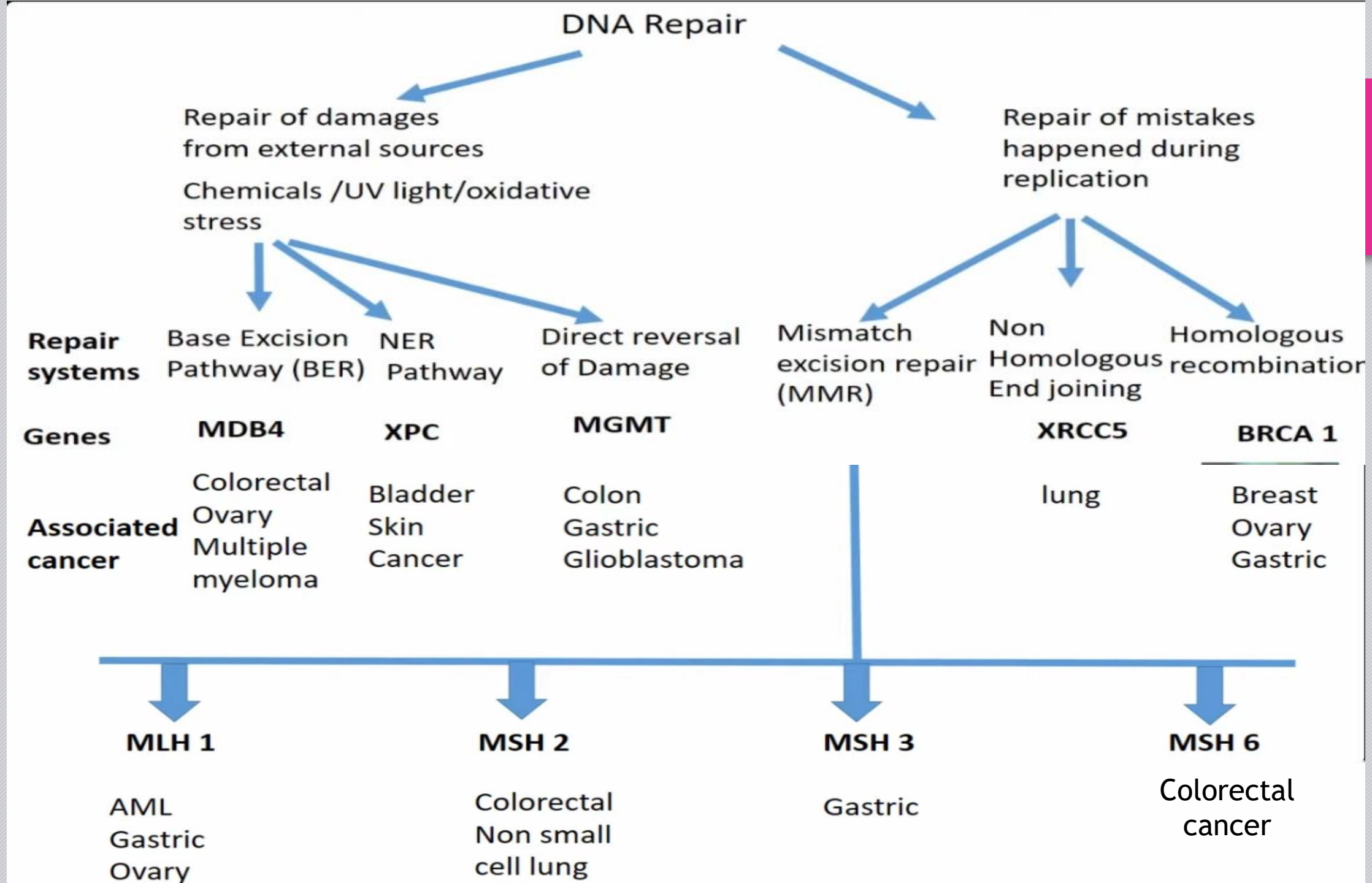
Types of DNA damage

1. Base pair mismatch
2. ssDNA breaks
3. DNA Adduct
4. dsDNA breaks

- If any kind of DNA damage is likely to lead to mutation, we call it genotoxic.
- Erroneous DNA repair lead to mutations.
- Individuals with inherited defects in DNA repair genes are **at increased risk of developing cancer**

DNA Repair Mechanisms




DNA Repair
Repair of damages from external sources
Chemicals /UV light/oxidative stress
Repair of mistakes happened during replication
Repair systems
Base Excision Pathway (BER)
NER Pathway
Direct reversal of Damage
Mismatch excision repair (MMR)
Non Homologous End joining
Homologous recombination
Genes
MDB4
XPC
MGMT
XRCC5
BRCA 1
Associated cancer
Colorectal Ovary Multiple myeloma
Bladder Skin Cancer
Colon Gastric Glioblastoma
lung
Breast Ovary Gastric
MLH 1
MSH 2
MSH 3
MSH 6
AML Gastric Ovary
Colorectal Non small cell lung
Gastric
Colorectal cancer

DNA repair

1- Mismatch Repair

Many spontaneous mutations are point mutations, a change in a single base pair in the DNA sequence.

• endonucleases, cut DNA near apurinic sites, then extended by exonucleases, and the resulting gap repaired by DNA polymerase and ligase.

2- Excision repair

chemically modified bases or DNA chemical adducts, are typically repaired by excision repair processes.

• Proteins that slide along the surface of a dsDNA molecule recognize the irregularities in the shape of the double helix, and affect the repair of the lesion.

3-Homologous recombination & non homologous End-Joining Repair

dsDNA breaks can be repaired by joining the free DNA ends.

• The joining of broken ends from different chromosomes, however, will lead to the translocation of DNA pieces from one chromosome to another, translocations that have the potential to enable abnormal cell growth.

Host and Environmental causative factors of Cancer

- Heredity- Mendelian inheritance of genes (BRCA 1,2)
- Reproductive hormones
- Obesity
- Immunodeficient diseases
- Chemical carcinogens (cigarette, alcohol, diet , heavy metals)
- Radiation or UV radiation(sun)
- Viruses , bacteria (Human papilloma virus HPV & Hepatitis B,C)
- Some medication (drugs that suppress the immune system, drugs used to treat cancer, hormonal therapy)
- Pollution

Human carcinogenic chemicals associated with medical therapy

Drug	Associated neoplasm
cyclophosphamide	Bladder cancer & leukemia
Azathioprine	Lymphoma, reticulum cell sarcoma & skin
Chloramphenicol	Leukemia
Estrogen	Liver cell adenoma , endometrium & skin
phenytoin	Lymphoma , neuroblastoma

Examples of International Agency for Research on Cancer (IARC) Carcinogenic Classifications

gmo answers


Hair coloring products


Insulation glass wool


Magnetic fields


Caffeine/Tea


Fluorescent lighting


Caprolactam

Note: Of the hundreds of agents IARC has reviewed, this chemical, primarily used in the manufacturing of synthetic fibers, especially nylon, is the ONLY item IARC has ever placed in this category.[3]


Coffee


Pickled vegetables (traditional in Asia)


Talc-based body powder


Aloe vera


Carpentry


Working as a barber/ hair dresser


Nightshift Work


Art glass, glass containers and pressed ware (manufacture of)


High temperature frying


Glyphosate


Tobacco


Wood dust


Sunlight


Outdoor air pollution


Alcoholic beverages

CATEGORY 4
Probably Not Carcinogenic to Humans[2]

CATEGORY 3
Not Classifiable as to Carcinogenicity in Humans[2]

CATEGORY 2B
Possibly Carcinogenic to Humans[2]

CATEGORY 2A
Probably Carcinogenic to Humans[2]

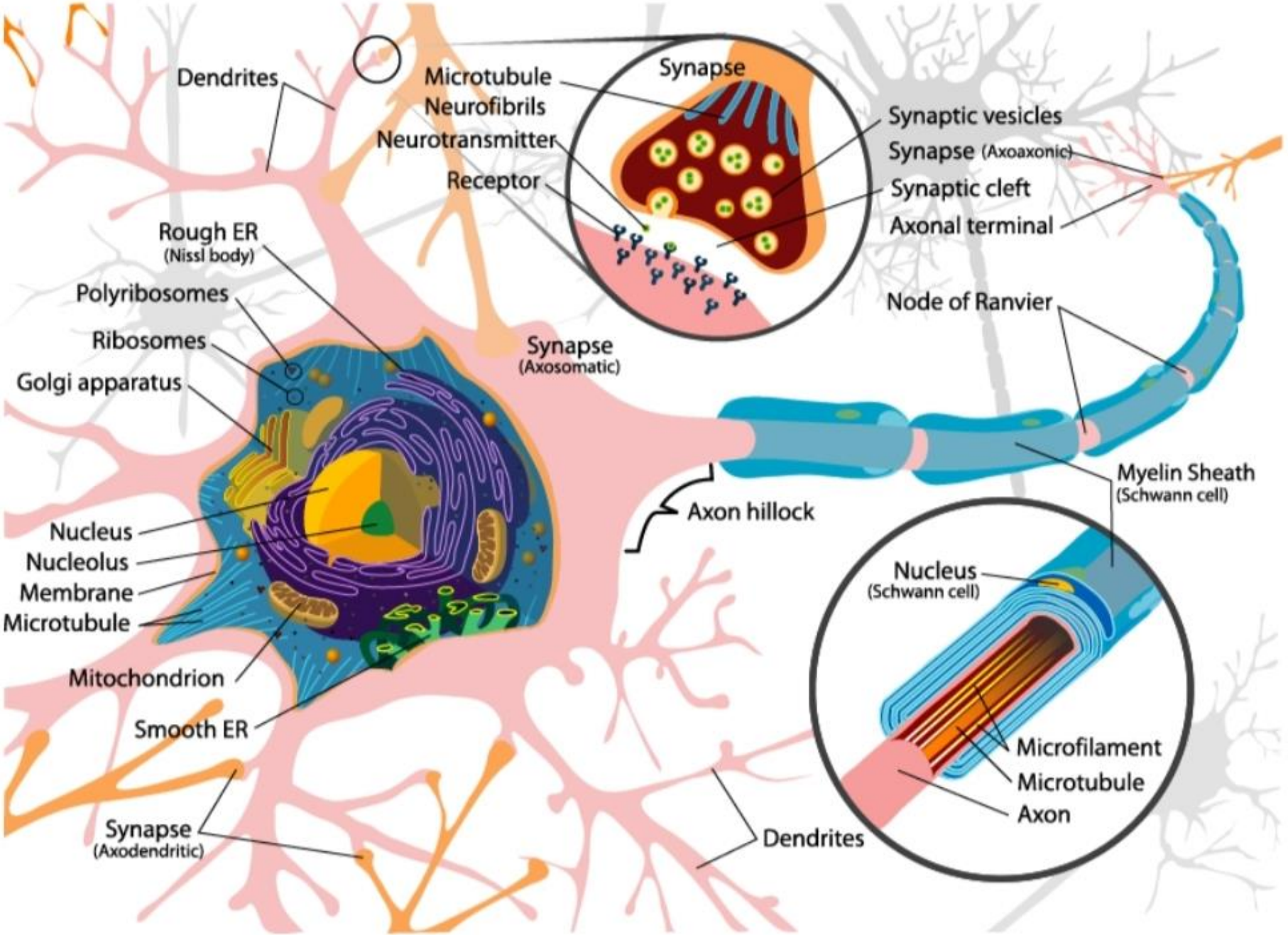
CATEGORY 1
Carcinogenic to Humans[2]

Since 1979, IARC has reviewed hundreds of products, chemical compounds, lifestyles, viruses, workplaces and other agents for their carcinogenic potential. Here are some examples of IARC's hazard identifications[1].

THANK YOU

Toxicology of the Nervous System

Assist.Lecturer
Safa h. Mohsin


Dendrites
Microtubule
Neurofibrils
Neurotransmitter
Receptor
Synapse
Synaptic vesicles
Synapse (Axoaxonic)
Synaptic cleft
Axonal terminal
Rough ER
(Nissl body)
Polyribosomes
Ribosomes
Golgi apparatus
Synapse
(Axosomatic)
Node of Ranvier
Myelin Sheath
(Schwann cell)
Axon hillock
Nucleus
Nucleolus
Membrane
Microtubule
Mitochondrion
Smooth ER
Nucleus
(Schwann cell)
Microfilament
Microtubule
Axon
Synapse
(Axodendritic)
Dendrites

Introduction

- Neurotoxicity refers to the ability of an agent to adversely affect the structural or integrity of the nervous system.

- Toxicant interactions with the normal signaling mechanisms of neurotransmission, resulting in alterations in NS function **but** little or no structural damage.

- Nervous system is protected from toxicants by BBB & blood–nerve barriers (BNB).

- Methyl mercury affects mainly the nervous system, although its concentration in the brain is similar to that in most other tissues, and in fact it is much lower than that in the liver and kidneys.

The reasons of greater susceptibility of nervous system to toxin

› The greater susceptibility may be attributed to:

1. neurons have a high metabolic rate, with little capacity for anaerobic metabolism.

2. electrically excitable, neurons tend to lose cell membrane integrity more readily.

3. great length of the axons, since the cell body must supply its axon structurally and metabolically.

BBB & BNB

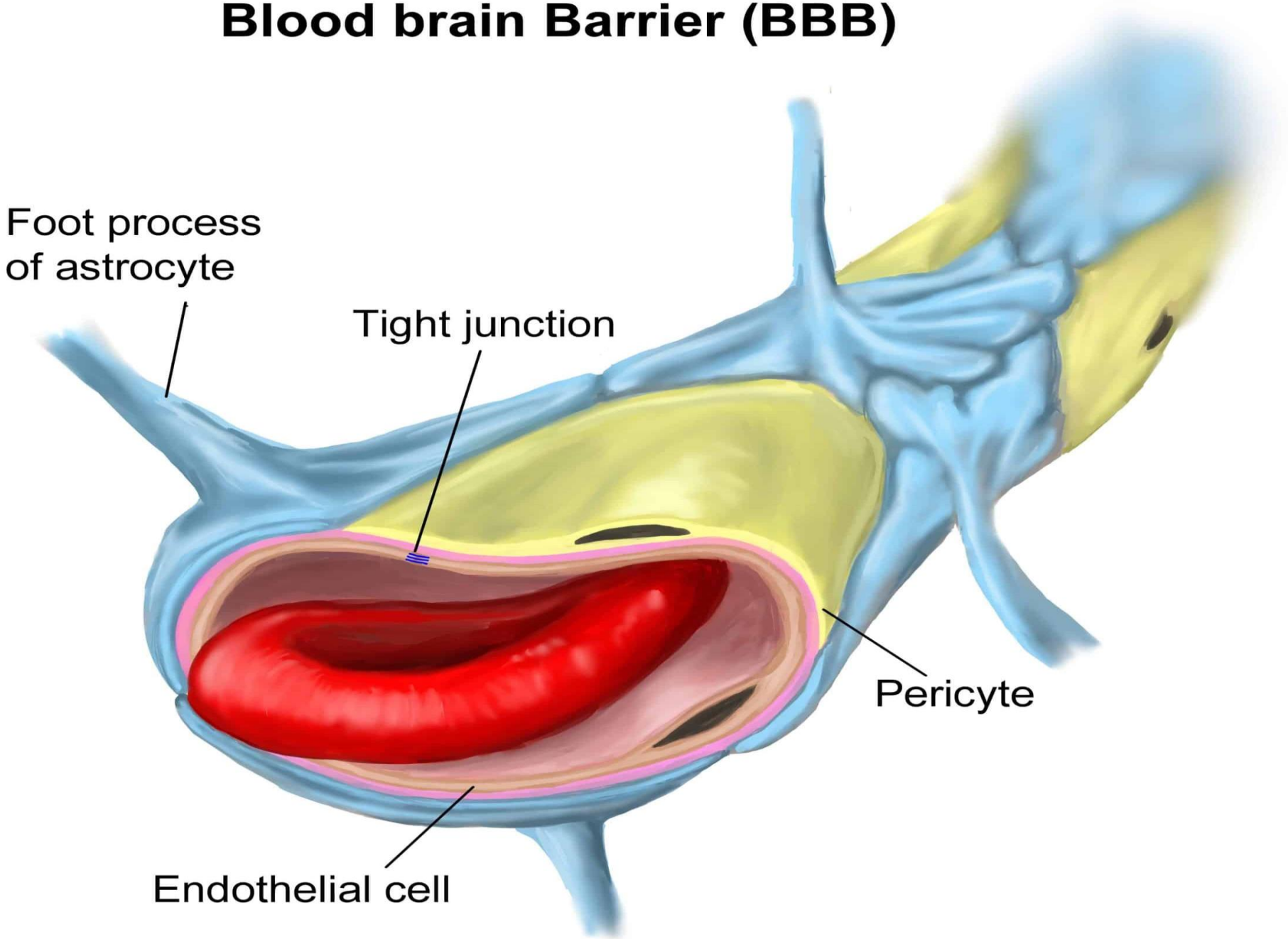
› BBB is effective in excluding neurotoxicants, e.g.:

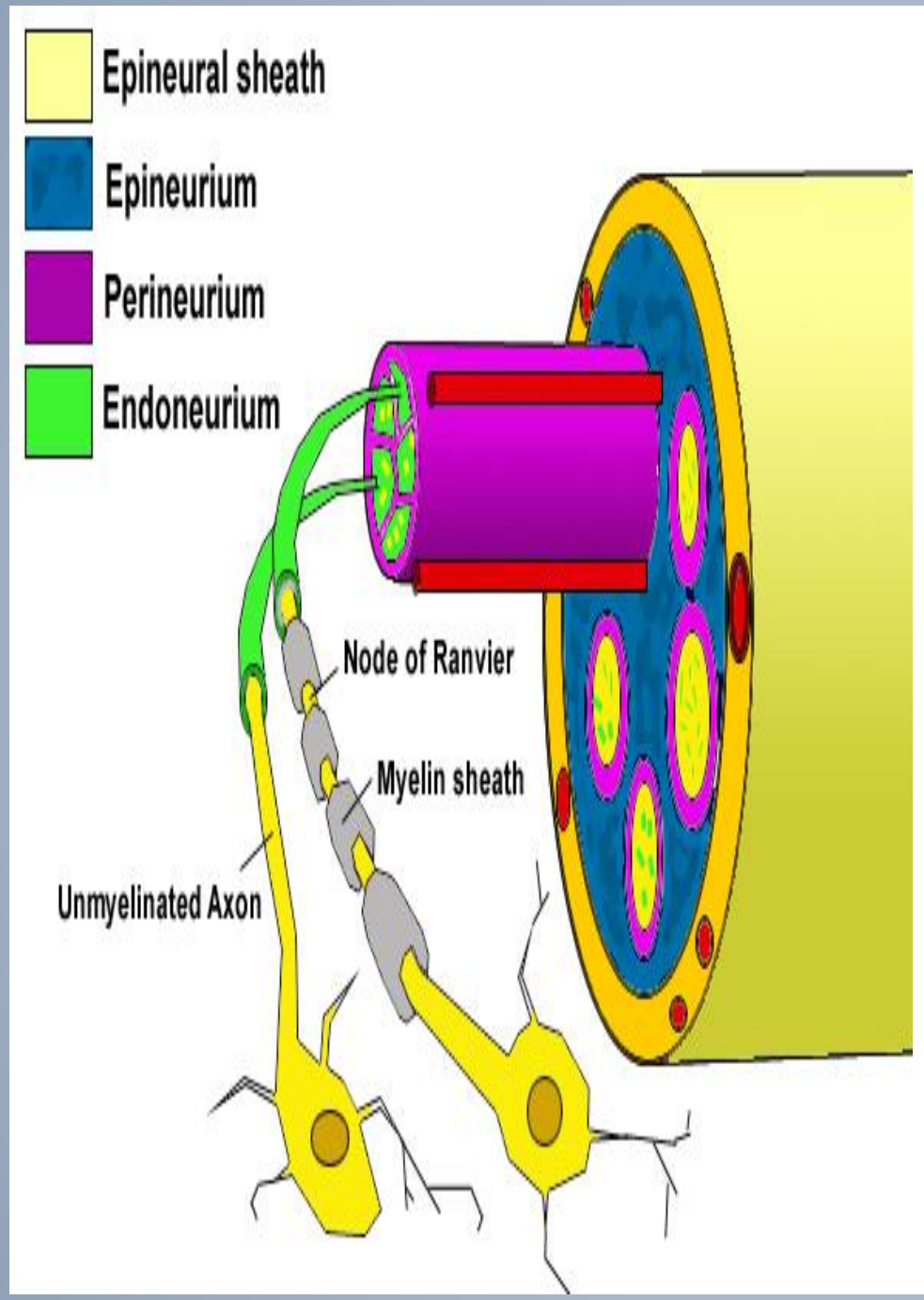
- Staphylococcus, diphtheria, & tetanus toxins.
- Mercury chloride has a small molecule but is hydrophilic and mainly in ionic form. Its concentration in the brain is minimal and so are its CNS effects.
- Methyl mercury is lipophilic, so crosses the BBB, and damaging the brain.

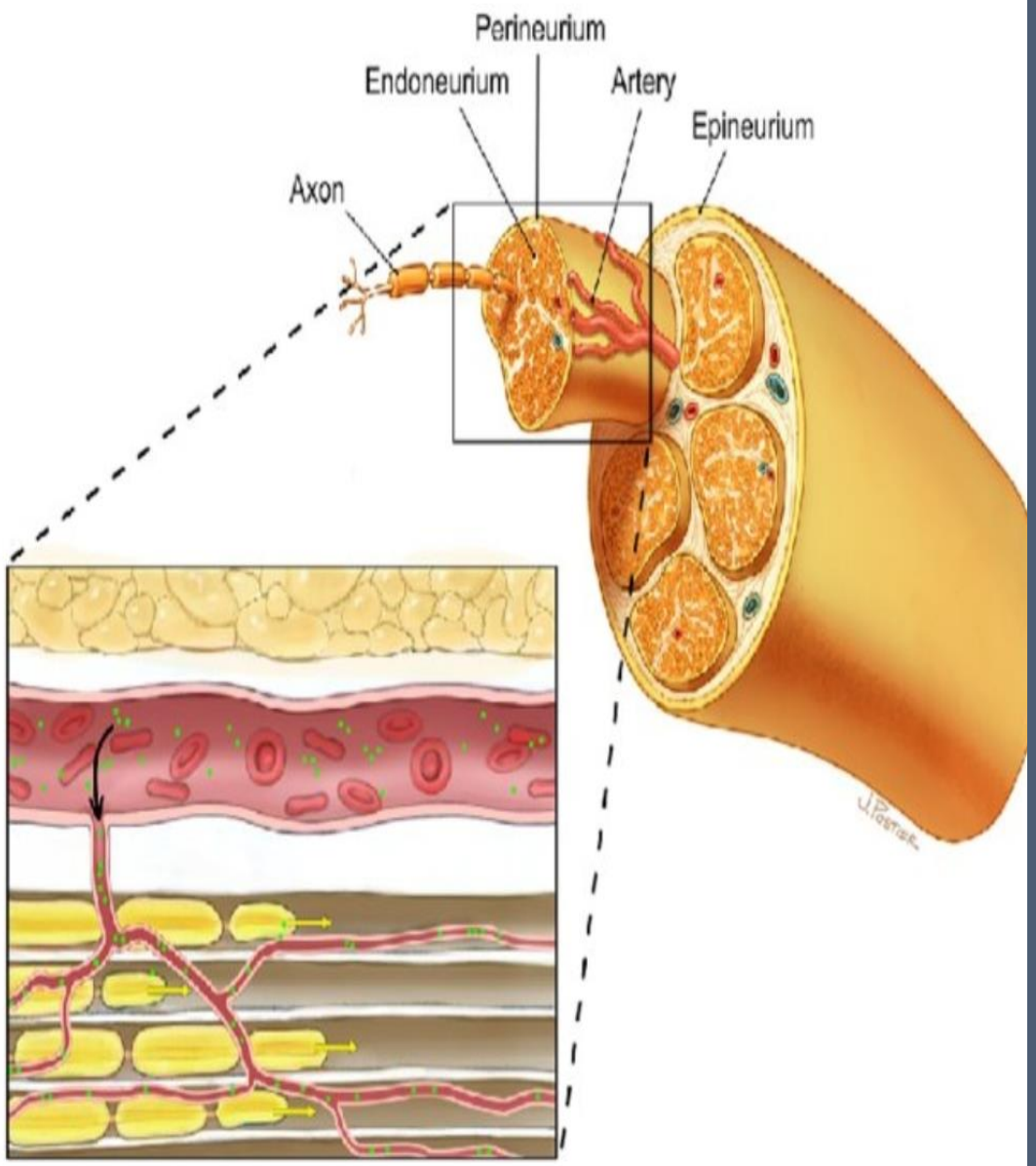
› Blood–nerve barrier (BNB) is not as effective as the BBB.

› e.g., doxorubicin affects neurons in the dorsal root ganglia but **not** those in the brain

Blood brain Barrier (BBB)




Epineural sheath
Epineurium
Perineurium
Endoneurium
Node of Ranvier
Myelin sheath
Unmyelinated Axon


Perineurium
Endoneurium
Artery
Epineurium
Axon

Neurotoxic effects and neurotoxicants (Mechanism of neurotoxicity)

1. Neuronopathy
2. Axonopathy
3. Interference with impulse conduction
4. Interference with synaptic transmission
5. Glial cells and myelin
6. Blood vessels and edema

1- Neuropathy

A- Neurons: mainly dependent on glucose as an energy source.

Neurons are susceptible to anoxic and hypoglycemic conditions.

✓ Chemicals with anoxigenic effects in the brain:

- **Barbiturates:** induce anoxia in brain, especially in hippocampus and cerebellum --- coma and permanent CNS damage (due to reduced cell metabolism)

- **Carbon monoxide:** diffuse sclerosis of the white matter (leukoencephalopathy).

- **Cyanide**: inhibits cytochrome oxidase ---cytotoxic anoxia.

B- The cell body of neurons: affected directly by toxicants.

- **Methyl mercury** --- focal loss of ribosomes then, nuclear and perinuclear changes and finally loss of the entire neuron including its axon
- **Doxorubicin** ---intercalating with DNA---inhibits the synthesis of RNA and neuronal protein. Since this drug does **not** cross the BBB, it can affect the neurons in the dorsal root ganglia and autonomic ganglia, but **not** those in the CNS.
- **Organotins**(used as pesticides & as plasticizers)--- accumulate in Golgi-like structures in the cell body--- cells swelling and necrosis
- **Glutamate**(in very large doses) ---neuroexcitatory and neurotoxicity (may be mediated through NO). It affects areas of the CNS lacking of BBB and the dendrites are the primary site of action ***but*** the axons are secure

2- Axonopathy

- Axons contain three types of neurofibrillary structures: neurotubules, neurofilaments, & microfilaments. Also they contain mitochondria and smooth endoplasmic reticulum. These structures are especially susceptible to a variety of neurotoxicants.

- Some axons are very long (up to 1m), and the elements in the axons (neurofibrils) are synthesized not locally but in the cell body, and are transported along the axon. Therefore, the axon may be attacked either **directly** by toxicants or **indirectly** through cell body damages.

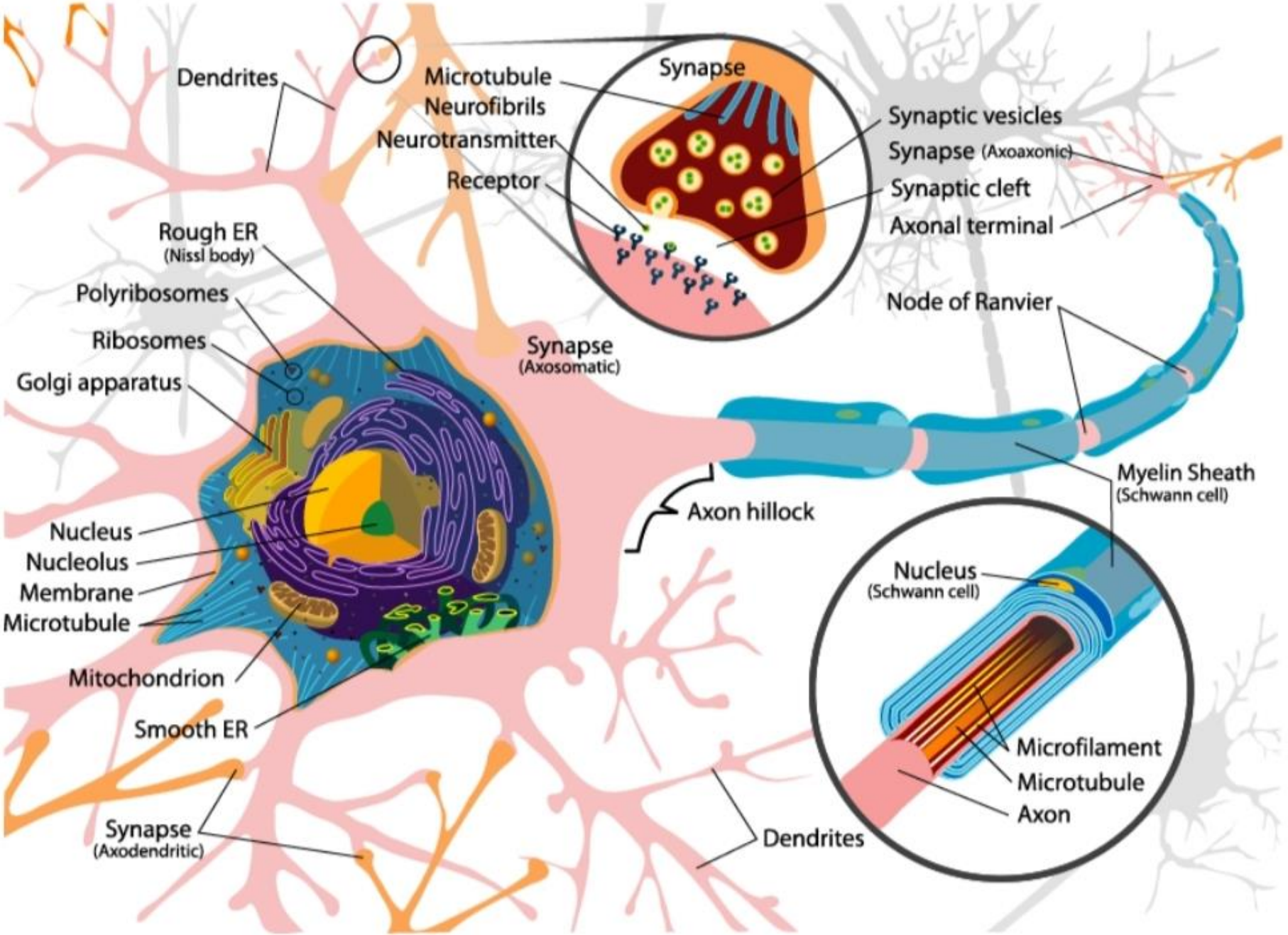
- Lesions may occur either in the proximal or in the distal sections of axons.

Proximal axonopathy

- **Iminodiproprionitrile** (IDPN):(used as a model to study motor neuron diseases such as amyotrophic lateral sclerosis)
- Its primary effect:
- abnormal phosphorylation of neurofilaments, while their synthesis is continued in the cell body.
- impairment of slow axonal transport of neurofilaments lead to
- accumulation of neurofilaments in the proximal axon causes it to enlarge and the distal axon to atrophy

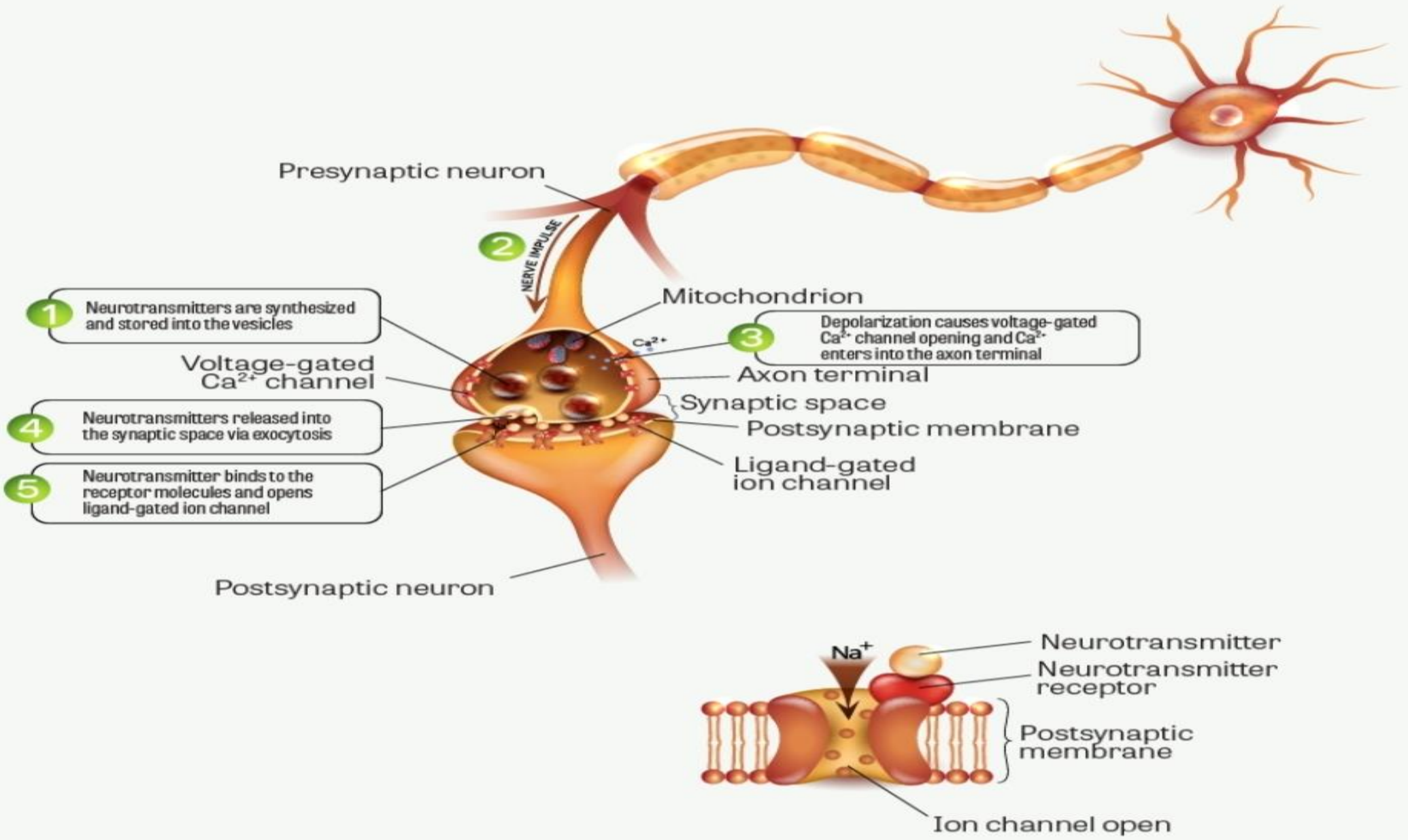
Distal axonopathy

- **Thallium**: mitochondrial swelling and degeneration
- **TOCP (tri-*o*-cresyl phosphate)** (organophosphorus compound): phosphorylation of the enzyme neuropathy target esterase (NTE) / derangement of neurofibrillary structures / *delayed neuropathy* (*distal axonopathy*) affects especially long and large nerve fibers/ paralysis of muscles.
- **Acrylamide**
- **Vincristine** accumulation of neurofibrils in the perikarya and axons/ disrupts the axonal neurotubules and neurofilaments/ blocks axoplasmic transport of these ultrastructures.


Dendrites
Microtubule
Neurofibrils
Neurotransmitter
Receptor
Synapse
Synaptic vesicles
Synapse (Axoaxonic)
Synaptic cleft
Axonal terminal
Rough ER
(Nissl body)
Polyribosomes
Ribosomes
Golgi apparatus
Synapse
(Axosomatic)
Node of Ranvier
Myelin Sheath
(Schwann cell)
Axon hillock
Nucleus
Nucleolus
Membrane
Microtubule
Mitochondrion
Smooth ER
Nucleus
(Schwann cell)
Microfilament
Microtubule
Axon
Synapse
(Axodendritic)
Dendrites

3- Interference with impulse conduction

- A number of toxicants act mainly on nerve membranes.
- These membranes normally maintain a negative resting potential. When stimulated, an action potential is generated. The resting and action potentials result from differences in the Na^+ and K^+ concentrations across the membrane, and their concentrations are maintained by the Na^+ channels.
- **Tetrodotoxin** (a toxin in frogs, pufferfish) **--- block** Na^+ channels ---block the action potential--- respiratory failure ----death
- **DDT & pyrethroids** (a synthetic insecticide) --- prolong the **opening** of Na^+ channel--- repetitive activity at the synapses and neuromuscular junctions.


Presynaptic neuron
2
NERVE IMPULSE
1
Neurotransmitters are synthesized and stored into the vesicles
Voltage-gated Ca^{2+} channel
4
Neurotransmitters released into the synaptic space via exocytosis
5
Neurotransmitter binds to the receptor molecules and opens ligand-gated ion channel
Postsynaptic neuron
Mitochondrion
3
Depolarization causes voltage-gated Ca^{2+} channel opening and Ca^{2+} enters into the axon terminal
Ca^{2+}
Axon terminal
Synaptic space
Postsynaptic membrane
Ligand-gated ion channel
Na^{+}
Neurotransmitter
Neurotransmitter receptor
Postsynaptic membrane
Ion channel open

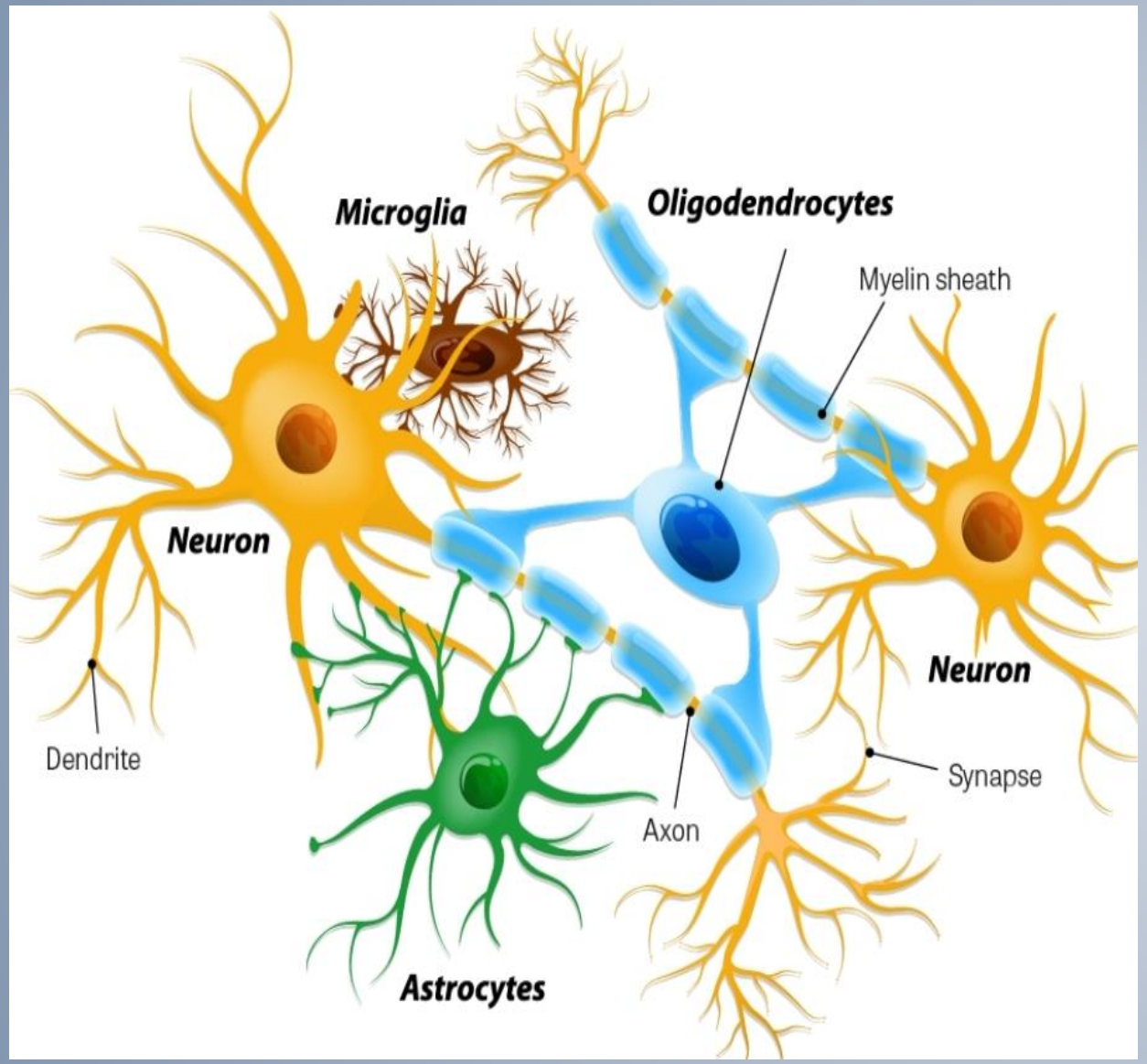
4- Interference with synaptic transmission (neurotransmitter)

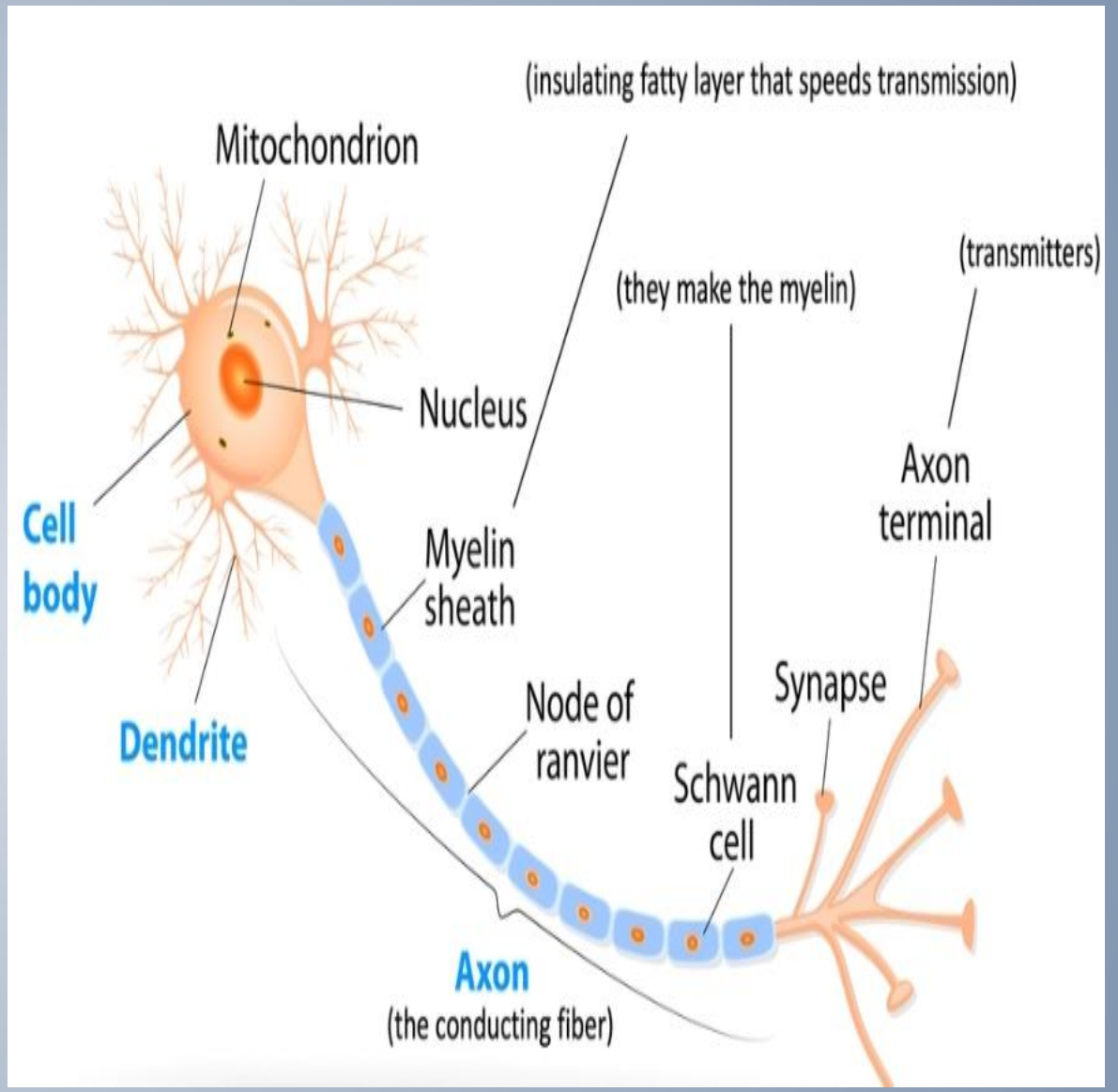
- **Botulinum toxin:** the most potent biologic toxin, is produced by *Clostridium botulinum* --- blocking the release of ACh from motor nerve endings --- paralysis of muscles.
- **Black widow spider venom** --- massive release of ACh --- cramps and paralysis.
- **Scorpion venom:** potentiate the release of Ach.
- **Tetanoplasmin**, from *Clostridium tetani* --- blocks release of the inhibitory amino acid transmitters GABA and glycine in CNS--- spastic paralysis (tetanus)

5- ***Glial cells and myelin***

A- Myelinating cells

- Demyelination can result from injuries to myelinating cells (oligodendrocytes and Schwann cells).
- **Lead**: affects Schwann cells by interfering with their Ca^{2+} transport.
- **Hypocholesterolemic agents** such as triparanol, disrupt myelin sheath because of the high (70%) lipid content of myelin. They produce ultrastructural changes in oligodendrocytes , then demyelination occurs.
- **Diphtheria toxin** causes loss of myelin by interfering with the production of protein by schwann cells that produce and maintain myelin in PNS.


Microglia
Oligodendrocytes
Myelin sheath
Neuron
Neuron
Dendrite
Synapse
Axon
Astrocytes


(insulating fatty layer that speeds transmission)
Mitochondrion
(they make the myelin)
(transmitters)
Nucleus
Cell body
Myelin sheath
Axon terminal
Dendrite
Node of ranvier
Synapse
Schwann cell
Axon
(the conducting fiber)

B- Myelin sheath

Demyelination can also result from effects on the myelin sheath. This type of effect generally involves a disruption of the membrane structure.

Other modes of action include:

1) inhibition of carbonic anhydrase or other enzymes involved in ion and water transport

2) inhibition of enzymes involved in oxidative phosphorylation, and chelation of metals.

Neurotoxicants that act **directly** on the myelin sheath: lysolecithin, isoniazid, cyanate, and lead causes myelinopathy

Lead:

- a neurotoxicant.
- affects various parts of the nervous system, including myelin sheath.
- PNS is affected before the CNS.
- affects motor nerves before the sensory, resulting in “wrist-drop” and “foot-drop.” effects on the blood vessels are discussed below.

6- Blood vessels and edema

The permeability of the vascular system in the CNS and PNS may be increased by:

1. higher blood pressure
2. lower plasma osmolarity
3. exposure to certain toxins.

› The greater permeability generally leads to an accumulation of fluids in the **extracellular** space.

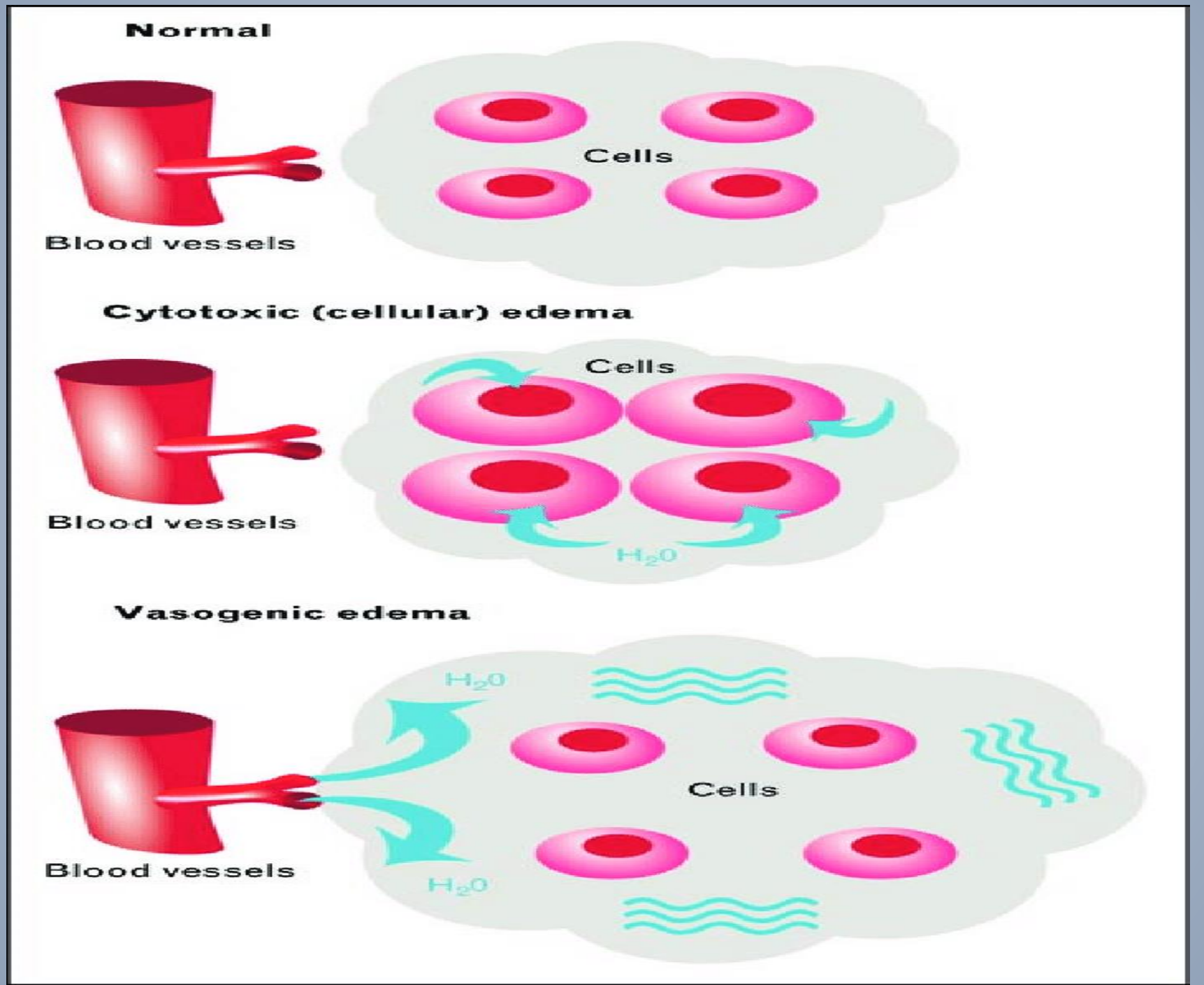
› A number of **neurotoxicants** are known to induce **cellular edema**.

Extracellular edema

- **Lead:**

1. damage the endothelial cells --- extravasation of plasma in the brain
2. similar effects on the endoneurium---increased endoneural fluid pressure and demyelination.

- **Organic lead**, such as tetraethyl lead, more readily penetrates the barriers and is therefore more toxic in this respect.
- **Mercury compounds**--- damage the endothelial cells ---increase their permeability.
- **Organic arsenicals**--- edema and focal hemorrhages in the brain.
- **Chronic alcoholism**--- endoneural edema.


Normal
Cells
Blood vessels
Cytotoxic (cellular) edema
Cells
Blood vessels
H_2O
Vasogenic edema
H_2O
Cells
Blood vessels
H_2O

Cellular edema

- **6-aminonicotinamide** ---affects the perikaryon --- edema of astrocytes and oligodendrocytes
- **CN & CO** --- affect the axon
- **Ouabain**---affect astrocytes.
- **Lead** --- edema of Schwann cells + extracellular edema
- **Isoniazid**---edema of myelin sheaths in CNS.
- **Hexachlorophene**--- edema of the myelin sheaths both in the white matter of the brain and in the peripheral nerves.

THANK YOU FOR YOUR ATTENTION

LEC 6. TOXIC SUBSTANCES:

RADIATION AND RADIOACTIVE MATERIALS

Assist. Lecturer

Safa H. Mohsin

10/3/2024

INTRODUCTION

- **Radiation** is a flow of energy through space or matter. It takes the form of :
- **particles (e.g., alpha and beta particles)**

or

- **electromagnetic waves (e.g., X rays, gamma rays, and visible and ultraviolet [UV] light).**

- **Radiation** can be classified as either **ionizing** or **nonionizing** depending on its ability to produce ions in the matter it interacts with.
- **Ionizing** radiation is more toxic than **nonionizing** radiation.

SOURCES OF RADIATION

Natural radiation

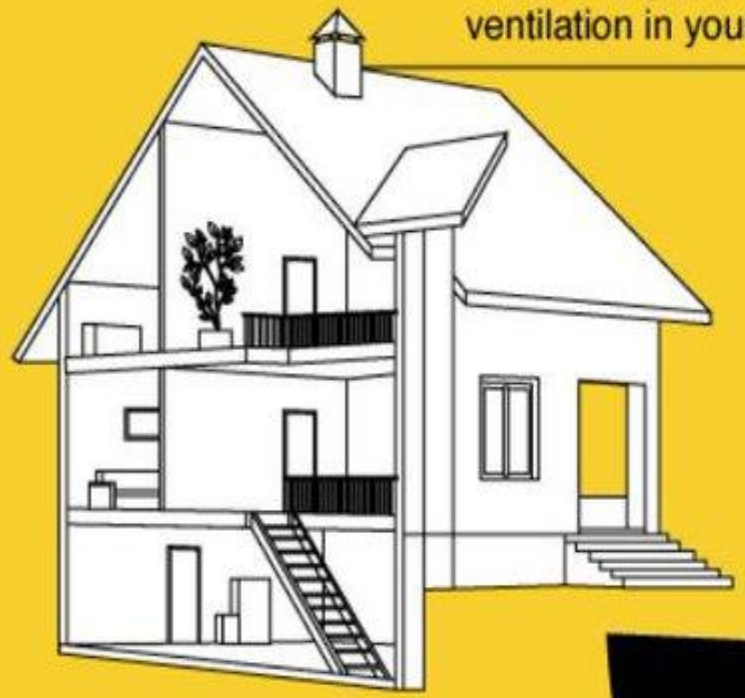
Man-made radiation

NATURAL RADIATION

- **Natural radiation** includes cosmic radiation, terrestrial radiation, radioisotopes inside human bodies, and radon gas.
- Cosmic radiation consists of charged particles from outer space,
- Terrestrial radiation of gamma rays from radionuclides in the Earth.
- Radioisotopes in human bodies come from the food, water, and air consumed.

- Cosmic and terrestrial radiation, together with radioisotopes inside human bodies, contribute only **one-third** of the total natural radiation dose. The remaining **two-thirds** can be attributed to radon, a radioactive gas released from soil that may reach a high level inside buildings with poor ventilation

Reduce your exposure to radon by increasing ventilation in your home

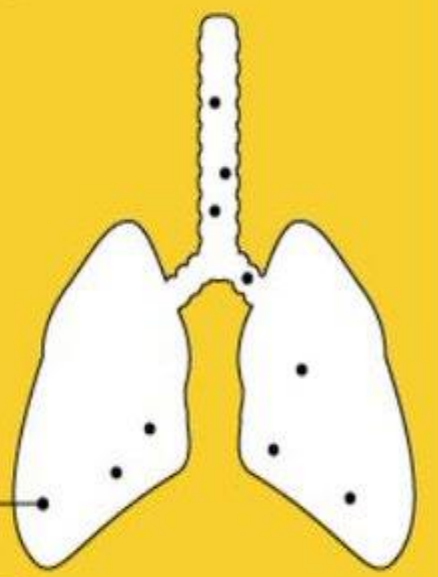


Have your home tested for radon regularly, not just when you're buying or selling a property

Radon is a naturally occurring radioactive gas produced in the ground through the normal decay of uranium and radium

Rn
Radon

Byproducts of radon decay attach to surfaces and air particles, such as dust, and once inhaled, can pose severe health risks



1/4 homes in MA have the potential to exceed the EPA's recommended radon level

Radon is responsible for an estimated 20,000 lung cancer deaths per year

MAN-MADE RADIATION

- **Man-made radiation** consists of radiation from:

1- medical and dental diagnostic procedures

2-atmospheric tests of atomic bombs

3- emissions from nuclear plants

4- certain occupational activities, and some consumer products.

- The largest non-occupational radiation sources are tobacco smoke for smokers and indoor radon gas for the nonsmoking population.

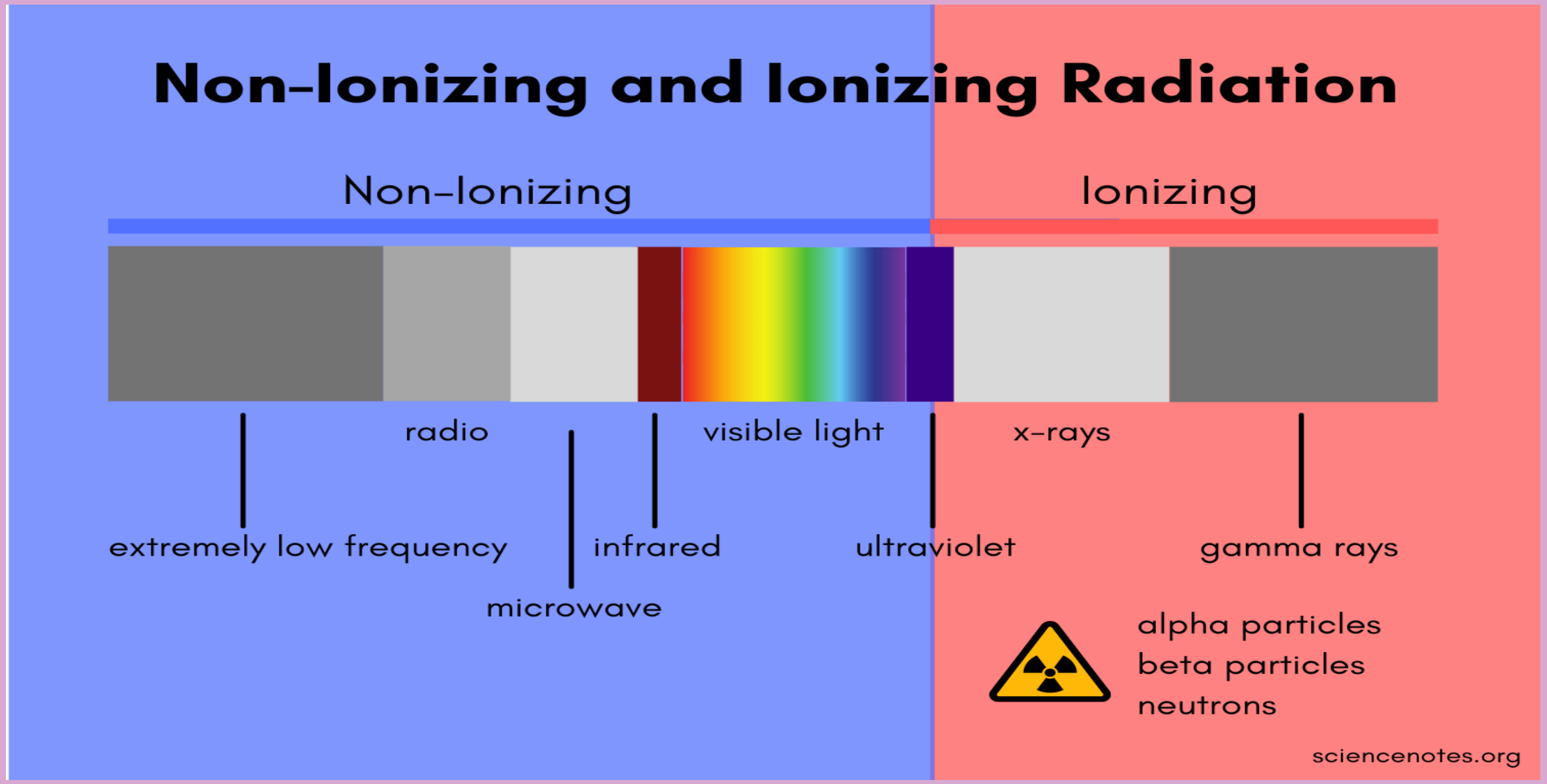
- Emissions from nuclear power plants contribute only a very small portion of the total yearly radiation received.

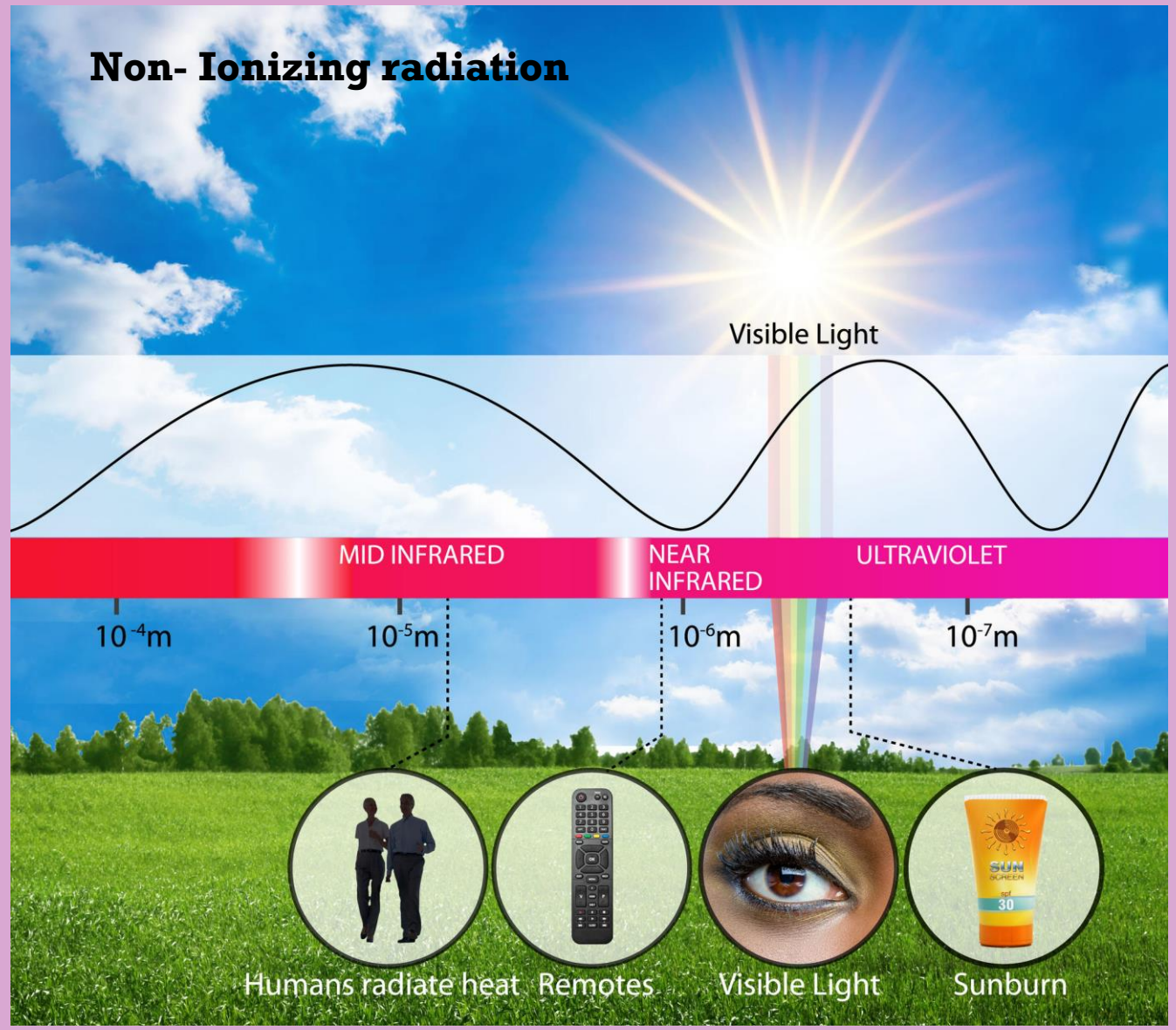
TYPED OF RADIATION

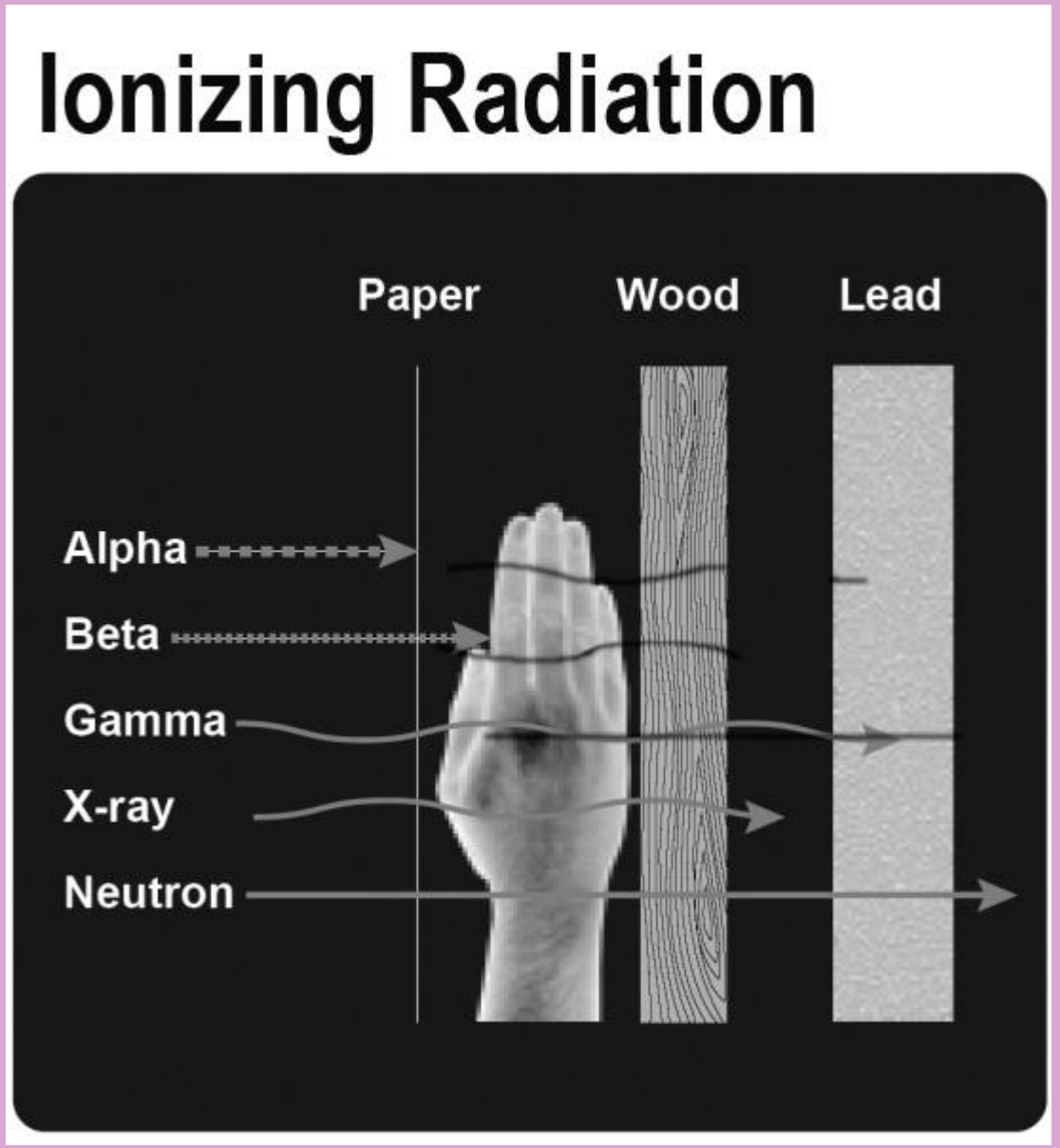
Ionizing radiation

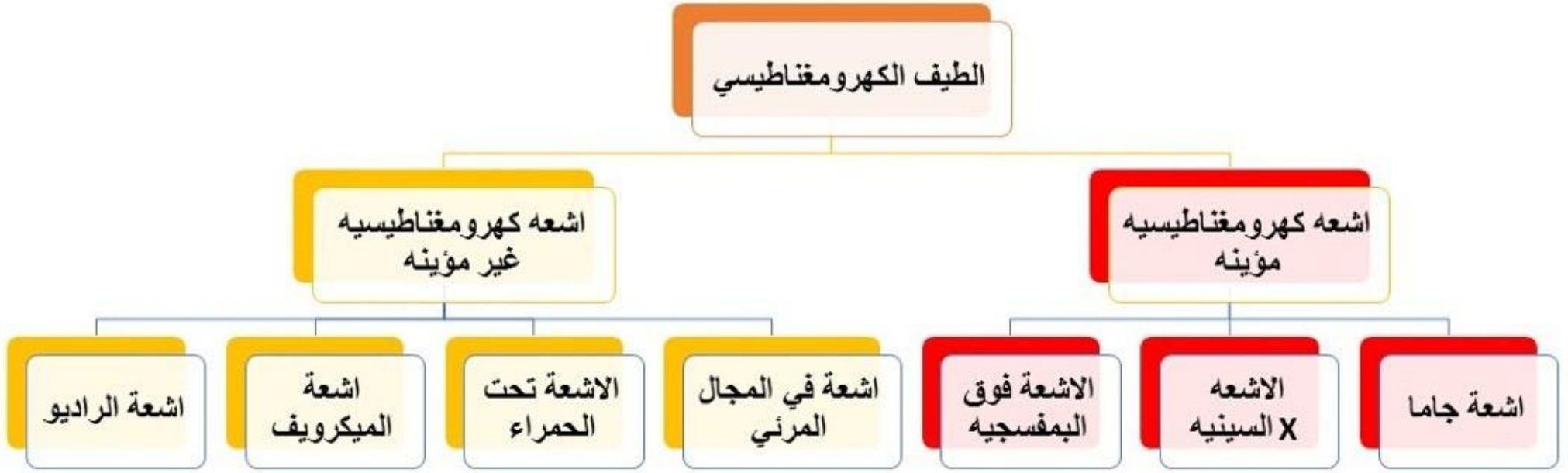
Non ionizing radiation

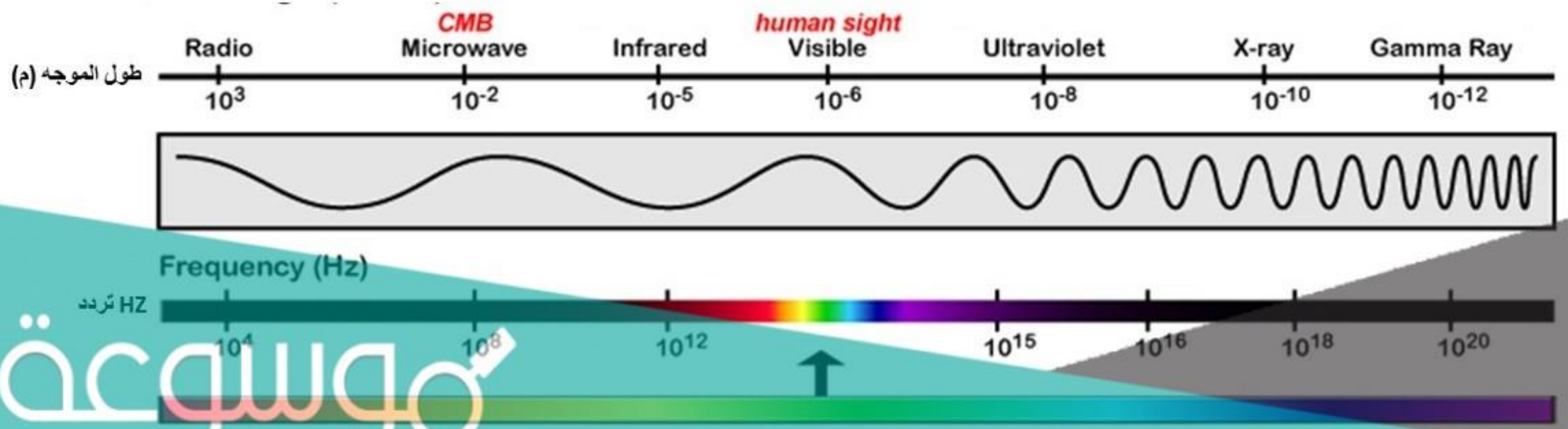
IONIZING & NONIONIZING RADIATION




Non- Ionizing radiation
Visible Light
MID INFRARED
NEAR INFRARED
ULTRAVIOLET
10-4m
10-5m
10-6m
10-7m
Humans radiate heat
Remotes
Visible Light
Sunburn


Ionizing Radiation
Paper
Wood
Lead
Alpha
Beta
Gamma
X-ray
Neutron


الطيف الكهرومغناطيسي
اشعه كهرومغناطيسيه مؤينه
اشعه كهرومغناطيسيه غير مؤينه
اشعة جاما
الاشعه X السينيه
الاشعة فوق البمفسجيه
اشعة في المجال المرئي
الاشعة تحت الحمراء
اشعة الميكروويف
اشعة الراديو


CMB
human sight
Radio
Microwave
Infrared
Visible
Ultraviolet
X-ray
Gamma Ray
طول الموجه (م)
10^3
10^-2
10^-5
10^-6
10^-8
10^-10
10^-12
Frequency (Hz)
HZ تردد
10^4
10^8
10^12
10^15
10^16
10^18
10^20

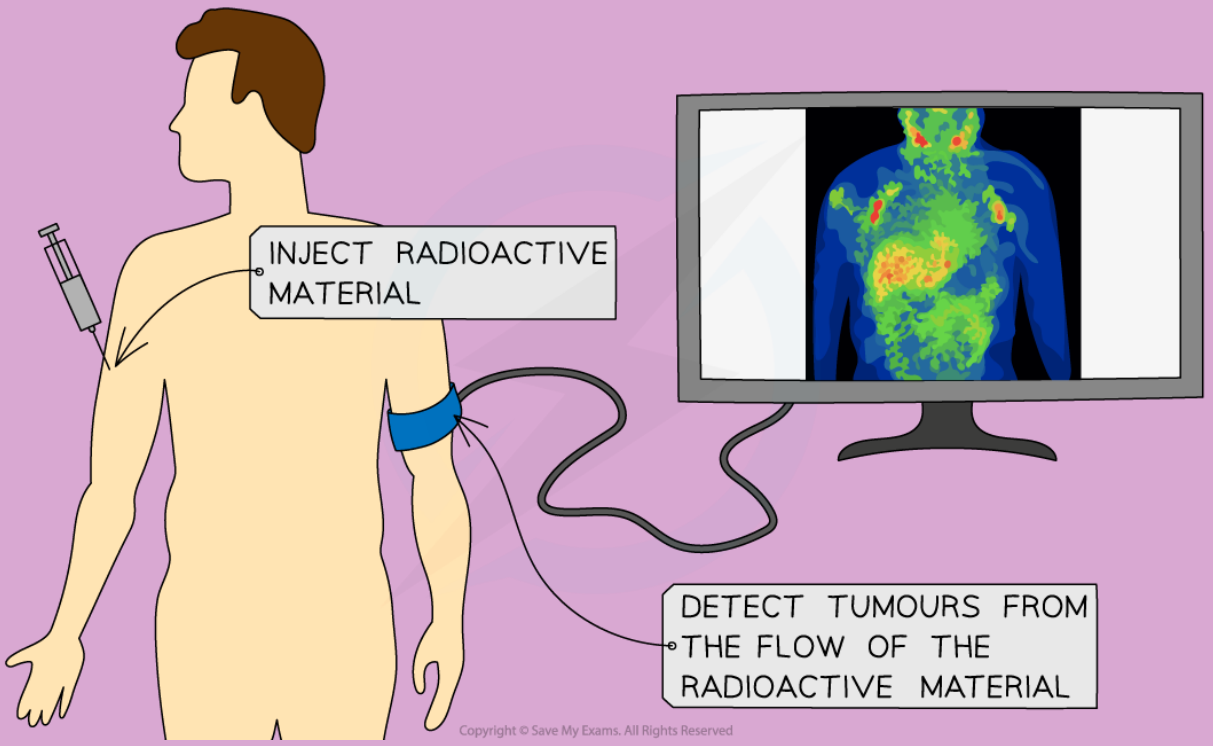
TYPES OF RADIATION

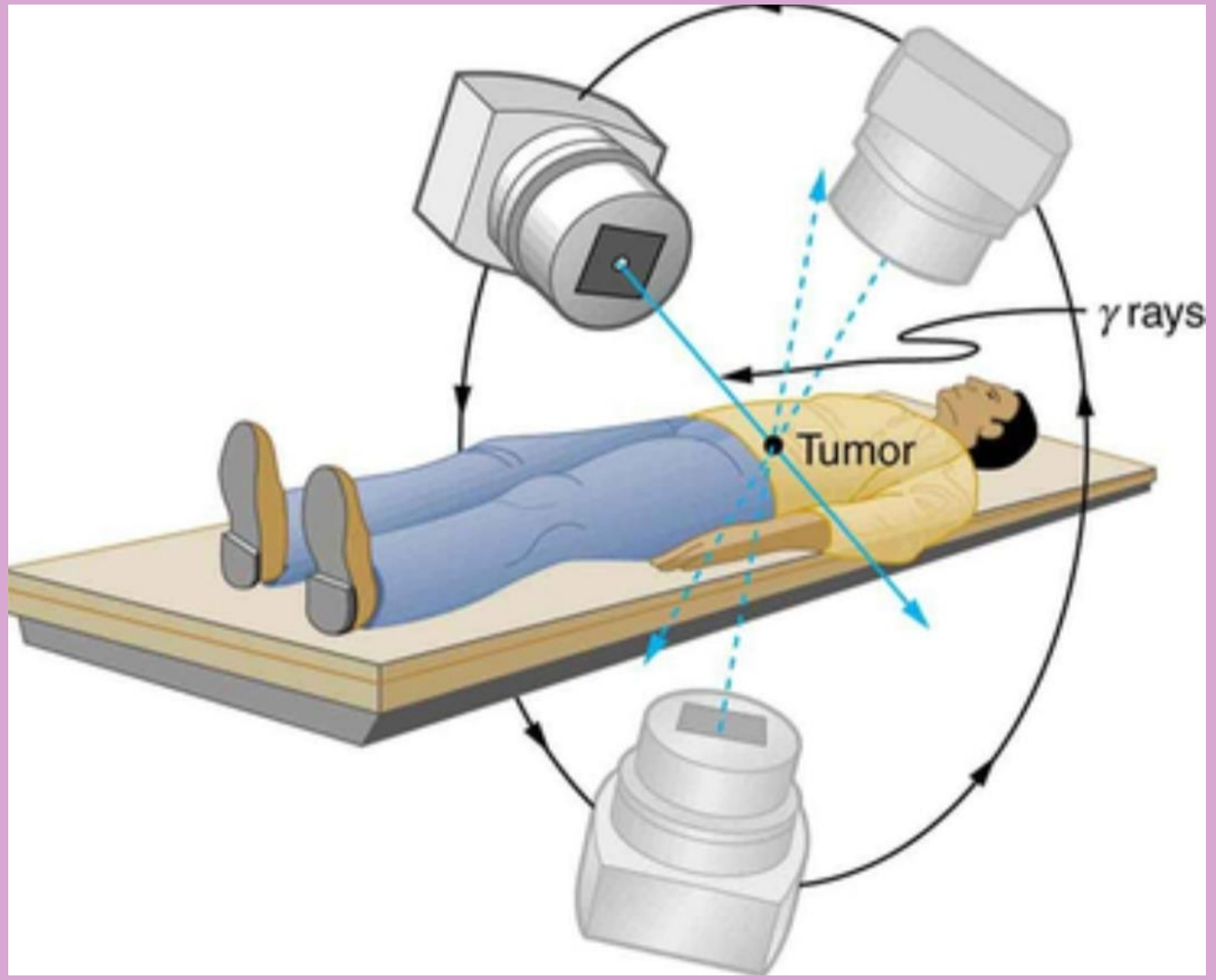
- **1- Ionizing radiation** is radiation that produces ions in matter during interaction with atoms in the matter. The toxic effect of ionizing radiation is related to the ionization. It is believed that ionization of tissues, composed mainly of water, generates H_2O^+ and H_2O^- ions, which in turn form **H** and **OH radicals**. Because radicals are very reactive chemically, biological damage, such as attacks on DNA and proteins.
- **Ionizing radiations** such as x-rays are radiations that have sufficient energy to displace electrons from molecules. These freed electrons then have the capability of damaging other molecules (**DNA)**. Biological effects of radiation are primarily damage to **DNA**. Atoms of the DNA target may be directly ionized or indirectly affected by the creation of a free radical that can interact with the DNA molecule. In particular, the hydroxyl radical is predominant in DNA damage.

ADVERSE EFFECTS OF IONIZING RADIATION

- Ionizing radiation quickly kills rapidly dividing cells. In general, immature blood cells in bone marrow, cells lining the mucosa of the GIT, and cells in the lower layers of the epidermis and in hair follicles are the most rapidly dividing cells in the body. As a result, **radiation** leads to the decreased production of blood cells, nausea, vomiting, diarrhea, malabsorption by the intestine, skin burns, and hair loss.

- Because of its relatively selective lethal effect on rapidly dividing cells, however, ionizing radiation is used in the treatment of certain cancers.
- Some cells in the embryo and fetus also divide rapidly, and thus ionizing radiation can cause malformations and even fetal death.
- Ionizing radiation can also produce mutations by **altering** the **DNA**, and it can result in **cancer**.
- **Cancer** has been the major adverse health effect of ionizing radiation.





TOXICITIES OF WHOLE-BODY IONIZING RADIATION

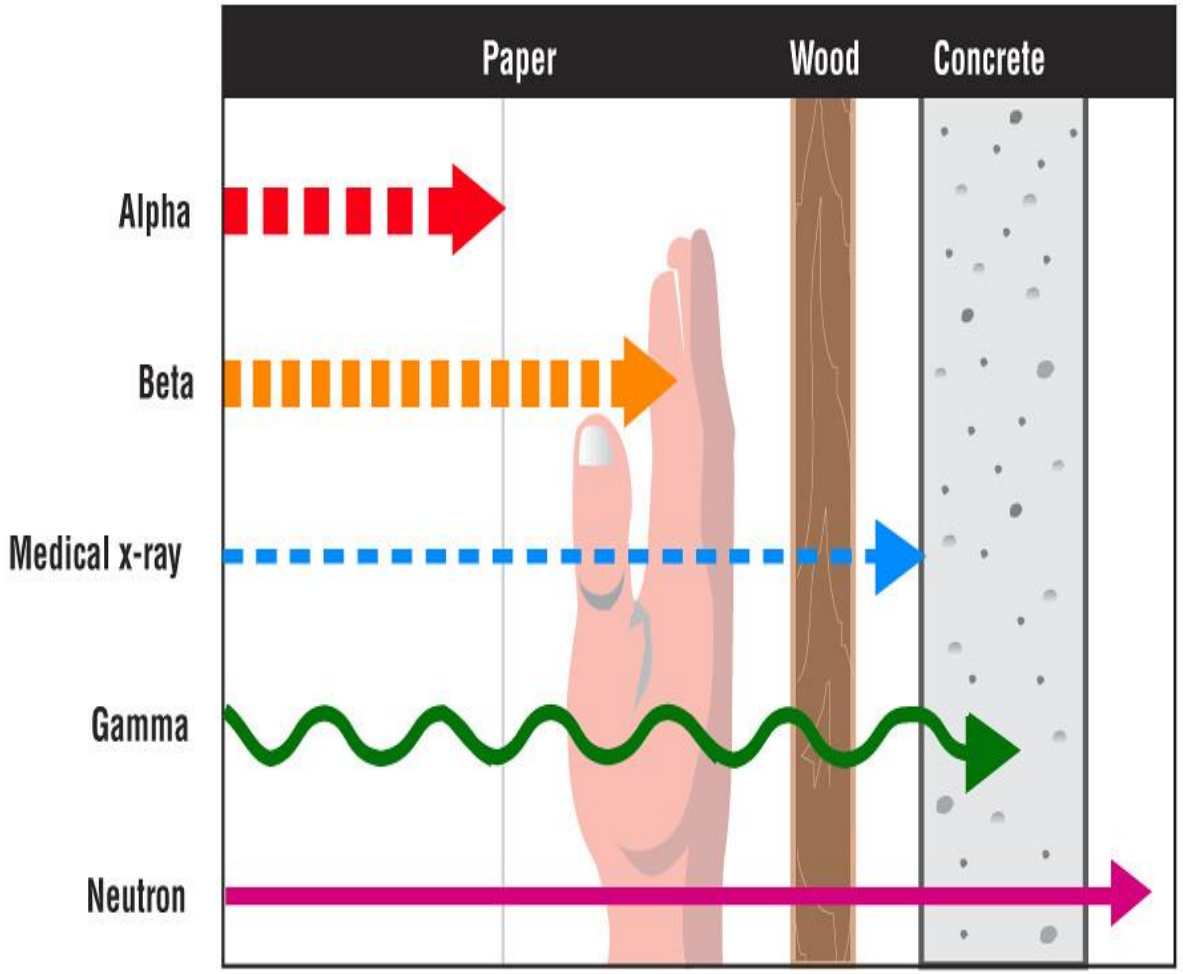
- X rays and gamma rays; at sufficiently high doses, can lead to a condition known as acute radiation syndrome.
- The most sensitive tissue is the bone marrow, where blood cells are generated.
- The next tissue affected is the GIT.
- If the dose is high, the CNS is affected and the person becomes uncoordinated and disoriented and experiences tremors, convulsions, and coma.
- At even higher doses, the skin, eyes, and ovaries and testes are affected.
- Death may follow from 2 to 35 days after exposure.
- Exposure to radiation can also result in cancers of the bone marrow (leading to leukemia), lungs, kidneys, bladder, esophagus, stomach, colon, thyroid, or breasts.
- e.g. **tritium** and **cesium-137** both of which release **beta** particles that can lead to **bone** marrow **toxicities** and even, in the case of **cesium-137**, to **death**.

LOCAL TOXICITIES OF COMMON BETA-PARTICLE EMITTERS

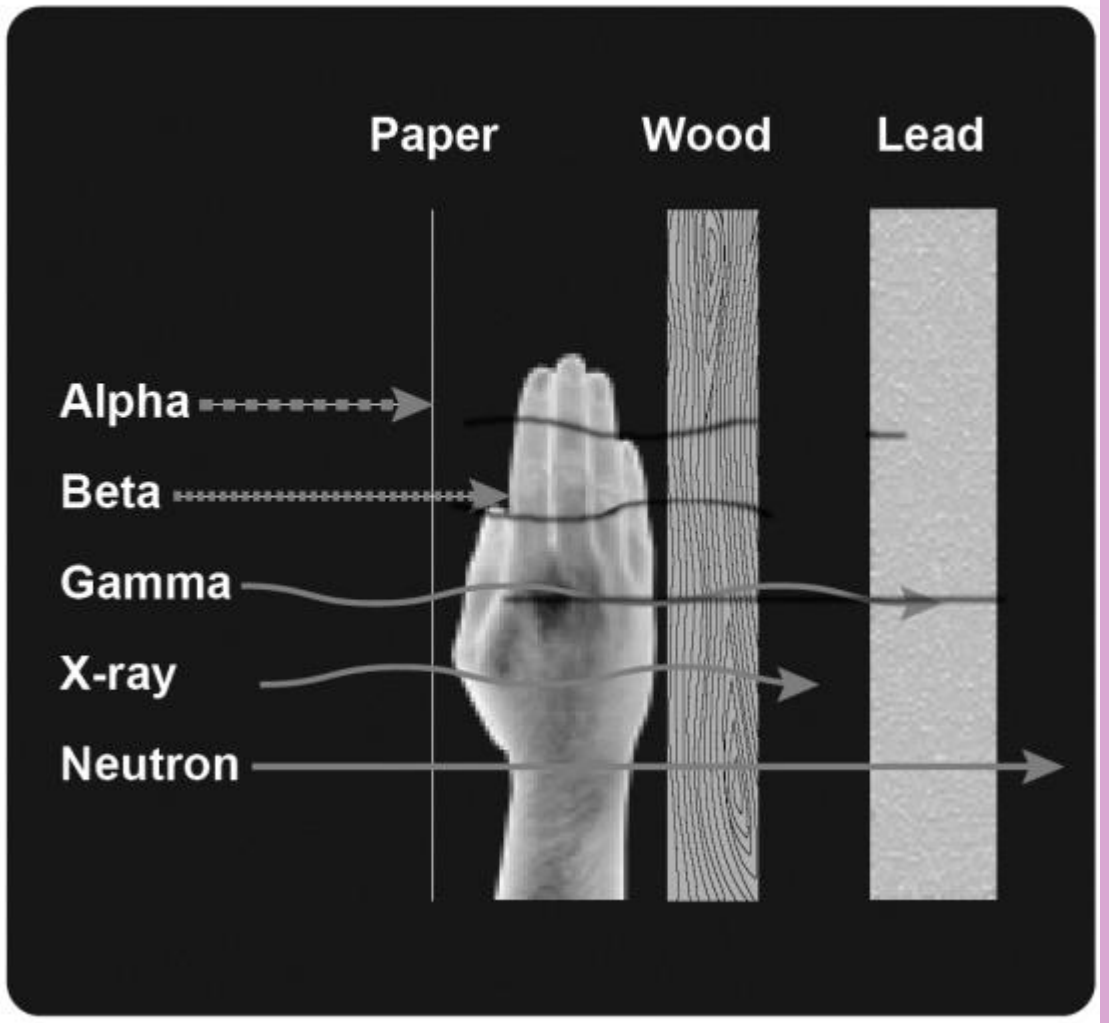
- The isotopes **strontium-90**, **iodine-131**, & **cerium-144** emit beta particles that are **not distributed equally** in the body.
- Strontium-90 releases only beta particles, while iodine-131 and cerium-144 release both beta particles and gamma rays, but their toxicities are primarily caused by the beta particles.
- These radioisotopes produce toxicities in the tissues where they are stored or concentrated.
- Strontium-90 and cerium-144 chemically **resemble calcium** and as a result are stored in **bone**. Therefore, produce bone cancer and leukemia, which is a result of the irradiation of bone marrow.
- Iodine-131 is concentrated in the **thyroid** and produces thyroid damage and tumors.

LOCAL TOXICITIES OF COMMON ALPHA-PARTICLE EMITTERS

- Most of the common **alpha-particle** emitters belong to the **uranium** series.
- The radioisotopes in the uranium series are important because uranium is the starting fuel for many nuclear reactors and because daughter nuclides in this series are commonly found in the environment.
- The toxicity of **uranium-238** depends on the water solubility of the uranium compound:
  - Water-soluble forms mainly cause **kidney injury**, while the insoluble forms produce **fibrosis** and **lung cancer**.
- Because of its similarity to calcium, **radium-226** is stored mainly in the **bone**, and it produces abnormal changes in the bone marrow, including anemia and leukemia, bone cancers.
- Also deposited on the respiratory tract when inhaled, the respiratory tract is irradiated by the alpha particles released, and lung cancer & paranasal sinuses cancer. can result.



Ionizing Radiation



2- NONIONIZING RADIATION

- Nonionizing radiation includes

A- ultraviolet light

B- infrared radiation

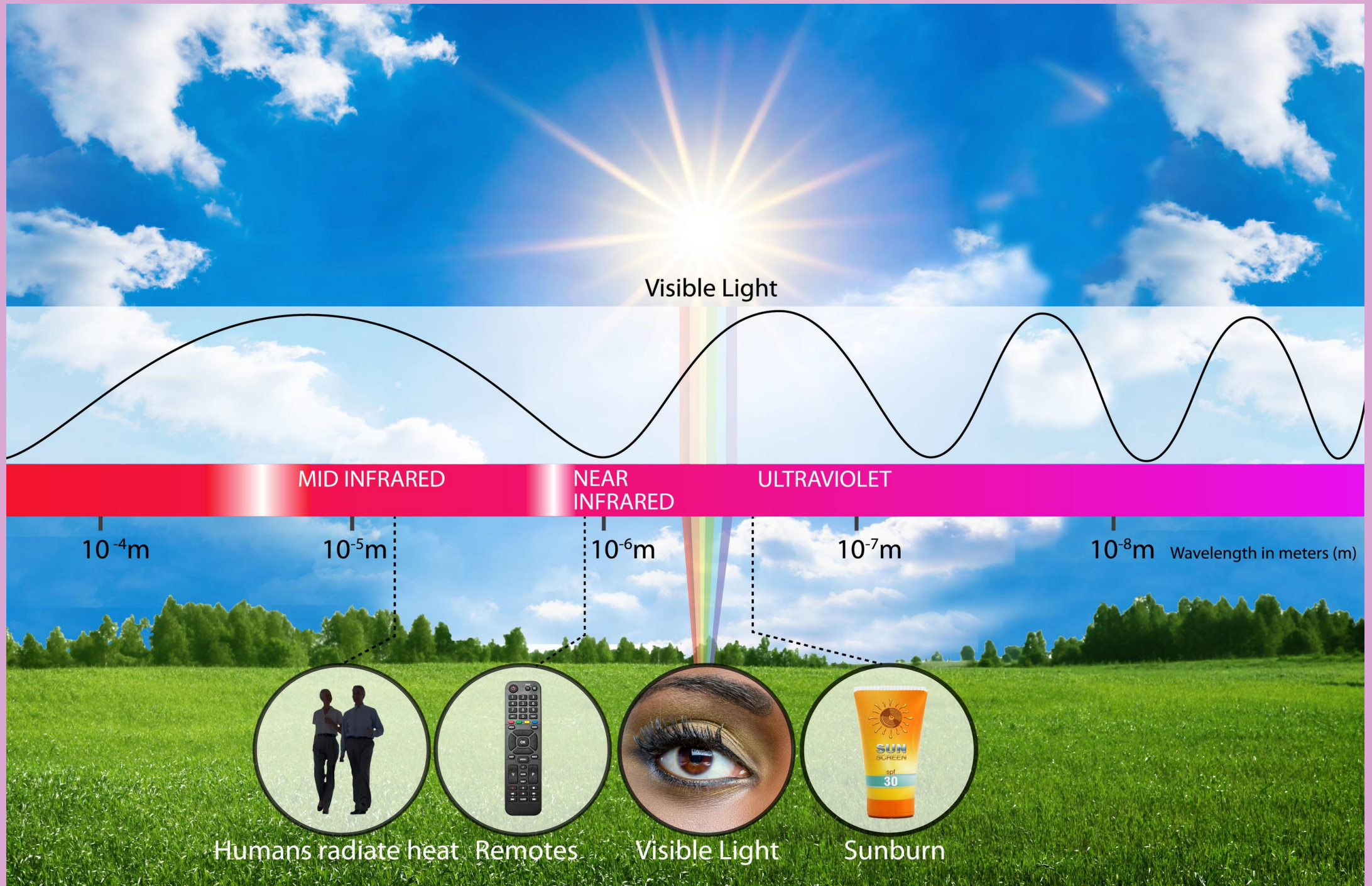
C- microwaves, and radio frequencies

all these are **electromagnetic waves.**

- Nonionizing radiation is **not** as toxic as ionizing radiation, and the various forms of non-ionization radiation share common target organs; particularly the **skin** and **eyes**

A- ULTRAVIOLET RADIATION

- The toxicity of ultraviolet light depends on its wavelength.
- **Ultraviolet-A** (near UV) has a wavelength of 315–400 nm (**skin**)
- **Ultraviolet-B** (mid UV) has WL of 280–315 nm **(skin & eye)**
- **Ultraviolet-C** (far UV) has WL of 200–280 nm. **(skin & eye)**
-
- **UV-A** affects primarily the **skin** and causes **burns** at high energy levels.
- The toxicities of **UV-B** and **UV-C** are similar, but UV-C is less toxic because it does not penetrate tissues as deeply. Both UV-B and UV-C cause injuries to the eyes and skin.
- UV-B is the major component of **sunlight** and accelerates the **aging of skin** by damaging the collagen fibers under it. UV-B also is the cause of an occupational disease known as "welder's flash," or "arc eye," which is characterized by photophobia, tears in the eyes, spasm of the eyelids, and eye inflammation. Finally, UV-B can cause **skin cancer** which may be a result of the linking of thymidines, a base in DNA, produced by UV-B radiation.

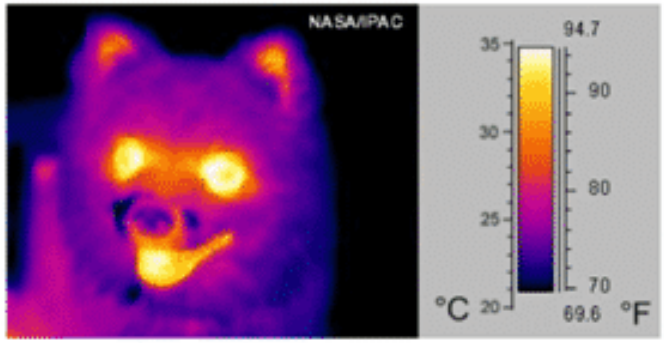

Visible Light
MID INFRARED
NEAR INFRARED
ULTRAVIOLET
10 -4m
10-5m
10-6m
10-7m
10-8m
Wavelength in meters (m)
SUN SCREEN
spf 30
Humans radiate heat
Remotes
Visible Light
Sunburn

B- INFRARED RADIATION AND MICROWAVES

- The major mechanism of toxicity of **infrared radiation** and **microwaves** is the production of **heat** in tissues.

- **Infrared-A** (WL 0.8–1.4 Mm) penetrates the skin, causing burns and pigmentation. Infrared-A also penetrates the liquid content of the eye to reach the retina and can therefore produce damage to all parts of the eye.

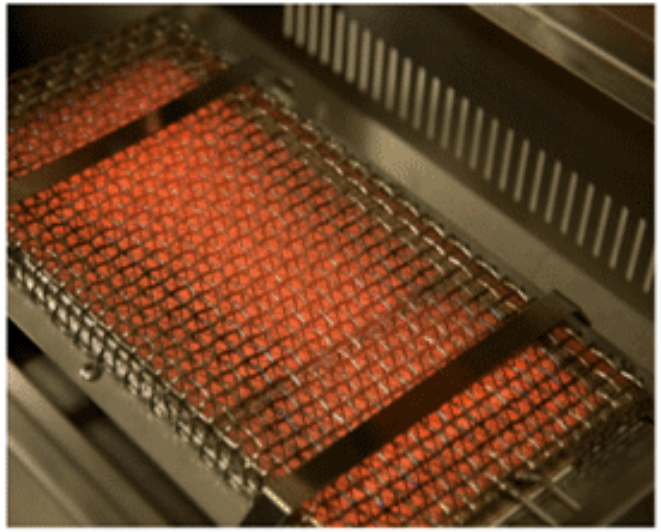
- In contrast, **infrared-B** and **infrared-C** (WL 1.4–3,000 Mm) are almost completely absorbed by the superficial layers of the skin and eyes, and the damage is thus confined to the surface.



Thermal imaging

Night vision

Remote controls for TV/VCR



Cooking

Short range communication

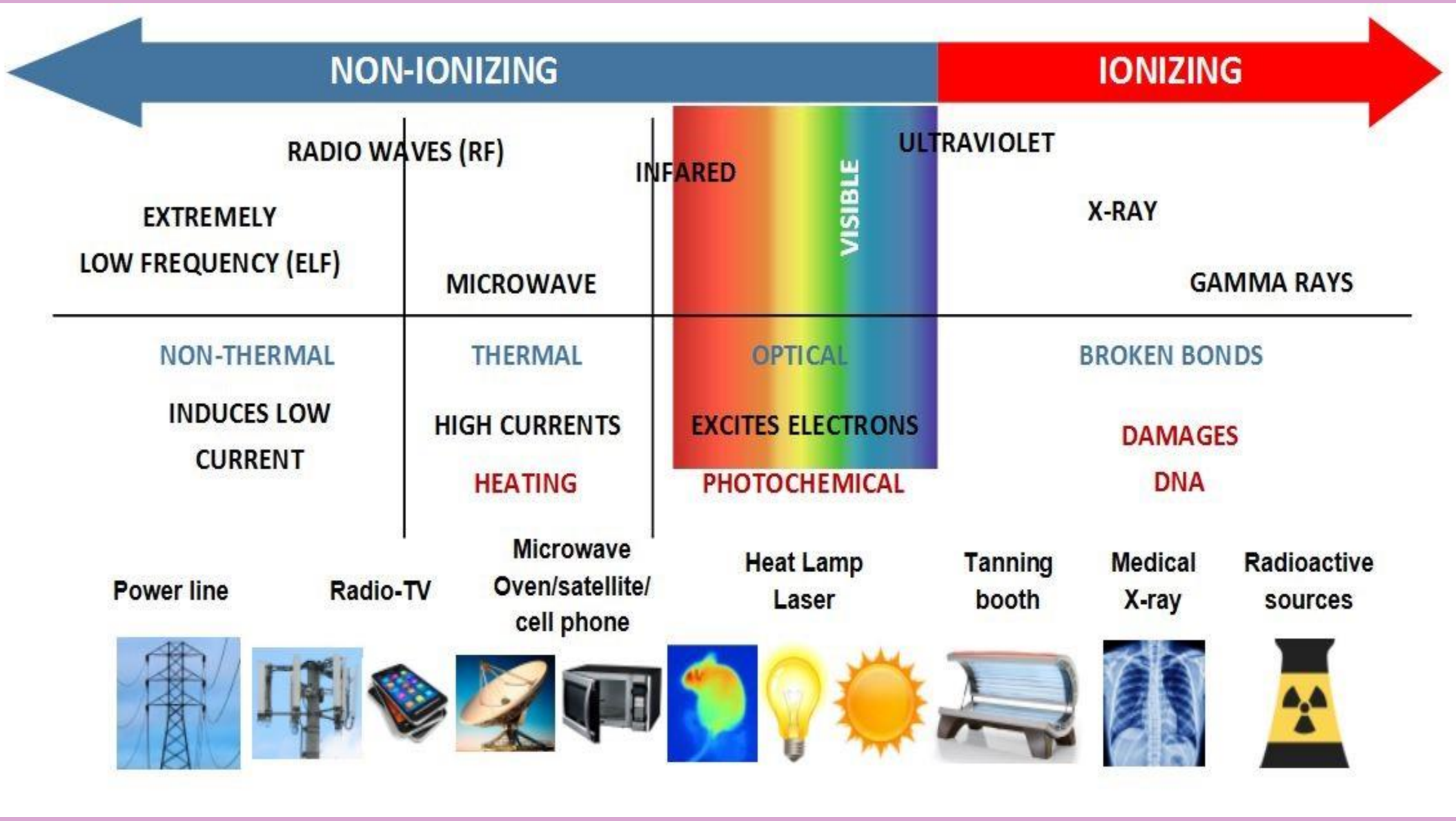
C-MICROWAVES & LASER

Microwaves

(wavelength 1 mm to 1 m.) produce heat in tissues. Because testes and eyes do not dissipate heat well, due to low blood flow through these organs, temporary sterility and cataracts can be produced by microwaves.

Lasers

- Lasers are high-energy light beams, visible and nonvisible, generated by atoms at an excited state and further amplified by optics.
- Like most other nonionizing radiation, **lasers** can produce **skin burns**.
- Visible lasers, with a wavelength from 0.4 to 1.4 Mm, will cause **retinal damage.**


NON-IONIZING
IONIZING
RADIO WAVES (RF)
INFARED
VISIBLE
ULTRAVIOLET
EXTREMELY
LOW FREQUENCY (ELF)
MICROWAVE
X-RAY
GAMMA RAYS
NON-THERMAL
THERMAL
OPTICAL
BROKEN BONDS
INDUCES LOW
CURRENT
HIGH CURRENTS
HEATING
EXCITES ELECTRONS
PHOTOCHEMICAL
DAMAGES
DNA
Power line
Radio-TV
Microwave
Oven/satellite/
cell phone
Heat Lamp
Laser
Tanning
booth
Medical
X-ray
Radioactive
sources

Toxicology
Lec 6. Toxic substances: Radiation and radioactive materials

Introduction:

Radiation is a flow of energy through space or matter. It takes the form of particles (e.g., alpha and beta particles) or electromagnetic waves (e.g., X rays, gamma rays, and visible and ultraviolet [UV] light).

Radiation can be classified as either ionizing or nonionizing depending on its ability to produce ions in the matter it interacts with. Ionizing radiation is more toxic than nonionizing radiation.

Radiation sources:

Radiation is either natural or man-made.

Natural radiation includes cosmic radiation, terrestrial radiation, radioisotopes inside human bodies, and radon gas. Cosmic radiation consists of charged particles from outer space, and terrestrial radiation of gamma rays from radionuclides in the Earth. Radioisotopes in human bodies come from the food, water, and air consumed. Cosmic and terrestrial radiation, together with radioisotopes inside human bodies, contribute only one-third of the total natural radiation dose. The remaining two-thirds can be attributed to radon, a radioactive gas released from soil that may reach a high level inside buildings with poor ventilation.

Man-made radiation consists of radiation from medical and dental diagnostic procedures, atmospheric tests of atomic bombs, emissions from nuclear plants, certain occupational activities, and some consumer products. The largest non-occupational radiation sources are tobacco smoke for smokers and indoor radon gas for the nonsmoking population.
Emissions from nuclear power plants contribute only a very small portion of the total yearly radiation received.

Radiation Types: 1- Ionizing 2- Non-ionizing

1- Ionizing radiation is radiation that produces ions in matter during interaction with atoms in the matter. The toxic effect of ionizing radiation is related to the ionization. It is believed that ionization of tissues, composed mainly of water, generates H_2O^+ and H_2O^- ions, which in turn form H and OH radicals. Because radicals are very reactive chemically, biological damage, such as attacks on DNA and proteins, results.

Ionizing radiations such as x-rays are radiations that have sufficient energy to displace electrons from molecules. These freed electrons then have the capability of damaging other molecules and, in particular, **DNA**. Biological effects of radiation are primarily damage to DNA. Atoms of the DNA target may be directly ionized or indirectly affected by the creation of a free radical that can interact with the DNA molecule. In particular, the hydroxyl radical is predominant in DNA damage.

Adverse effects of ionizing radiation

Ionizing radiation quickly kills rapidly dividing cells. In general, immature blood cells in bone marrow, cells lining the mucosa of the gastrointestinal tract, and cells in the lower layers of the epidermis and in hair follicles are the most rapidly dividing cells in the body. As a result, radiation leads to the decreased production of blood cells, nausea, vomiting, diarrhea, malabsorption by the intestine, skin burns, and hair loss. Because of its relatively selective lethal effect on rapidly dividing cells, however, ionizing radiation is used in the treatment of certain cancers. Some cells in the embryo and fetus also divide rapidly, and thus ionizing radiation can cause malformations and even fetal death. Ionizing radiation can also produce mutations by altering the DNA, and it can result in cancer.

Cancer has been the major adverse health effect of ionizing radiation.

Toxicities of whole-body ionizing radiation

X rays and gamma rays; at sufficiently high doses, this type of radiation can lead to a condition known as acute radiation syndrome. The most sensitive tissue is the bone marrow, where blood cells are generated. The next tissue affected is the GIT. If the dose is high, the CNS is affected and the person becomes uncoordinated and disoriented and experiences tremors, convulsions, and coma. At even higher doses, the skin, eyes, and ovaries and testes are affected. Death may follow from 2 to 35 days after exposure. Exposure to radiation can also result in cancers of the bone marrow (leading to leukemia), lungs, kidneys, bladder, esophagus, stomach, colon, thyroid, or breasts.e.g. **tritium** and **cesium-137** both of which release beta particles that can lead to bone marrow toxicities and even, in the case of cesium-137, to death.

Local toxicities of common beta-particle emitters

The isotopes strontium-90 iodine-131, and cerium-144 emit beta particles that are **not** distributed equally in the body. Strontium-90 releases only beta particles, while iodine-131 and cerium-144 release both beta particles and gamma rays, but their toxicities are primarily caused by the beta particles.
These radioisotopes produce toxicities in the tissues where they are stored or concentrated. Strontium-90 and cerium-144 chemically **resemble calcium** and as a result are stored in **bone**. Therefore, these two radioisotopes produce bone cancer and leukemia, which is a result of the irradiation of bone marrow. Iodine-131 is concentrated in the **thyroid** and produces thyroid damage and tumors.

Local toxicities of common alpha-particle emitters

Most of the common alpha-particle emitters belong to the **uranium** series.
The radioisotopes in the uranium series are important because uranium is the starting fuel for many nuclear reactors and because daughter nuclides in this series are commonly found in the environment. The toxicity of **uranium-238** depends on the water solubility of the uranium compound. Water-soluble forms mainly cause kidney injury, while the insoluble forms produce fibrosis and cancer of the lung. Because of its similarity to calcium, radium-226 is stored mainly in the bone, and it produces abnormal changes in the bone marrow, including anemia and leukemia, cancers of the bone, and paranasal sinuses. Also deposited on the respiratory tract when inhaled, the respiratory tract is irradiated by the alpha particles released, and lung cancer can result.

2- Nonionizing radiation

Nonionizing radiation includes ultraviolet light, infrared radiation, microwaves, and radio frequencies, all of which are **electromagnetic waves**. Nonionizing radiation is not as toxic as ionizing radiation, and the various forms of non-ionization radiation share common target organs; particularly the skin and eyes.

A- Ultraviolet radiation

The toxicity of ultraviolet light depends on its wavelength.
Ultraviolet-A (near UV) has a wavelength of 315–400 nanometres (skin)
Ultraviolet-B (mid UV) has one of 280–315 nanometres (skin& eye)
Ultraviolet-C (far UV) has one of 200–280 nanometres. (skin & eye)

UV-A affects primarily the skin and causes burns at high energy levels. The toxicities of UV-B and UV-C are similar, but UV-C is less toxic because it does not penetrate tissues as deeply. Both UV-B and UV-C cause injuries to the eyes and skin.

UV-B is the major component of **sunlight** and accelerates the aging of skin by damaging the collagen fibres under it. UV-B also is the cause of an occupational disease known as “welder’s flash,” or “arc eye,” which is characterized by photophobia, tears in the eyes, spasm of the eyelids, and eye inflammation. Finally, UV-B can cause skin cancer which may be a result of the linking of thymidines, a base in DNA, produced by UV-B radiation.

B- Infrared radiation and microwaves

The major mechanism of toxicity of infrared radiation and microwaves is the production of **heat** in tissues.
Infrared-A (wavelength 0.8–1.4 Mm) penetrates the skin, causing burns and pigmentation. Infrared-A also penetrates the liquid content of the eye to reach the retina and can therefore produce damage to all parts of the eye. In contrast, infrared-B and infrared-C (wavelength 1.4–3,000 Mm) are almost completely absorbed by the superficial layers of the skin and eyes, and the damage is thus confined to the surface.

C- Microwaves (wavelength 1 millimetre to 1 metre) produce heat in tissues. Because testes and eyes do not dissipate heat well, due to low blood flow through these organs, temporary sterility and cataracts can be produced by microwaves.

D- Lasers

Lasers are high-energy light beams, visible and nonvisible, generated by atoms at an excited state and further amplified by optics. Like most other nonionizing radiation, lasers can produce skin burns. Visible lasers, with a wavelength from 0.4 to 1.4 Mm, will cause retinal damage if they enter the eyes and are focused by the lens onto the retina.

Toxicity of food additives & contaminants

Assist.Lecturer

Safa H.Mohsin

Introduction

- Food additives are substances intentionally added to food to perform certain technological functions, for example, to preserve flavour or to enhance its taste, appearance, and other qualities. (preservative, antioxidant).
- Food contaminants are substances that are not intentionally added to food, but can be present because of the various stages of food production, packaging, transport, or holding, as well as from environmental pollution. (environmental contaminants such as toxins).
- Both have in common that they become part of the food, and are therefore ingested by humans. Consequently, their possible toxic effects should be well-known in advance in order to guarantee food safety.

The degree of toxicity by food additives

- The degree of hazard associated with the presence of **additives** in our foods is quite low for several reasons:

1- First, the level of exposure to most food additives, especially flavoring ingredients, is generally low.

2- The oral toxicity of food additives tends to be extremely low, especially for acute toxicity. Still, some concerns have arisen about the chronic toxicity of a few food additives, including saccharin, cyclamate.

3- Another reason for the low hazard associated with food additives is the established safety of many additives. Many food additives have been subjected to safety evaluations in laboratory animals. In these cases, the toxicity of these food additives is well known, and exposure can be limited to levels far below any dose that would be hazardous.



Food Additives



Food additives

- Numerous chemical substances are added knowingly to foods to provide a wide variety of technical benefits, including nutrients.
- Food additives can be classified on the basis of their regulatory standing in the United States:

(a) generally recognized as safe (GRAS) substances

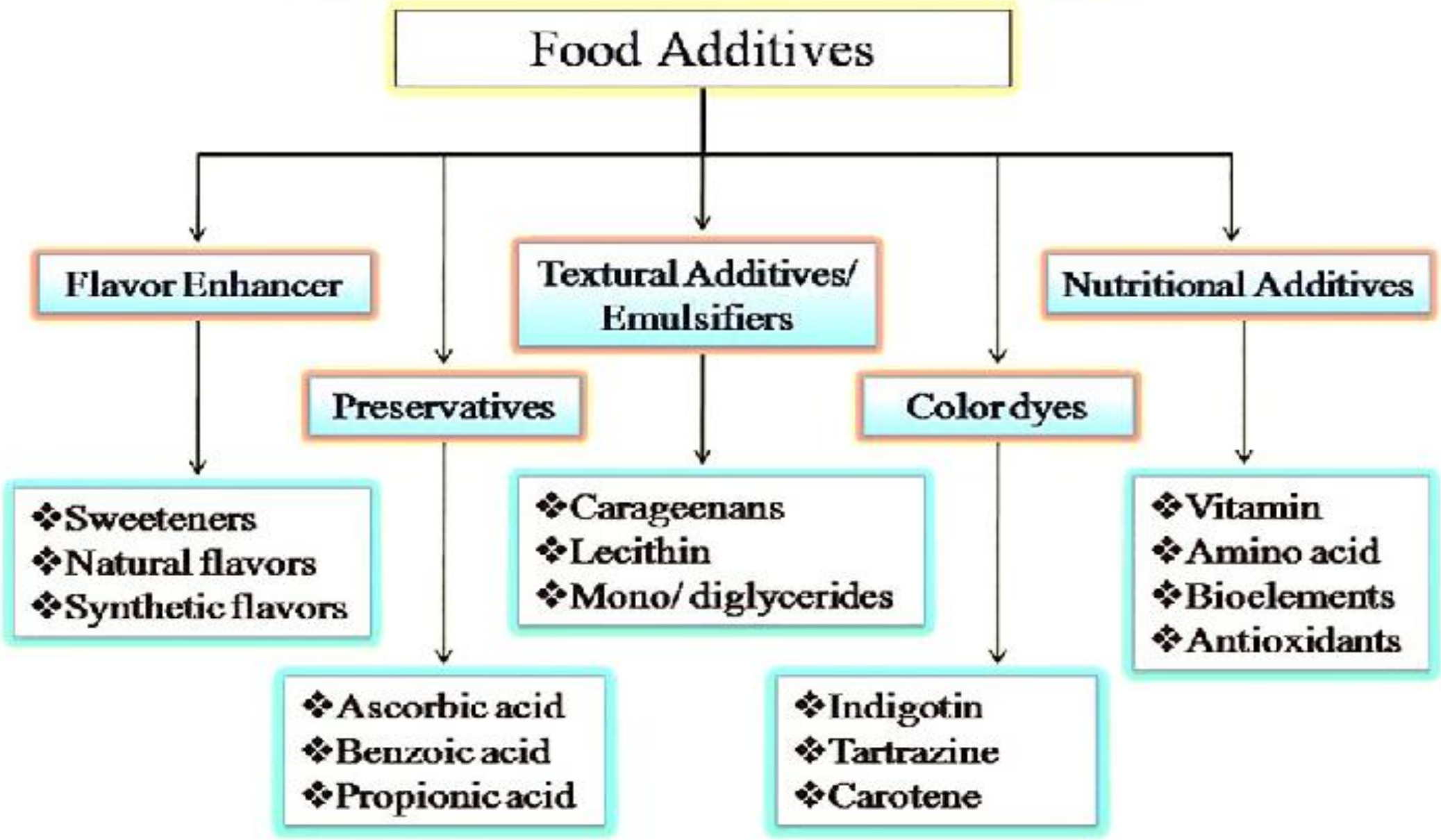
(b) flavors and extracts

(c) direct additives

(d) color additives.

- Food additives are added to foods intentionally and carefully evaluated for safety.
- Food additives are generally **not** hazardous under normal circumstances of exposure.

Classification of Food Additives



Sweeteners

Sorbitol

- Sorbitol is commonly used alternative sweeteners.
- Dietetic food diarrhea associated with this food additives is a good example of an intoxication resulting from the excessive consumption of a food additive.
- Sorbitol is widely used sweeteners in dietetic foods, especially common in noncariogenic candies and chewing gum.
- Although this sugar is not as easily absorbed as sugar, it is equally as caloric as sugar once absorbed.
- Because of its slow absorption, this sweetener can cause an osmotic-type diarrhea if excessive amounts be consumed.

Sweeteners

Saccharin

- Saccharin was one of the first nonnutritive sweeteners approved for food use in the United States.
- High doses of saccharin have been shown to cause bladder cancer in laboratory animals. However, the extrapolation of these results to humans, who typically ingest much lower levels of the ingredient, has stimulated argument. Thus, the carcinogenicity of saccharin to humans at typical levels of intake is, at best, uncertain, and saccharin remains on the market in the United States.
- Despite the uncertain relevance of the toxicologic data, warning labels remain on saccharin products indicating that saccharin is known to cause cancer in laboratory animals.


pmw
SODIUM
SACCHARINE
SWEETER than SWEET
fssai
USED IN BAKING AS A SUBSTITUTE OF SUGAR
INCREASES STABILITY & IMPROVES TASTE AT LOW COST
SWEETENS FOODS & BEVERAGES WITOUT CALORIES
Ingredients
SODIUM SACCHARINE
Weight :
Mfg. Dt :
Exp. Dt :
M.R.P Rs. :
Marketed by :
PADMAVATHI DISTRIBUTORS
Gollapudi 521 225, Vijayawada (A.P)
Customer Care : +91 9866724364
www.pmwkart.com e-mail : bvss.jagadish@gmail.com


TÖUfood
PRODUCTS FOR MODERN GASTRONOMY
POLYOLS
Sorbitöl
Sweetens chocolates and candies
Powdered Sorbitol
Sorbitol en polvo
Sorbitol en poudre
Sorbitol i pulver
Net Weight
600g/21.1oz

Preservatives

Sulfites

- Sulfites (sodium & potassium metabisulfite, sodium & potassium bisulfite, sodium sulfite, sulfur dioxide).
- Sulfites serve several important technologic functions, including as **antimicrobial agent**, **inhibitor of enzymatic and nonenzymatic browning**, and **bleaching agent**.
- Sulfite-induced asthma is well established as an example of sensitivity to a food additive that affects only a small percentage of the population.

Sulfite Sensitivity

Sulfites may be in a wide variety of foods and drugs. Here's a look at the most common. Not all of these products always have sulfites, so be sure to read labels. Look for sulfur dioxide, potassium bisulfite, potassium metabisulfite, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

Products with High Probability of Containing Sulfite

Alcoholic Beverages

Beer, cocktail mixes, wine, wine coolers.

Fish & Shellfish

Canned clams; shrimp; frozen lobster; scallops; dried cod.

Drinks

Instant tea, liquid tea concentrates, fruit juices, dried citrus fruit beverage mixes.

Sweet Sauces & Toppings

Corn & maple syrups, fruit toppings, high-fructose corn syrup.

Soups & Soup Mixes

Canned seafood soups, dried soup mixes.

Condiments and Relishes

Horseradish, onion relishes, pickles, olives, salad dressing mixes, wine vinegar.

Jarred Fruit

Jams, jellies, & preserves.

Gelatins, Puddings, & Fillings

Fruit fillings, gelatin, pectin jelling agents.

Nuts & Nut Products

Shredded coconut.

Grain Products & Pastas

Cornstarch, modified food starch, spinach pasta, gravies, hominy, breadings, batters, noodle/rice mixes.

Snack Foods

Dried fruit snacks, trail mixes, filled crackers.

Confections & Frostings

Brown, raw, powdered or white sugar from sugar beets.

Processed Vegetables

Canned & pickled vegetables, dried vegetables, instant mashed potatoes, frozen potatoes and potato salad.

Drugs

Cardiovascular drugs, antiemetics, antibiotics, tranquilizers, intravenous muscle relaxants, analgesics, anesthetics, steroids and nebulized bronchodilator solutions.

Baked Goods

Cookies, crackers, pie crust, pizza crust, quiche crust, flour tortillas.

Colorant

Tartrazine (FD&C Yellow #5)

- Tartrazine, is an approved artificial food color. This colorant has been widely used in foods and pharmaceuticals for many years.
- Tartrazine is a color additive that is associated with adverse reactions (asthma and chronic urticaria) in a sensitive subpopulation of consumers.


colourmist
TARTRAZINE
FROM THE HOUSE OF
BAKERSVILLE

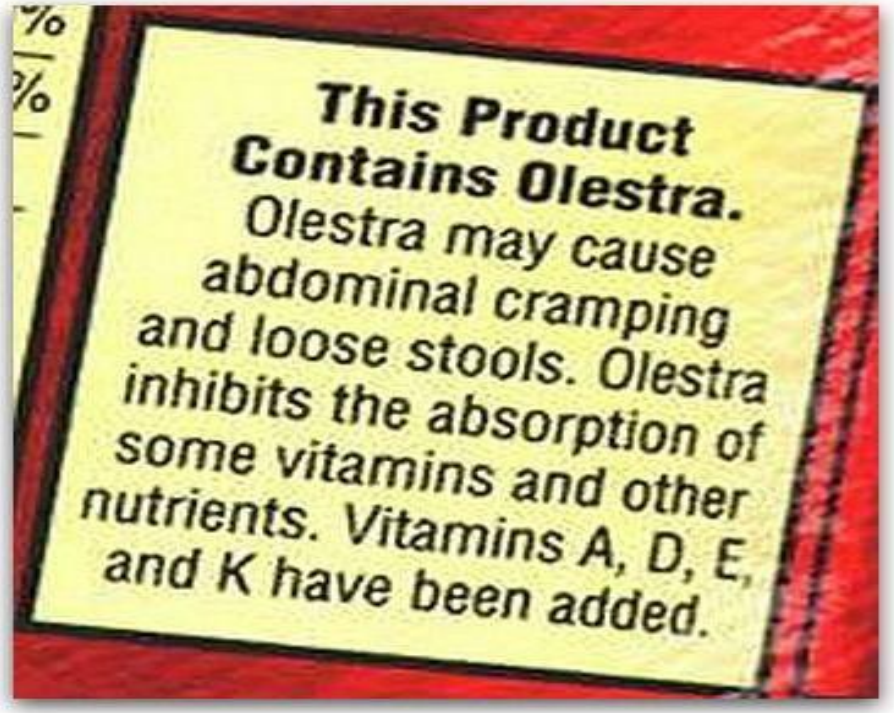

FDCYELLOW5
3 Ounces
Tartrazine
FD&C Yellow No. 5
CAS: 1934-21-0
Food Yellow 4 - Acid Yellow 23
$C_{16}H_9N_4Na_3O_9S_2$
CERTIFIED by the US FDA for Food, Drug and Cosmetics Use.
(FDA Lot BC 4419-91%)
Do not use in products used in the area of the eye, for coloring drugs, for injection or for surgical sutures. See Title 21 CFR Section 74.705 and 74.1705.
Lot No.:
NAC860
Serial:
45349
CHEMICALSTORE.COM

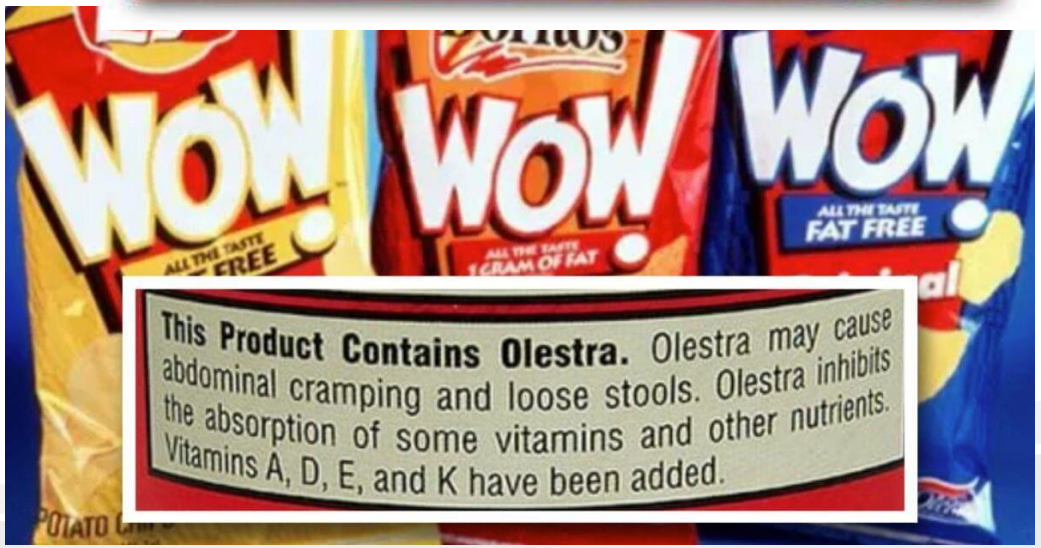
Other food additives

Olestra

- Olestra received food additive approval more recently and can be used as a **fat replacer**.
- Because Olestra is poorly absorbed and is not metabolized, it does not provide the calories that would be obtained with fat in similar products.
- But, the use of Olestra has been associated with acute gastrointestinal complaints, including anal leakage & postprandial gastrointestinal problems.


Lay's
max
This Product Contains Olestra. Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A,D,E, and K have been added.


This Product Contains Olestra.
Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E, and K have been added.


WOW
WOW
WOW
ALL THE TASTE
FAT FREE
This Product Contains Olestra. Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E, and K have been added.

Nutritional food additives

- Many food additives, including vitamins and minerals, serve nutritional functions.

Niacin

- Excessive consumption of **Vitamin B**, **niacin**, can cause an acute onset of flushing, pruritus, rash, and burning or warmth in the skin especially on the face and upper trunk; and gastrointestinal discomfort has been noted by some patients.

Vitamin A

- Vitamin A intoxication was reported in twin infants who were provided a diet consisting largely of pureed chicken livers, pureed carrots, milk, and vitamin supplements. Apparently, the mother of these infants initiated this diet because she did not trust commercial baby foods. After several weeks on this diet, the infants began to vomit and developed a skin rash. The symptoms disappeared when a more normal diet was instituted.

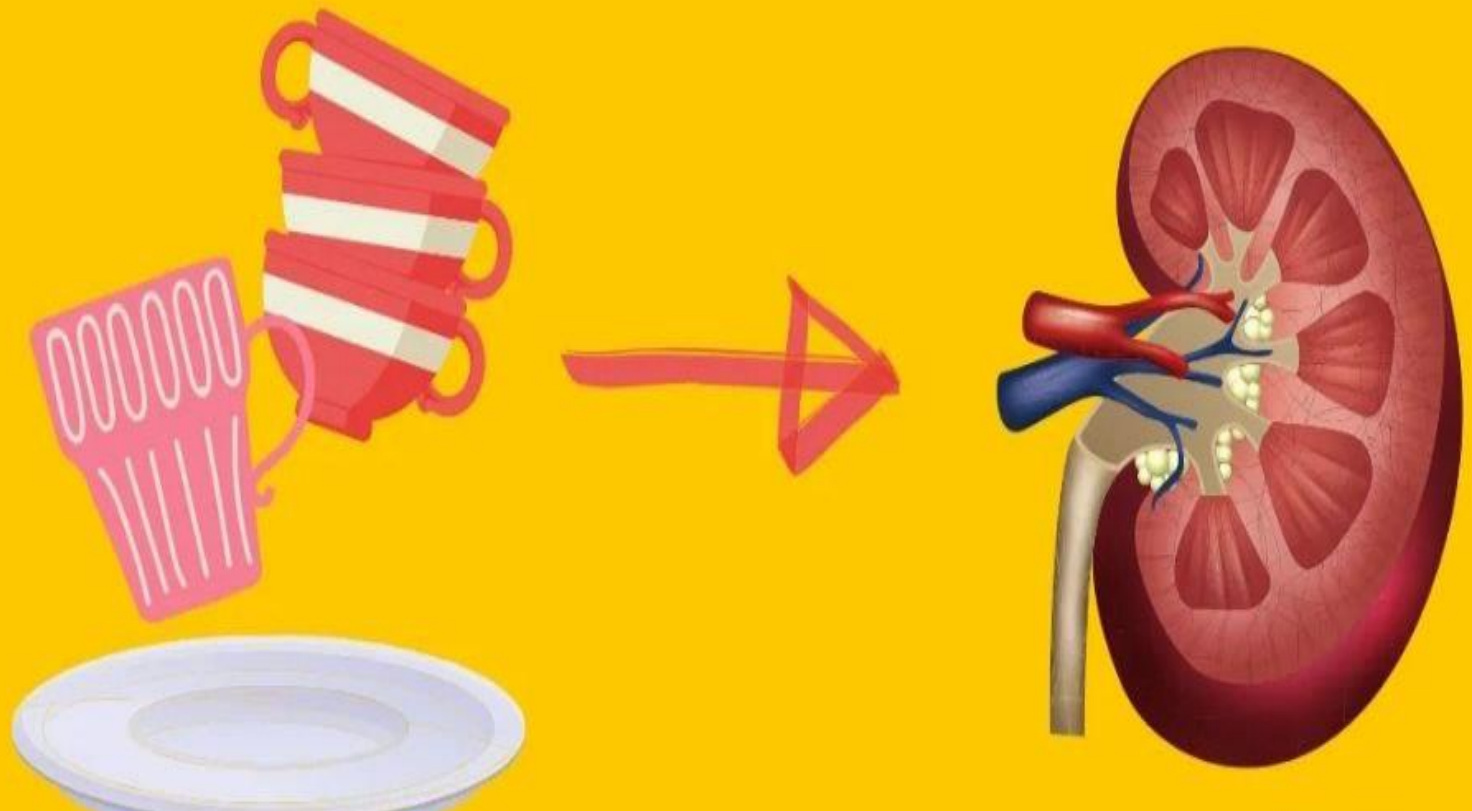

Carbohydrate
INGREDIENTS: Sugar, ro
enriched unbleached flour (wh
flour, niacin, reduced iron, thiamin
mononitrate, riboflavin, folic acid, may
contain malted barley flour), corn
syrup solids. Contains 2% or less of the
following: molasses powder, canola
or soybean oil, spices, artificial flavors
(contains barley), salt, soy lecithin
(emulsifier), caramel color.
ITAINS: Wheat and soy.
equipment that makes
ining eggs, milk and

Intentional food additives

Melamine

- Melamine is an industrial chemical used for manufacturing of plastics, adhesive, fabrics, and flame retardants. Several years ago, melamine was intentionally added to pet foods and dairy products including infant formula in China to increase the "apparent" protein content. Many pets in North America suffered renal toxicity as a result of consuming the pet food contaminated with melamine and the related substance, cyanuric acid. When melamine and cyanuric acid are consumed together, crystals of melamine cyanurate form readily in the kidney tubules leading to acute renal failure.
-

CONSUMING FOOD THAT IS ADULTERATED WITH MELAMINE MAY CAUSE FORMATION OF KIDNEY STONES AND KIDNEY FAILURE



Did you know that your food can become contaminated with melamine: which is an industrial chemical commonly used in the manufacture of products like melamine crockery, plastic materials, gum, tiles, filters, dyes, fabric & fertilizers.

Food Contaminants

- Foods may be contaminated because the air, water, & soil are polluted, for example, by heavy metals (such as lead, cadmium, and mercury) or PCBs (polychlorinated biphenyls). PCBs used to be used as coolants and in many other products and are now present in the air, soil, and water in many places.
- Foods may be contaminated by pesticides or packaging materials or during cooking or processing.
- In addition, so-called endocrine-disrupting chemicals in the environment (such as some insecticides, petrochemicals, and industrial solvents) can affect the body's endocrine system and alter hormone levels, causing alterations in sex organs, immune function, nervous system function, growth and development, and certain cancers; they may also promote obesity.
- Foods may also be contaminated by drugs (such as antibiotics and growth hormone) that are given to animals.

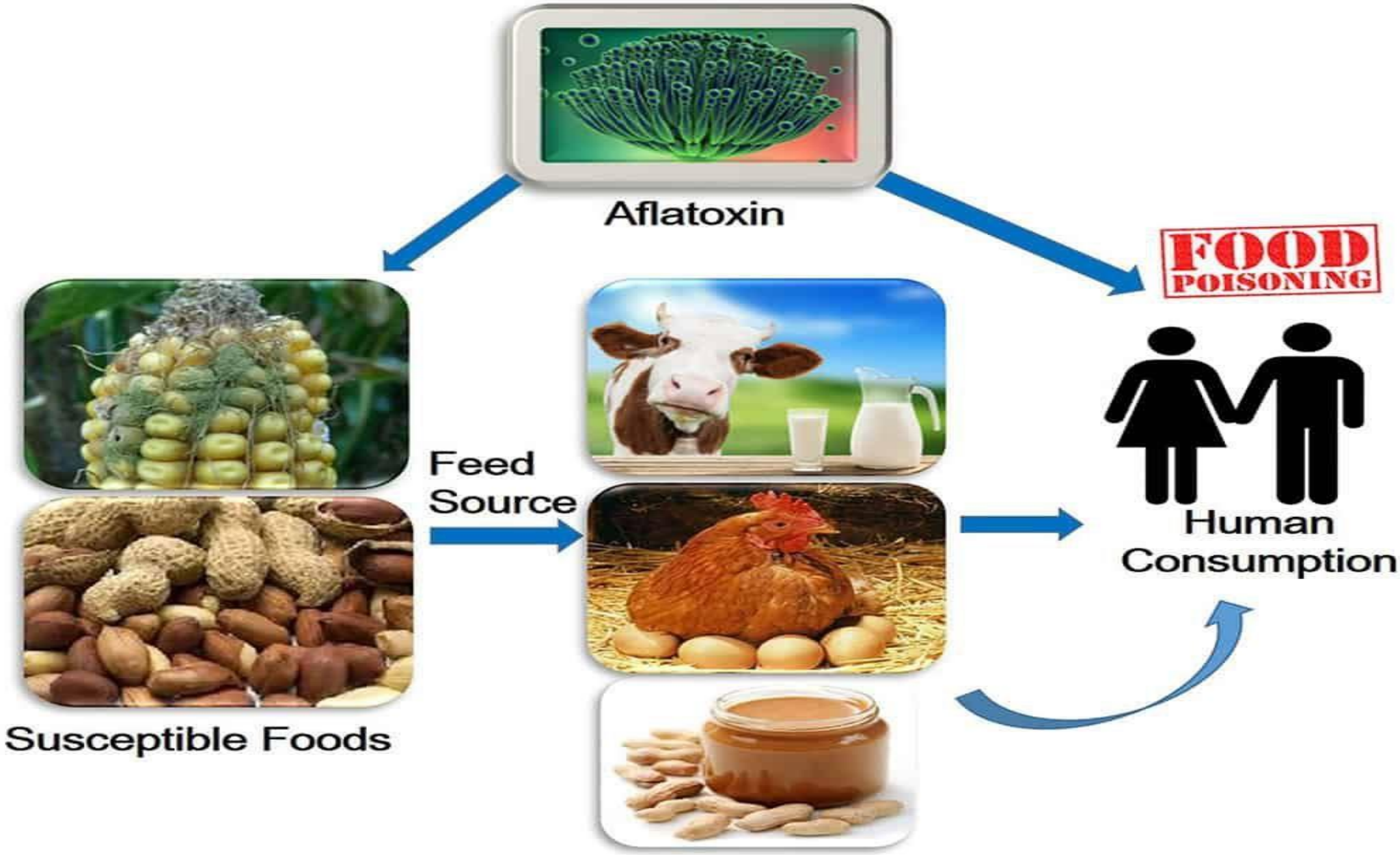
Potentially hazardous chemicals may contaminate foods from a variety of sources, including natural contaminants, agricultural chemicals, industrial contaminants, and processing-induced contaminants

- **Natural contaminants** can include:
- mycotoxins from molds
- phycotoxins from marine algae
- bacterial toxins
- **Agricultural Chemicals** include insecticides, herbicides, fungicides, fertilizers, and veterinary drugs including antibiotics.

Common contaminants include

- Pesticides (insecticide)
- Heavy metals
- Nitrates (in green leafy vegetables)
- Aflatoxins, produced by molds (in nuts and milk)
- Growth-promoting hormones (in dairy products and meat)
- Foods may contain animal hairs, animal feces, and insect parts in such tiny amounts that removal is impossible.

Natural Contaminants
Aflatoxin


Aflatoxin
FOOD POISONING
Feed Source
Susceptible Foods
Human Consumption

Insecticides

- Insecticides are added to foods to control insect pests.
- Insecticides fall into several major categories including **organochlorine** compounds (dichlorodiphenyltrichloroethane [DDT], chlordane,
- organophosphate compounds (e.g., parathion and malathion)
- carbamate compounds (e.g., carbaryl and aldicarb)
- botanical compounds (e.g., nicotine and pyrethrum)
- inorganic compounds (e.g., arsenicals).
- Most episodes of pesticide intoxications have resulted from the **misuse of pesticides, including contamination of foods during storage and transport, the use of pesticides in food preparation because of their mistaken identity as common food ingredients such as sugar and salt.**
- Aldicarb poisonings are one of the best examples of acute food poisoning episodes associated with pesticides. The symptoms of aldicarb intoxication include nausea, vomiting, diarrhea, and mild neurologic manifestations such as dizziness, headache, blurred vision, and loss of balance.
-

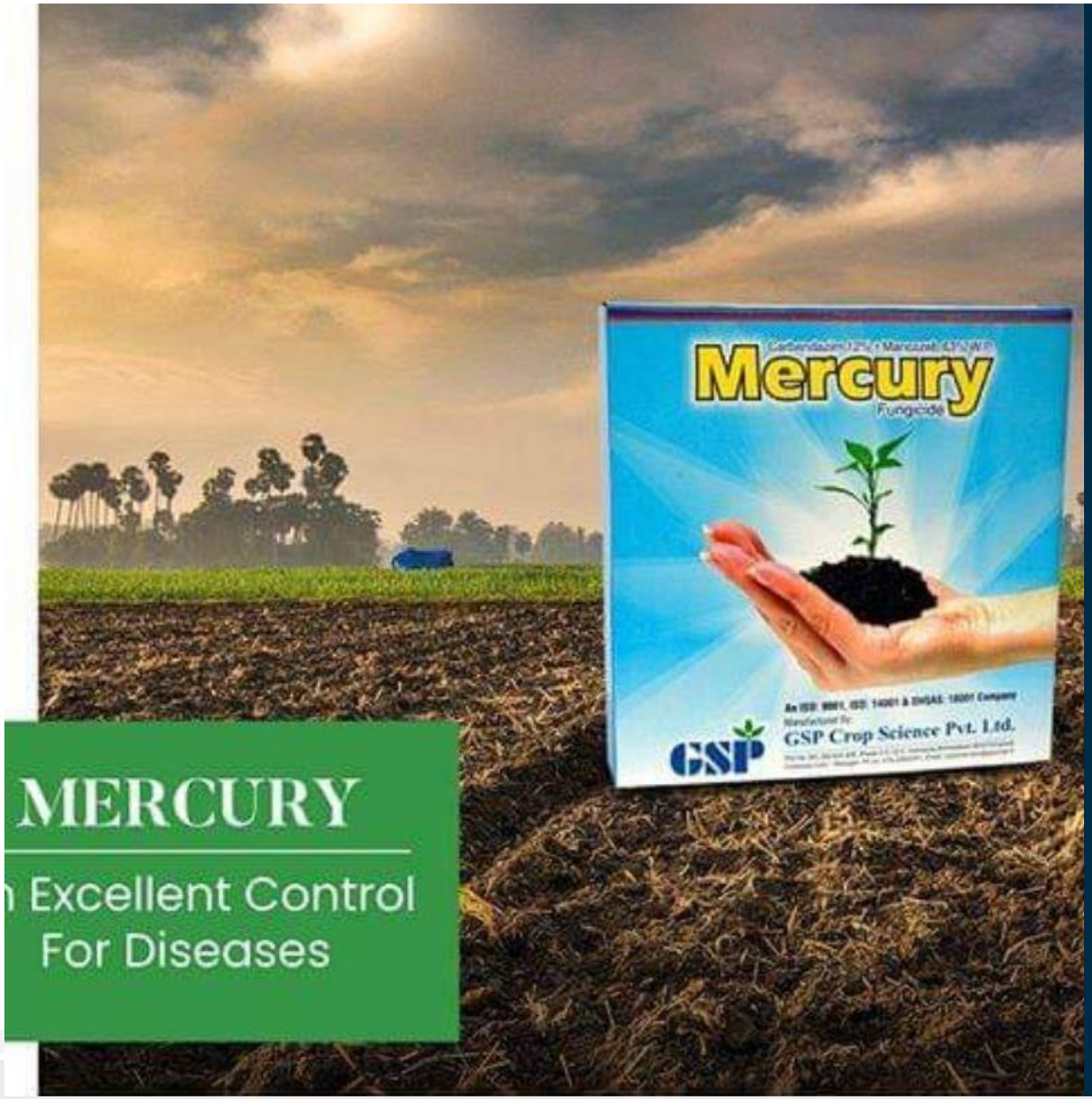
Herbicides & Fungicides

Herbicides

- Herbicides are applied to agricultural crops to control the growth of weeds.

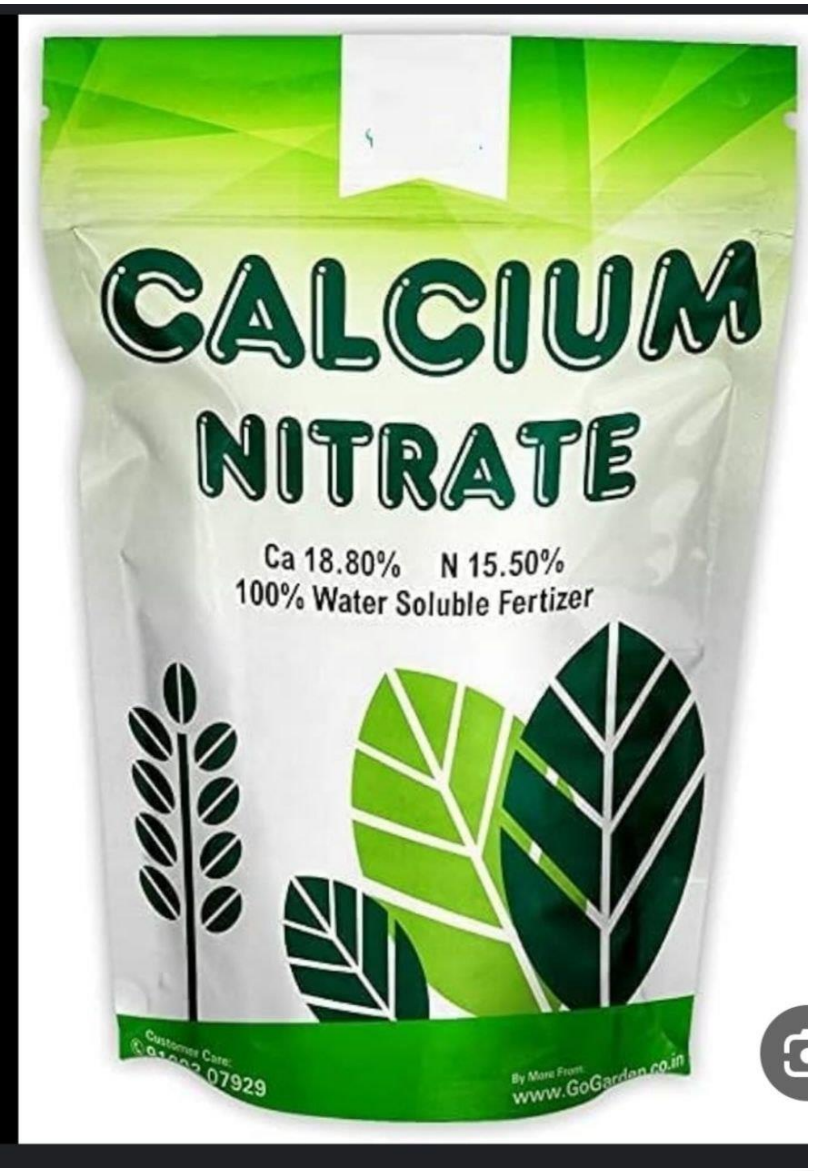
Fungicides

- Fungicides are used to limit the growth of molds on food crops. Mercurial fungicides often are used to treat seed grains to prevent mold growth during storage. These seed grains are typically colored pink and are intended for planting rather than consumption. However, especially in times of famine, consumers are tempted to eat the seed grain. On several occasions, consumers have eaten these treated seed grains and developed mercury poisoning. Mild cases of mercury intoxication can be manifested in gastrointestinal symptoms such as abdominal cramps, nausea, vomiting, and diarrhea and dermal symptoms such as acrodynia and itching.
- Hexachlorobenzene had been used to treat the seed grain. The symptoms were severe with a 10% mortality rate, porphyria cutanea tarda, ulcerated skin lesions, alopecia, porphyrinuria, hepatomegaly, and thyroid enlargement.


Mercury
Fungicide
GSP
GSP Crop Science Pvt. Ltd.
MERCURY
Excellent Control
For Diseases

Fertilizers

- Fertilizers are typically combinations of nitrogen and phosphorus compounds.
- Nitrogen fertilizers are oxidized to nitrate and nitrite in the soil. Both nitrate and nitrite are hazardous to humans if ingested in large amounts.
- Infants are particularly susceptible to nitrate and nitrite intoxication.
- Some plants, such as spinach, can accumulate nitrate to hazardous levels if allowed to grow on overly fertilized fields. Because nitrite is more toxic than nitrate, the situation can be worsened if nitrate-reducing bacteria are allowed to proliferate on these foods.
- As another example, improper storage of carrot juice has allowed the proliferation of nitrate-reducing bacteria, resulting in the accumulation of hazardous levels of nitrite in the product. After ingestion of low doses, the symptoms include flushing of the face and extremities, gastrointestinal discomfort, and headache; in larger doses, cyanosis, methemoglobinemia, nausea, vomiting, abdominal pain, collapse, and death can occur. The lethal dose of nitrite is estimated at approximately 1 g in adults.


CALCIUM
NITRATE
Ca 18.80% N 15.50%
100% Water Soluble Fertizer
Customer Care:
07929
By More From
www.GoGarden.co.in


1 Kg
IMPORTED
IFFCO
Wholly Owned by Cooperatives
POTASSIUM NITRAT
13:0:45
(N) 13% : (P(WS)) 0% : (K) 45%
100% Water Soluble Fertiliser
100% जल घुलनशील उर्वरक
For Foliar Application And Fertigation
Imported, Packed & Marketed By:
Indian Farmers Fertiliser Cooperative Limited (IFFCO)

Food additives are substances intentionally added to food to perform certain technological functions, for example, to preserve flavour or to enhance its taste, appearance, and other qualities.

Food contaminants are substances that are not intentionally added to food, but can be present because of the various stages of its production, packaging, transport, or holding, as well as from environmental pollution.

Both have in common that they become part of the food, and are therefore ingested by humans. Consequently, their possible toxic effects should be well-known in advance in order to guarantee food safety.

The degree of hazard associated with the presence of additives in our foods is quite low for several reasons:

1- First, the level of exposure to most food additives, especially flavoring ingredients, is generally low.

2- The oral toxicity of food additives tends to be extremely low, especially for acute toxicity. Still, some concerns have arisen about the chronic toxicity of a few food additives, including saccharin, cyclamate, and others.

3- Another reason for the low hazard associated with food additives is the established safety of many additives. Many food additives have been subjected to safety evaluations in laboratory animals. In these cases, the toxicity of these food additives is well known, and exposure can be limited to levels far below any dose that would be hazardous.

FOOD ADDITIVES

Numerous chemical substances are added knowingly to foods to provide a wide variety of technical benefits, including nutrients.
Food additives can be classified on the basis of their regulatory standing in the United States:
(a) generally recognized as safe (GRAS) substances
(b) flavors and extracts
(c) direct additives
(d) color additives.
Food additives are added to foods intentionally and carefully evaluated for safety. Food additives are generally not hazardous under normal circumstances of exposure.

Sorbitol and Hexitols

Sorbitol and various other hexitols are commonly used alternative sweeteners. Dietetic food diarrhea associated with these food additives is a good example of an intoxication resulting from the excessive consumption of a food additive. The hexitols and sorbitol are widely used sweeteners in dietetic foods. The hexitols and sorbitol are especially common in noncariogenic candies and chewing gum. Although these sugar alcohols are not as easily absorbed as sugar, they are equally as caloric as sugar once absorbed. Because of their slow absorption, these sweeteners can cause an osmotic-type diarrhea if excessive amounts happen to be consumed.

Sulfites

Sulfites (sodium and potassium metabisulfite, sodium and potassium bisulfite, sodium sulfite, sulfur dioxide). Sulfites serve several important technologic functions, including as antimicrobial agent, inhibitor of enzymatic and nonenzymatic browning, and bleaching agent. Sulfite-induced asthma is well established as an example of sensitivity to a food additive that afflicts only a small percentage of the population.

Tartrazine (FD&C Yellow #5)

Tartrazine, is an approved artificial food color. This colorant has been widely used in foods and pharmaceuticals for many years. Tartrazine is a color additive that is associated with adverse reactions (asthma and chronic urticaria) in a sensitive subpopulation of consumers.

Olestra

Olestra received food additive approval more recently and can be used as a fat replacer. Because Olestra is poorly absorbed and is not metabolized, it does not provide the calories that would be obtained with fat in similar products. However, the use of Olestra has been associated with acute gastrointestinal complaints, including anal leakage. Obviously, many consumers occasionally experience postprandial gastrointestinal maladies.

Saccharin

Saccharin was one of the first nonnutritive sweeteners approved for food use in the United States. High doses of saccharin have been shown to cause bladder cancer in laboratory animals. However, the extrapolation of these results to humans, who typically ingest much lower levels of the ingredient, has stimulated controversy. Thus, the carcinogenicity of saccharin to humans at typical levels of intake is, at best, uncertain, and saccharin remains on the market in the United States. Despite the uncertain relevance of the toxicologic data, warning labels remain on saccharin products indicating that saccharin is known to cause cancer in laboratory animals.

Nutritional food additives

Many food additives, including vitamins and minerals, serve nutritional functions.

Niacin

Excessive consumption of Vitamin B, niacin, can cause an acute onset of flushing, pruritus, rash, and burning or warmth in the skin especially on the face and upper trunk; and gastrointestinal discomfort has been noted by some patients.

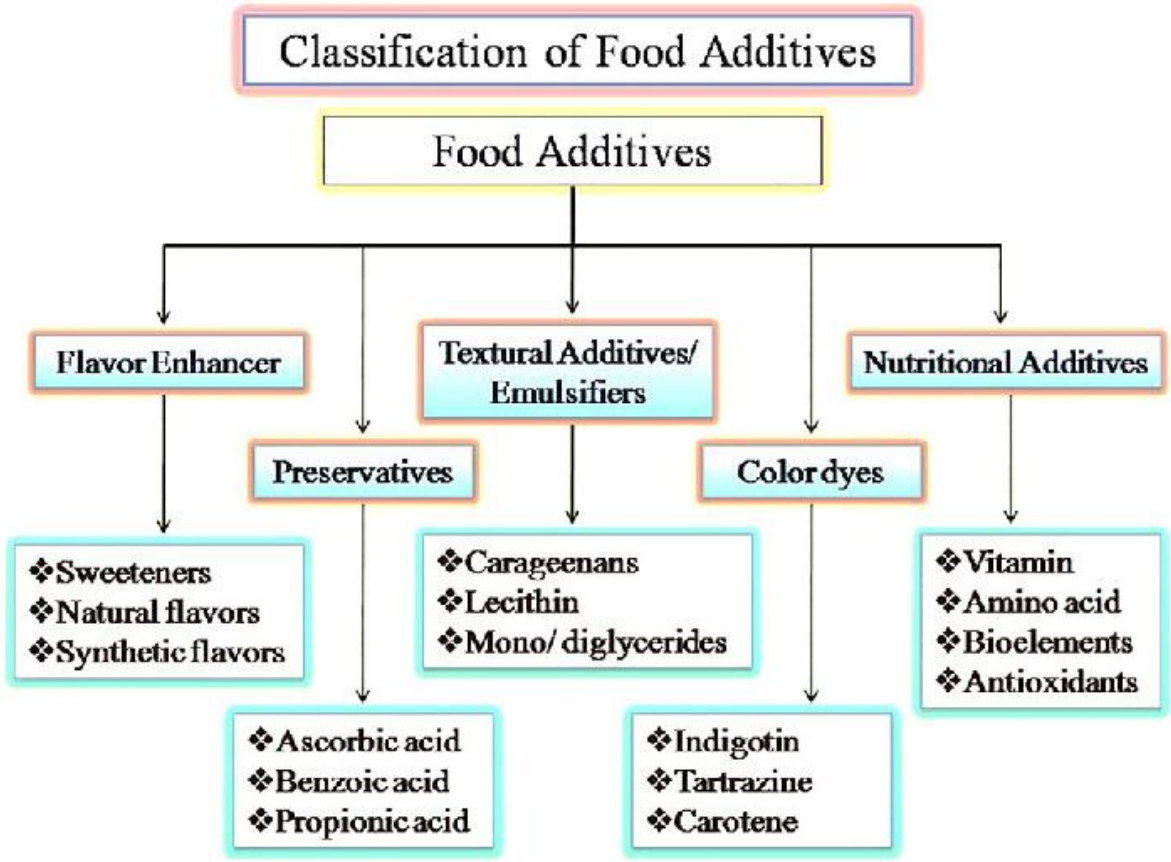
Vitamin A

Vitamin A intoxication was reported in twin infants who were provided a diet consisting largely of pureed chicken livers, pureed carrots, milk, and vitamin supplements. Apparently, the mother of these infants initiated this diet because she did not trust commercial baby foods. After several weeks on this diet, the infants began to vomit and developed a skin rash. The symptoms disappeared when a more normal diet was instituted.

Intentional food additives

Melamine

Melamine is an industrial chemical used for manufacturing of plastics, adhesive, fabrics, and flame retardants. Several years ago, melamine was intentionally added to pet foods and dairy products including infant formula in China to increase the “apparent” protein content. Many pets in North America suffered renal toxicity as a result of consuming the pet food contaminated with melamine and the related substance, cyanuric acid. When melamine and cyanuric acid are consumed together, crystals of melamine cyanurate form readily in the kidney tubules leading to acute renal failure.



FOOD CONTAMINANTS

Foods may be contaminated because the air, water, and soil are polluted, for example, by heavy metals (such as lead, cadmium, and mercury) or PCBs (polychlorinated biphenyls). PCBs used to be used as coolants and in many other products and are now present in the air, soil, and water in many places.

Foods may be contaminated by pesticides or packaging materials or during cooking or processing. In addition, so-called endocrine-disrupting chemicals in the environment (such as some insecticides, petrochemicals, and industrial solvents) can affect the body's endocrine system and alter hormone levels, causing alterations in sex organs, immune function, nervous system function, growth and development, and certain cancers; they may also promote obesity.

Foods may also be contaminated by drugs (such as antibiotics and growth hormone) that are given to animals.

Common contaminants include

Pesticides

Heavy metals

Nitrates (in green leafy vegetables)

Aflatoxins, produced by molds (in nuts and milk)

Growth-promoting hormones (in dairy products and meat)

Foods may contain animal hairs, animal feces, and insect parts in such tiny amounts that removal is impossible.

Potentially hazardous chemicals may contaminate foods from a variety of sources, including natural contaminants, agricultural chemicals, industrial contaminants, and processing-induced contaminants.

Natural contaminants can include mycotoxins from molds, phycotoxins from marine algae, and bacterial toxins.

Agricultural Chemicals include insecticides, herbicides, fungicides, fertilizers, and veterinary drugs including antibiotics.

Insecticides

Insecticides are added to foods to control insect pests. Insecticides fall into several major categories including organochlorine compounds (dichlorodiphenyltrichloroethane [DDT], chlordane, and organophosphate compounds (e.g., parathion and malathion), carbamate compounds (e.g., carbaryl and aldicarb), botanical compounds (e.g., nicotine and pyrethrum), and inorganic compounds (e.g., arsenicals).

Most episodes of pesticide intoxications have resulted from the misuse of pesticides, including contamination of foods during storage and transport, the use of pesticides in food preparation because of their mistaken identity as common food ingredients such as sugar and salt.

Aldicarb poisonings are one of the best examples of acute food poisoning episodes associated with pesticides. The symptoms of aldicarb intoxication include nausea, vomiting, diarrhea, and mild neurologic manifestations such as dizziness, headache, blurred vision, and loss of balance.

Herbicides

Herbicides are applied to agricultural crops to control the growth of weeds.

Fungicides

Fungicides are used to limit the growth of molds on food crops. Mercurial fungicides often are used to treat seed grains to prevent mold growth during storage. These seed grains are typically colored pink and are intended for planting rather than consumption. However, especially in times of famine, consumers are tempted to eat the seed grain. On several occasions, consumers have eaten these treated seed grains and developed mercury poisoning. Mild cases of mercury intoxication can be manifested in gastrointestinal symptoms such as abdominal cramps, nausea, vomiting, and diarrhea and dermal symptoms such as acrodynia and itching.

Hexachlorobenzene had been used to treat the seed grain. The symptoms were severe with a 10% mortality rate, porphyria cutanea tarda, ulcerated skin lesions, alopecia, porphyrinuria, hepatomegaly, and thyroid enlargement.

Fertilizers

Fertilizers are typically combinations of nitrogen and phosphorus compounds. Nitrogen fertilizers are oxidized to nitrate and nitrite in the soil. Both nitrate and nitrite are hazardous to humans if ingested in large amounts. Infants are particularly susceptible to nitrate and nitrite intoxication. Some plants, such as spinach, can accumulate nitrate to hazardous levels if allowed to grow on overly fertilized fields. Because nitrite is more toxic than nitrate, the situation can be worsened if nitrate-reducing bacteria are allowed to proliferate on these foods. As another example, improper storage of carrot juice has allowed the proliferation of nitrate-reducing bacteria, resulting in the accumulation of hazardous levels of nitrite in the product. After ingestion of low doses, the symptoms include flushing of the face and extremities, gastrointestinal discomfort, and headache; in larger doses, cyanosis, methemoglobinemia, nausea, vomiting, abdominal pain, collapse, and death can occur. The lethal dose of nitrite is estimated at approximately 1 g in adults.

PLANT TOXICITY

Assist. Lecturer
Safa H. Mohsin

Introduction

- History is full with stories of the earliest humans using plant extracts and animal venoms for hunting, war, assassination, and political intrigue for millennia. The toxic properties of plants and animals often enhance their ability to survive. These toxic Adaptations reflect how the organism interacts with its surroundings and with its predators. Some toxic compounds are used primarily to aid an animal in obtaining food while plants have developed toxic properties to specifically ward off being used as food.

- The plant kingdom contains potentially 300,000 species, and the toxic effects of plants serve primarily as defense mechanisms against natural predators. Toxicity in humans can result from simply touching as well as ingesting plants to cause a truly wide array of deleterious effects. Toxic Effects on humans can range from simple hay fever caused by exposure to plant pollen all the way to serious systemic reactions caused by ingestion of specific plants.

Poisoning Syndromes Caused by Plants

SYNDROME	GENERA	MECHANISM(S)
Antimuscarinic	*Atropa, Datura, Hyoscyanmus, Solanum*	Blockade of muscarinic cholinoceptors
Cardiotoxic	*Adenium, Digitalis, Convallaria, Nerium*	Inhibition of cellular Na^+,K^+-ATPase increases contractility, enhanced vagal effect
Convulsants	*Anemone, Conium, Labrunum, Nicotinia, Ranunculus*	Blockade of gamma-aminobutyric acid (GABA) receptor on the neuronal chloride channel, alteration of acetylcholine homeostasis, mimic excitatory amino acids, sodium channel alteration, hypoglycemia
Cyanogenic	*Eriobotrya, Hydrangea, Prunus*	Gastric acid hydrolysis of cyanogenic glycosides releases cyanide
Dysrhythmia	*Acotinum, Rhododendron, Veratrum*	Sodium channel activation
Nicotinic	*Conium, Laburnum, Lobelia, Nicotinia*	Stimulation of nicotinic cholinoceptors
Pyrrolizidine	*Crotalaria, Heliotropium, Senecia*	Pyrroles injure endothelium of hepatic or pulmonary vasculature leading to veno-occlusive disease and hepatic necrosis
Toxalbumin	*Abrus, Ricinus*	Protein synthesis inhibitors leading to multiple organ system failure

TOXIC EFFECTS OF ORGANS

1- Skin

- **Irritant Contact Dermatitis:** Narcissus نرجس, Oleander دفلى, Eucalyptus, Tomato, potato, Stinging nettle القراص نبات لاذع : (puncture skin on contact and release an irritating sap containing mixture of formic acid, acetylcholine, & serotonin)

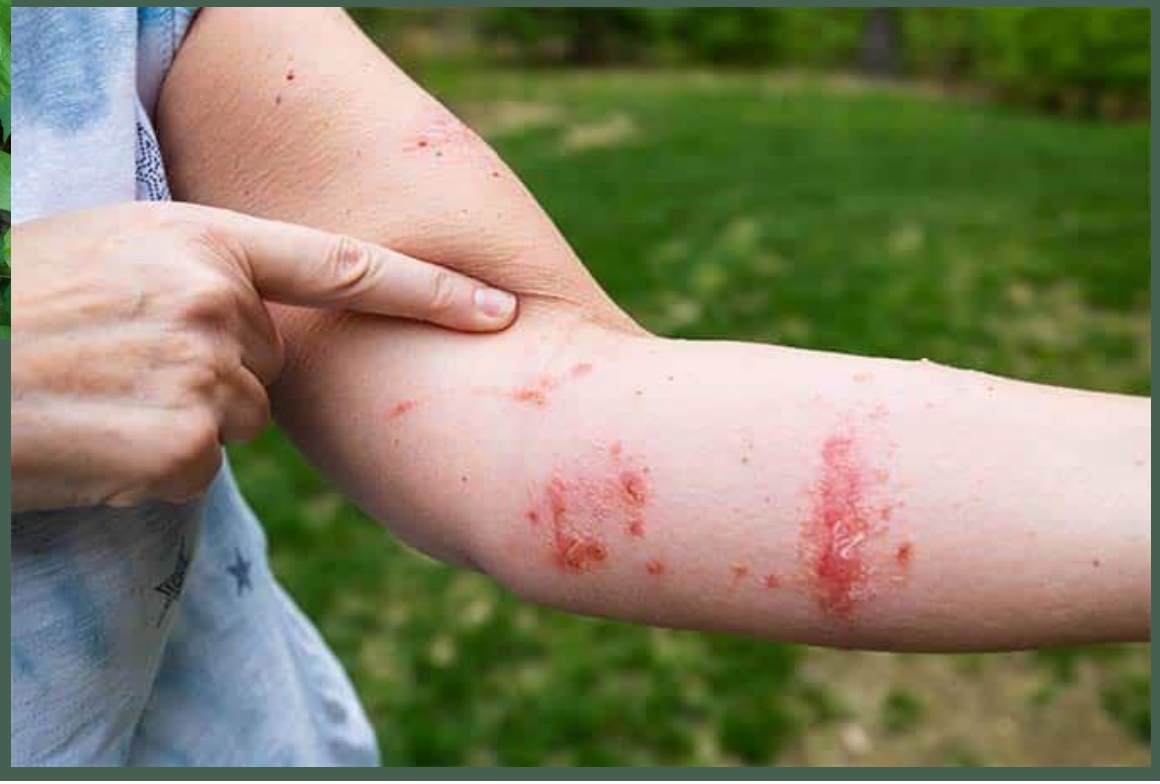
- **Allergic Contact Dermatitis:** poison ivy, poison oak

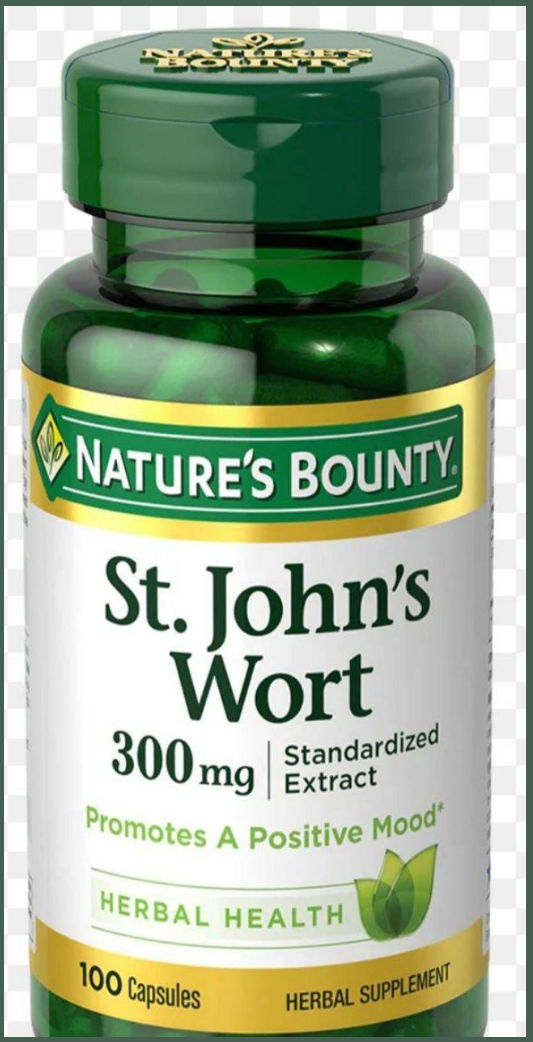
- **Photosensitivity:** Dermatitis does not necessarily have to be caused by skin contact. Consumption of (St. John's wort) by animals can lead to serious dermatitis and even may be life threatening. The toxic agent is hypericin. Photosensitization in humans is a rare occurrence; however, an increased response to therapeutic exposure to ultraviolet therapy has been reported

الدفلى

نبات القراص لاذع

poison ivy




NATURE'S BOUNTY
St. John's Wort
300 mg | Standardized Extract
Promotes A Positive Mood*
HERBAL HEALTH
100 Capsules
HERBAL SUPPLEMENT

2- Respiratory Tract

- **Allergic Rhinitis**: pollen, trees, weeds, grasses

- **Cough Reflex**: Capsaicin in red pepper, sweet pepper Specific nerves in the airway have been found to be capsaicin-sensitive, which leads to the irritation and cough

Allergic Rhinitis

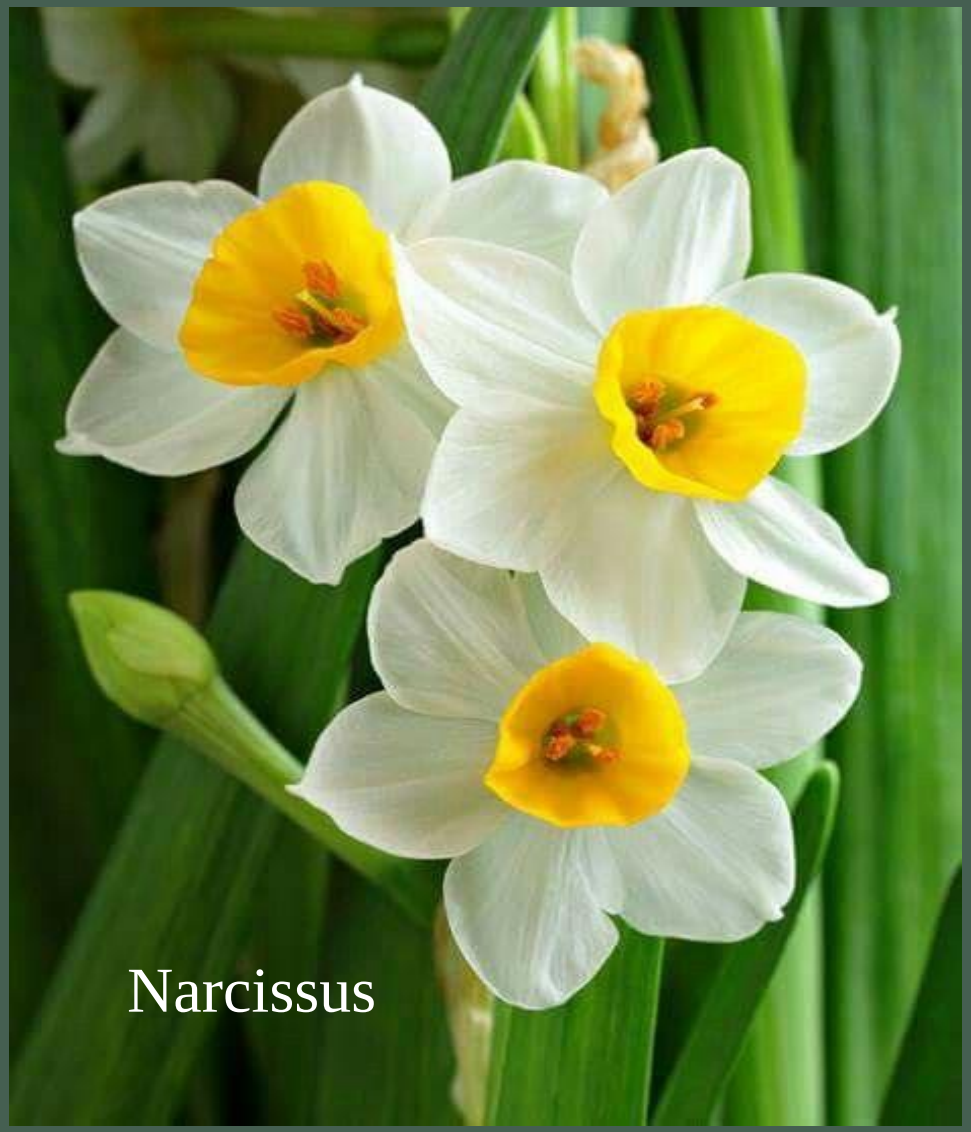
Red pepper

3- Gastrointestinal System

- **Direct Irritant Effects:** Ingestion of a toxic plant can cause irritation of the GIT tract often resulting in nausea, vomiting, and diarrhea. (Narcissusنرجس , Iris سوسن)

- **Protein Synthesis Inhibition:** The castor bean is an ornamental plant that produces seeds that, if eaten by children or adults, causes no symptoms of poisoning for several days after ingestion. Gradually, gastroenteritis develops resulting in some loss of appetite, with nausea, vomiting, and diarrhea. If a fatal dose is ingested, the gastroenteritis becomes extremely severe and is marked by persistent vomiting, bloody diarrhea, and icterus followed by death within six to eight days. A fatal dose for a child can be as few as **5** seeds and may be as low as **20** seeds for an adult.

Castor bean



Narcissus

4- Cardiovascular System

- **Cardioactive Glycosides:** Digitalis Purpurea (Foxglove) inhibits Na-K ATPase

- **Vasoactive Chemicals:** Ingestion of the fungus *Claviceps purpurea* ***(ergot)****, which* grows on grains that are used for food, causes vasoconstriction in blood vessels, blackened limb and even gangrene, and abortion in pregnant women with severe poisoning.

قفاز الثعلب

5- Liver

- **Mushroom Toxins:** Amanita phalloides (death cap) s it inhibits protein synthesis in hepatocytes by binding to RNA polymerase II*. In addition to liver, intestinal mucosa and kidneys are* also affected and serious clinical signs develop about three days after ingestion. In cases of severe poisoning, a liver transplant may be required.

- **Mycotoxins:** Aflatoxin has been shown to form guanine adducts and induce apoptosis in human hepatocytes

Aflatoxin

Amanita phalloides

6- Kidney and Bladder

Carcinogens : The bracken fern, which is extremely common worldwide, is the only higher plant known to be carcinogenic in animals under natural feeding conditions.

Kidney Tubular Degeneration: Asteraceae have been found to contain the toxin carboxyatractyloside, which causes microvascular hemorrhages in multiple organs

Bracken fern

Asteraceae

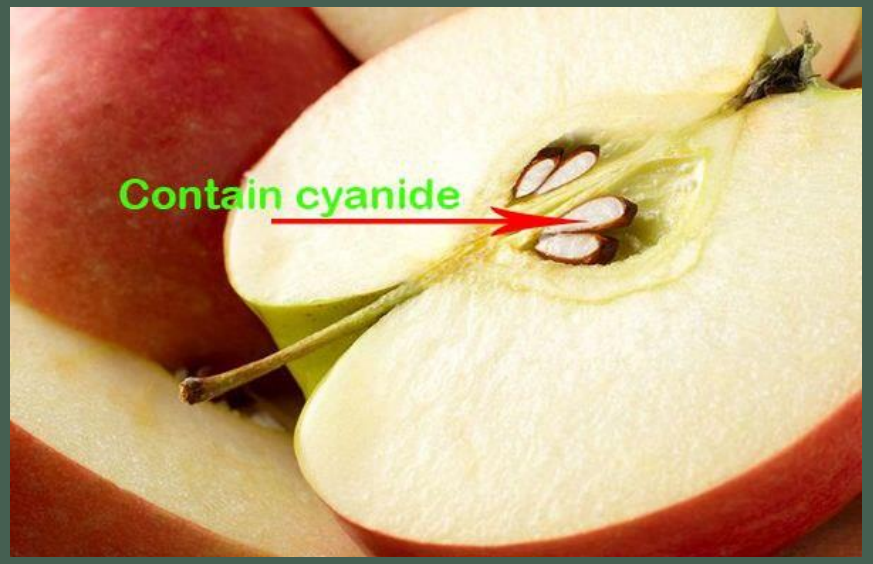
7- Blood and Bone Marrow

Anticoagulants: Fungal infections in sweet clover have been found to produce dicumarol, a coumarin derivative that is a potent anticoagulant. Deaths in cattle have been reported and are caused by hemorrhages.

Bone Marrow Genotoxicity: *Argemone* (Papaveraceae), a species of poppy, produces sanguinarine, a benzophenanthridine alkaloid that is known to intercalate DNA and have carcinogenic potential.

Cyanogens: Cyanogens are found in a wide variety of plants including the kernels of apples, cherries, and peaches. The highest concentrations are found in the seeds of the bitter almond. Metabolism of amygdalin releases hydrocyanic acid that binds to the ferric ion in methemoglobin, which, if severe enough, results in cyanide poisoning with death from asphyxiation.

sweet clover



8- Nervous System

- **Parasympathetic Block:** (Atropine in Atropa belladonna): Atropine, L -hyoscyamine, and scopolamine are belladonna alkaloids. These alkaloids all effectively block the muscarinic receptor, essentially turning off the parasympathetic drive at the target organ. This explains why tachycardia, dry mouth, dilated pupils, and decreased gastrointestinal motility.
- **Sensory Neuron Block:** (Capsaicin in sweet pepper & red pepper red pepper) causes a burning sensation on vanilloid-type (VR1) sensory receptors. It also desensitizes the transient potential vanilloid 1 receptor (TRPV1) of sensory endings of C-fiber nociceptors to stimuli, a property which has therapeutic use in treating chronic pain. Capsaisin also can relax ileal smooth muscle.
- **Cerebellar Neurons**
- **Motor Neuron Demyelination**
- **Excitatory Amino Acids**
- **Parasympathetic Stimulation**
- **Epileptiform Seizure**

Atropa belladonna

9-Skeletal Muscle and Neuromuscular Junction

- **Neuromuscular Junction:** Curare, which is used as a poison placed on the tips of arrows, is also a potent neuromuscular blocking agent

Summary

- Toxic chemicals produced by plants can cause something as innocuous as a mild rash on the skin all the way to death by respiratory arrest. It is important to remember that these toxins are first and Foremost defense mechanisms against natural predators. However, we benefit greatly from plants as many Have produced potent antibiotics and pharmacologic therapies for myriad diseases that afflict humans.

Curare


THANK YOU FOR
LISTENING

Acute toxicity study

Determination of LD50

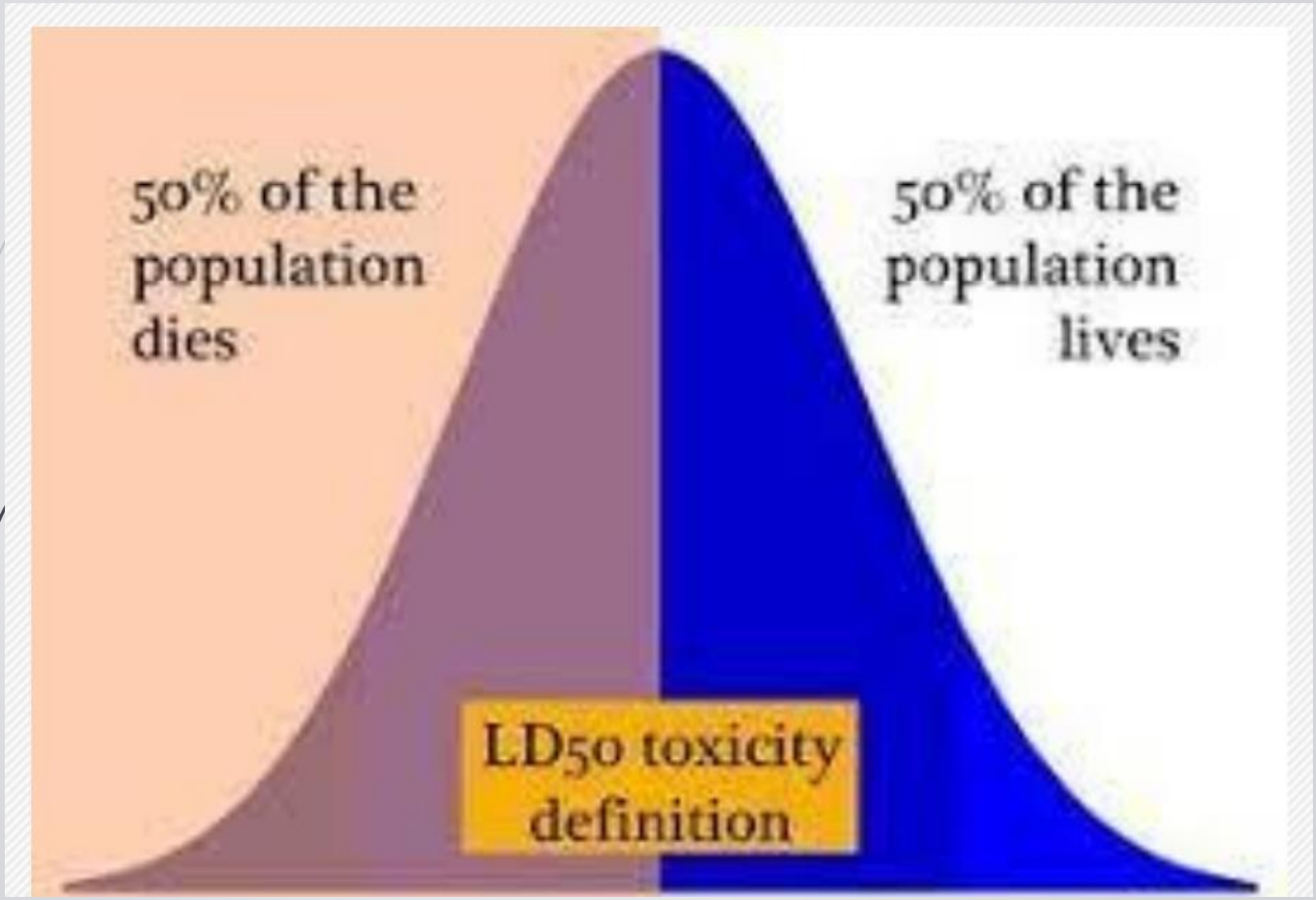
Assist. Lecturer

Safa Hameed Mohsin

Introduction

- Originally developed in 1927 by J.W. Trevan the LD50 test was used to determine the potency of **digitalis extracts**, **insulin**, and **diphtheria antitoxin**.

- **LD50** is beneficial for assessing the toxic effects of products ranging from drugs, pesticides to industrial solvents.


50% of the population dies
50% of the population lives
LD50 toxicity definition

Definition

LD 50: is the median lethal dose.

- **LD50**: dose of drug (Xenobiotic) **mg/kg** that is lethal to **50%** of a population of test animals.
- Reported by **mg of toxicant/kg** of body weight
- It is an index determination of drugs and poison's virulence.
- **Smaller the LD_{50} = more toxicity of drug (xenobiotic).**
- **Greater the LD_{50} = less toxicity of chemicals**

Chemical	*LD50 (mg/kg)**
Aspirin	1750.0
Ethanol	1000.0
Morphine	500.0
Caffeine	200.0
Heroin	150.0
Lead	20.0
Cocaine	17.5
Sodium cyanide	10.0
Nicotine	2.0
Strychnine	0.8

*Administered orally to rats.
Source: M. D. Josten and J. L. Wood.

Toxicological Significance of LD50

1- It is the most common test of acute toxicity assessment.

2- Before a product on new drug formulation is released to the market, its potential safety to the users is evaluated by a series of biological tests on lab. animals.

- **Median effective dose** or **ED50:** This is the dose (mg/kg), which produces a desired response in 50% of test population.

- **Therapeutic index:** is the ratio of the median lethal dose and the median effective dose. It is an approximate assessment of the safety of the drug. Also called as therapeutic window or safety.

- **Therapeutic index (T. I) = LD50/ED50**

The **larger** T.I = the **safer** is the drug.
The **smaller** T.I. = the **dangerous** drug
e.g. Penicillin has a very high therapeutic index, while it is much smaller for the digitalis preparation

Types of exposures

1- **Acute**, which is exposure to a chemical for **24 hours or less**.

2- **Sub-acute**, which is exposure to a chemical for **1 month or less**.

3- **Sub-chronic**, which is exposure to a chemicals **between 1 to 3 months**.

4- **Chronic**, which is exposure to a chemical for **more than 3 months**.

Toxicity rating for humans (70 kg body wt.)

Probable oral lethal dose:

- **Super toxic <5 mg/kg**
- **Extremely toxic 5-50 mg/kg**
- **Very toxic 50-500 mg/kg**
- **Moderately toxic 0.5-5 g/kg**
- **Slightly toxic 5- 15 g/kg**
- **Practically non toxic > 15 g/kg**

Acute Toxicity

1-Sudden, sever exposure, rapid absorptions of toxicant.

2- Involve single large dose exposure.

3- Reversible.

4- Interfere with essential physiological processes.

Chronic Toxicity

1- Prolong exposure lasting overs days, months , years.

2- Symptoms may not be immediately apparent, require multiple doses

3- Often irreversible.

4- Affect on chains of biochemical events

Animals & Routes

Mice, rats, rabbits, guinea pigs, cats, dogs, fish, monkeys and birds are use for LD50 study.

• The LD50 values of a new drug are determined by various route of administration such as the intravenous, intraperitoneal, subcutaneous, and oral

Factors affecting LD_{50} determination

1. Species, Age, and Sex
2. Amount of food
3. Environment
4. Route of exposure (oral, dermal, inhalation)
5. Physical environment such as temperature & humidity

Example, some LD50s (with different rout of exposure) for Dichlorvos, an insecticide commonly used in household pesticide strips: -

- **Oral LD50(rat): 56 mg/kg**
- **Dermal LD50(rat): 75 mg/kg**
- **Intraperitoneal LD50(rat): 15 mg/kg**

Which route is more potent to induce toxicity, why?

LD50 Study Design

For calculating LD50:

✓find out the least tolerated (smallest) dose (100% mortality) and most tolerated (highest) dose (0%mortality) by hit and trial method.

✓Once these two doses are determined, select at least 5 doses in between the least tolerated and most tolerated doses, and observe mortality due to these doses.

Dose range calculation

At beginning a pilot study done on small numbers of mice to select dose range.

•**Method 1** an ascending doses of tested chemical should be given for example 10, 30, 50, 70, & 100mg.

• **Method 2** is the up and down methods (staircase method) in which only **2** mice or rats are used as fellow:

1. E.g. 50 mg of chemical administered then both animals observed for 24 hr.

2. Then subsequent dose increased by factor **1.5** if tolerated

or decreased by factor **0.7** if found to lethal.

Experimental method & calculations

The method described by Thompson and Weil:

$$\text{Log } M = \text{Log } Da + d\,(f+1)$$

M= estimated LD50

D= dosage

Da= lowest dose level

d= Log of constant ratio between the doses (log of geometric factor)

f = the function of (r) used in the calculation of an LD50.

n = number of animals used for each dose level.

K= number of doses

r - Vales: the number of death for each dose levels.

.

- Weils table for calculation of LD50

Where n= 6 k=3

r-values	*f*	*6f*	r-values	*f*	*6f*
0, 0, 3, 6	1.000 000	0.22361	1, 1, 4, 6	0.060000	0.3226
0, 0, 4, 6	0.83333	0.21082	1, 1, 5, 6	0.400000	0.30724
0, 0, 5, 6	0.66666	0.16667	1, 2, 5, 6	0.20000	0.36000
0, 0, 6, 6	0.50000	0.0000	1, 2, 6, 6	0.0000	0.26833
0, 1, 2, 6	1.00000	0.26874	1, 3, 3, 6	0.40000	0.39799
0, 1, 3, 6	0.83333	0.27889	1, 3, 4, 6	0.20000	0.42000
0, 1, 4, 6	0.66667	0.26874	1, 1, 4, 6	0.0000	0.36878
0, 3, 6, 6	*0.00000*	0.22361	2, 0, 4, 6	*0.75000*	*0.32566*
1, 1, 2, 6	*1.00000*	*0.32249*	2, 0, 5, 6	*0.50000*	*0.29580*
1, 1, 3, 6	*0.80000*	*0.33706*	2, 0, 6, 6	*0.25000*	*0.23717*
0, 2, 4, 6	*0.50000*	*0.29814*	2, 0, 3, 6	*1.0000*	*0.33541*

Example:

Group of **six** rats were administered single oral dose of drug X at **four** successive dose levels; namely **1.00 mg/kg, 1.2 mg/kg, 1.44 mg/kg, and 1.77 mg/kg**. Death occurring in each group were **0, 2, 4, and 6**. Calculate the LD50?

Answer:

Log M = Log Da + d (*f+1*) **K= 3 & n= 6**

= 0.00 + 0.0792(0.50000+1)

= 0.0792(1.5000)

Log M = 0.1188

Anti log or (LD50) = 1.314 mg/kg

example

Five groups of mice, each group contain 10 mice; group1 administered 10mg/kg , group 2 administered 15mg/kg , group 3 administered 20mg/kg and group 4 administered 25mg/kg , group 5 administered 30 mg/kg of digoxin. Death occurring in each group were 0, 3, 5, 7 and 10 respectively.

What is the LD50 ?

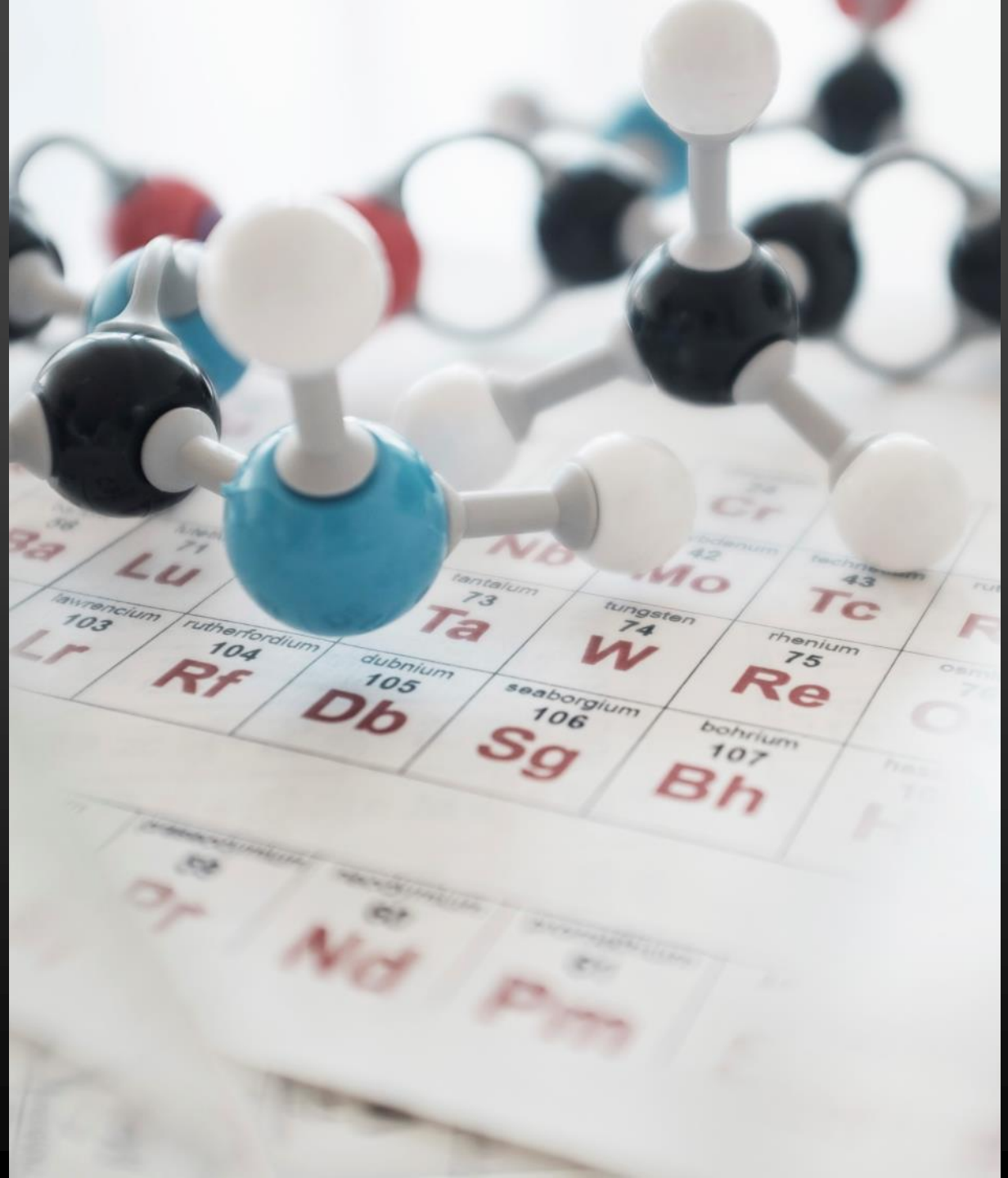
What is the LD100?

What is the LD0 ?

Organophosphorus toxicity

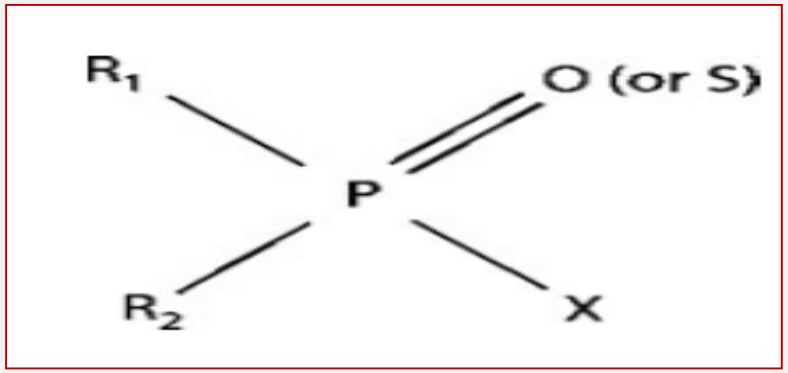
Assist. Lecturer

Safa Hameed Mohsin



Organophosphours compound

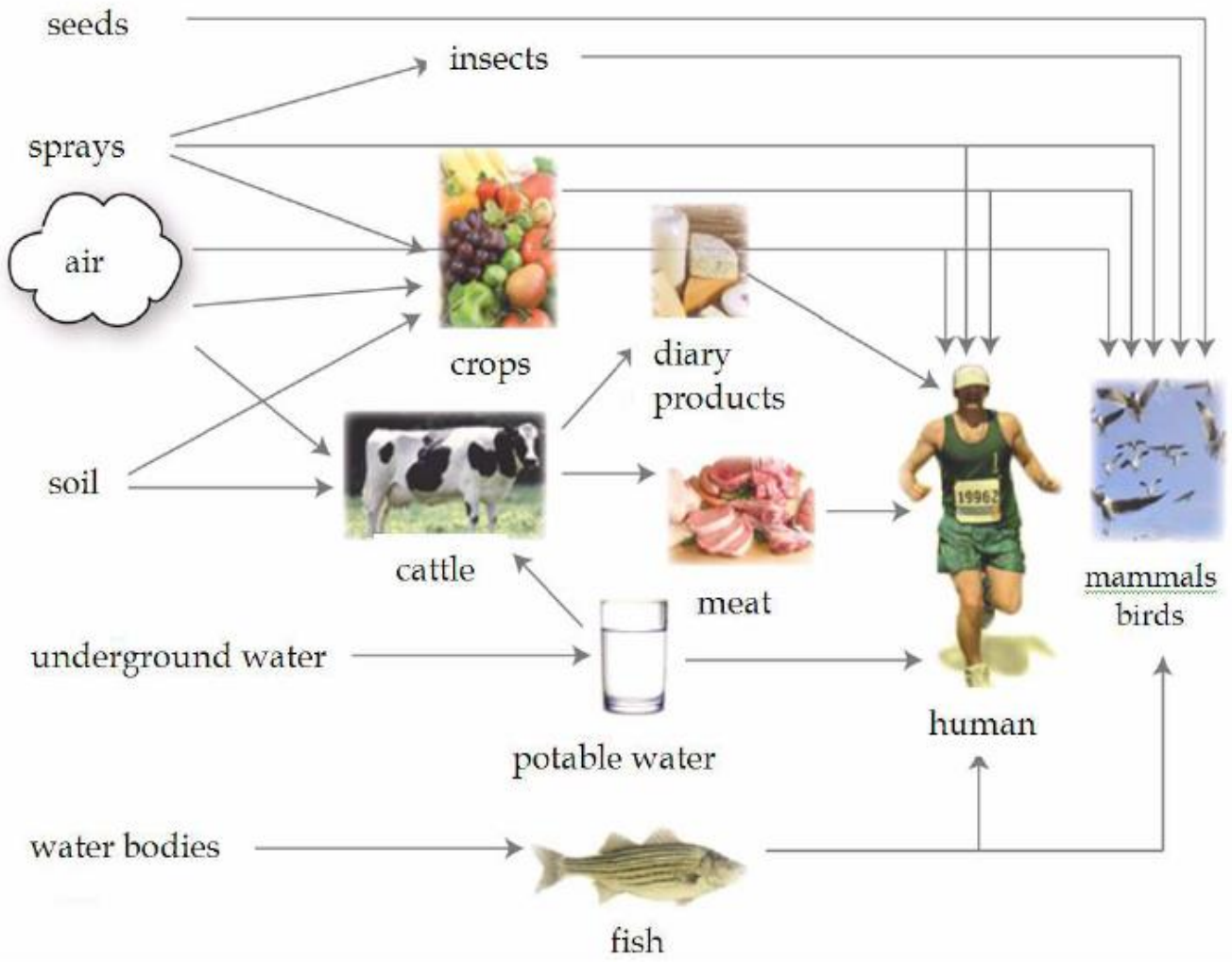
- **<u>Organophosphorus pesticides (OPs):</u>** most widely used pesticides for insects control. Its a large group of chemicals used over the past 60 years for protecting **crops, livestock, human health and as warfare agents**.



- Where X is the so-called “leaving group,” that is displaced when the OP phosphorylates acetylcholinesterase (AChE), and is the most sensitive to hydrolysis;R1 and R2 are most commonly alkoxy groups (OCH3 or OC2H5).

Jens Martensson

Route of exposure



Humans are exposed to Ops by:

1-ingested food & drink

2- breathing polluted air

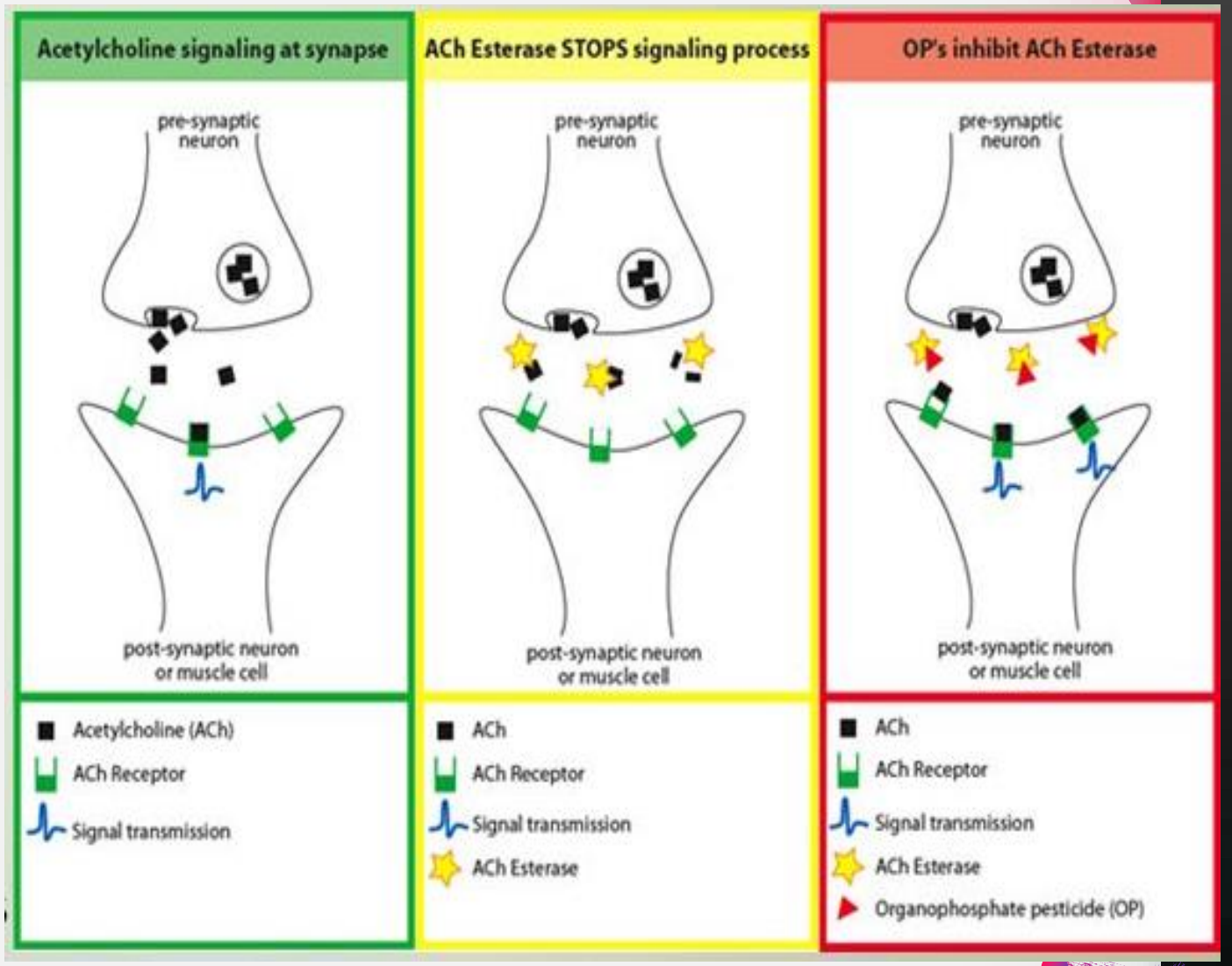
3- Skin contact.

The exposure of workers in **closed areas and of agricultural workers** or **people living near farms**, is also very important.

Jens Martensson

Mechanism of toxicity

- **Orgnophosphates** inactivate the enzyme Cholinesterase (ChE) by reacting at the esterase site, which leads to an increase in Acetylcholine (ACh) at the muscarinic receptors, nicotinic receptors and in CNS leading to toxic effects.
- The phosphorylated enzyme complex subsequently undergoes hydrolysis spontaneously (phosphorylated enzyme complexes take some 60 minutes to several weeks).
- The reactivation time can be enhanced by oximes.



Toxicokinetics

1- Absorotion: OPs can be absorbed through skin, conjunctiva, oral mucosa, GI tract, respiratory tract, by: direct contact, ingestion, inhalation and injection.

-Most patients become symptomatic rapidly, though the onset and severity of symptoms depend on the nature of the compound, amount, route of exposure and rate of metabolic degradation.

2- Distribution: After absorption they are rapidly distributed in all body tissues. Lipid solubility makes easy access to CNS and fat stores. They are recurrently released from fat stores to circulation/secreted to stomach and have been implicated for the sudden deterioration in a stable patient.

3- Metabolism occurs principally by oxidation in the liver with conjugation and esterase hydrolysis producing a half life of minutes to hours.

4- Elimination occurs via urine, bile and faeces.

Jens Martensson

Diagnosis

1- History of exposure & clinical features.

2- Measurement of **AChE** in serum and RBC

3- Detection of **metabolic products in urine**

Clinical features of toxicity

1- **Muscarinic effects** of OP are include:

Cardiovascular - **Bradycardia**, hypotension

Respiratory - Rhinorrhea, bronchorrhea, **bronchospasm**, cough, severe respiratory distress

Gastrointestinal – **Hyper-salivation**, nausea and **Emesis**, abdominal pain, **diarrhea**, fecal incontinence

Genitourinary - Incontinence / **urination**

Ocular - Blurred vision, **miosis**

Glands - Increased **lacrimation**, diaphoresis.

DUMBBLES

2-Nicotinic effects : muscle fasciculations, cramping, weakness, and diaphragmatic failure. Autonomic nicotinic effects include hypertension, tachycardia, mydriasis, and pallor.

3- CNS effects: Anxiety, Emotional liability, Restlessness, Confusion , Ataxia, Tremors Seizures Coma

Jens Martensson

Management

As in any medical emergency:

- Airways must be secured. (A)
- Respiratory / Breathing function is assisted. (B)
- Cardiovascular monitoring and support. (C).

- OP poisoning is a medical emergency. They need to be nursed in general ICU with adequate ventilation unless specific complications need Specific ICU care.

- The health care workers need protection through personnel protecting equipment's:

1- Rubber Gloves and gowns are recommended as these compounds are known to penetrate latex /vinyl gloves.

2- Charcoal cartridge masks are recommended for respiratory protection. The staff may need to be rotated if they can't stand the noxious order.

Jens Martensson

Management & Treatment

- **General management**

1-A B C

Airway protection

Breathing

Circulation

2- Decontamination

Skin decontamination

GIT decontamination

3- Supportive treatment

- **Specific management**

1- Atropine sulfate

2- Parlidoxime

1- Airway protection

- Maintain clear airway.
- Intubate the patient and aspirate the secretions with a large-bore suction device if necessary.
- Administer O2 by mechanically assisted pulmonary ventilation if respiration is depressed.

- **Improve tissue oxygenation as much as possible before administering atropine, so as to minimize the risk of ventricular fibrillation???why.**

- In severe poisonings, it may be necessary to support pulmonary ventilation mechanically for several days.

2- Skin decontamination

- Besides, the decontamination at the site, in the emergency department all clothing, hair assistant are to be removed and placed in appropriate waste bags. The person is to be washed with large amount of water and soap (OPs are hydrolyzed in an aqueous solution in high PH) .Skin folds and underside of fingernails and long hairs require particular attention. Ocular decontamination is to be carried out by washing eyes with water/normal saline.

3- GIT decontamination

Gastric lavage **Activated charcoal**

If the patient has already vomited, which is most likely in serious exposures, further efforts at GI decontamination may not be indicated.

In significant ingestions, diarrhea and/or vomiting are so constant that charcoal adsorption and catharsis are not indicated.

Jens Martensson

4-Atropine sulfate

- Administer atropine sulfate IV (IM or Intratracheal by endotracheal tube if intravenous injection is not possible).
- Depending on the severity of poisoning, doses of atropine ranging from very low to as high as **300 mg** per **day** may be required, or even continuous infusion.
- The objective of atropine antidotal therapy is to antagonize the effects of excessive concentrations of Ach at end-organs having muscarinic receptors. Atropine does not reactivate the ChE or accelerate disposition of OP.
- Recurrence of poisoning may occur if tissue concentrations of OP remain high when the effect of atropine removed.
- **Atropine** is ineffective against nicotinic actions, specifically muscle weakness and twitching, and respiratory depression.
- **Atropine** is often a life-saving agent in OP poisonings.

- The additions use of **nebulized atropine** has been reported to improve respiratory distress, decrease bronchial secretions, and increase oxygenation

Jens Martensson

5- Pralidoxime

- Before administration of pralidoxime, draw a blood sample (heparinized) for cholinesterase analysis (since pralidoxime tends to reverse the AchE depression).
- Administer **pralidoxime** (2-PAM) a cholinesterase reactivator, in cases of severe poisoning by OP pesticides in which respiratory depression, muscle weakness, and/or twitching are severe.

- When administered early (usually less than **48** hours after poisoning), **pralidoxime** relieves the **nicotinic** + **muscarinic** effects of poisoning.

- **Pralidoxime** works

1- by **reactivating** the **ChE** 2- by **slowing** the "**aging**" process of phosphorylated cholinesterase to a non-reactivatable form.

6- Observation & other treatment

- Observe patient closely for at least **72** hr. to ensure that symptoms (sweating, visual disturbances, vomiting, diarrhea, chest and abdominal distress, pulmonary edema) do not recur as atropinization is withdrawn.

- In very severe poisonings by ingested OP, particularly the more lipophilic and slowly hydrolyzed compounds, metabolic disposition of toxicant may require as many as **5-14 days**.

- **Furosemide:** may be considered if pulmonary edema persists in the lungs even after full atropinization.
- **Diazepam :** an for seizure control.

ALGORITHMIC MANAGEMENT OF OPC POISONING

ASHISH SINGH, MEDICOWESOME

GENERAL MEASURES:

Assess for **A**irway, **B**reathing and **C**irculation

↓

Remove patient from site of exposure + wash skin with soap and water

↓

If ingested, perform gastric lavage + Oral activated charcoal at 1-2 g/kg

SPECIFIC MEASURES:

MAIN ANTIDOTE: ATROPINE; INITIAL DOSE: 1.8 to 3 mg i.v.

↓ Review after 5 minutes

SIGNS OF ATROPINIZATION

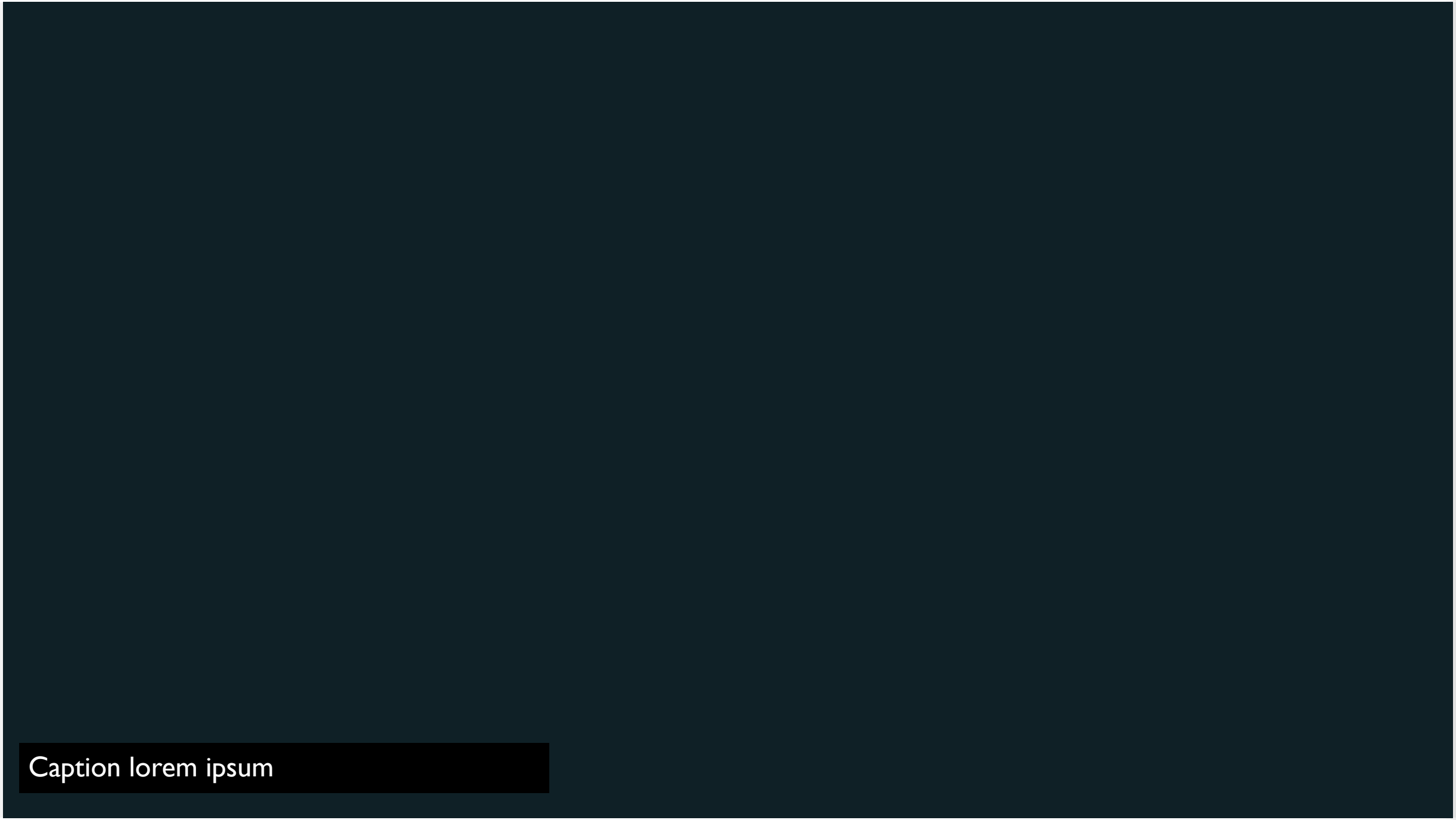
NO → Repeat i.v bolus with double dose → Review after 5 minutes → SIGNS OF ATROPINIZATION

NO → Repeat i.v bolus with double dose

YES → MAINTENANCE DOSE: 10-20% of total initial dose over 1 hour i.v. Infusion

2-Pralidoxime can be given as a cholinesterase activator.
Initial dose: 30 mg/kg over 20 minutes.
Maintenance dose: 9 mg/kg/hr

Jens Martensson



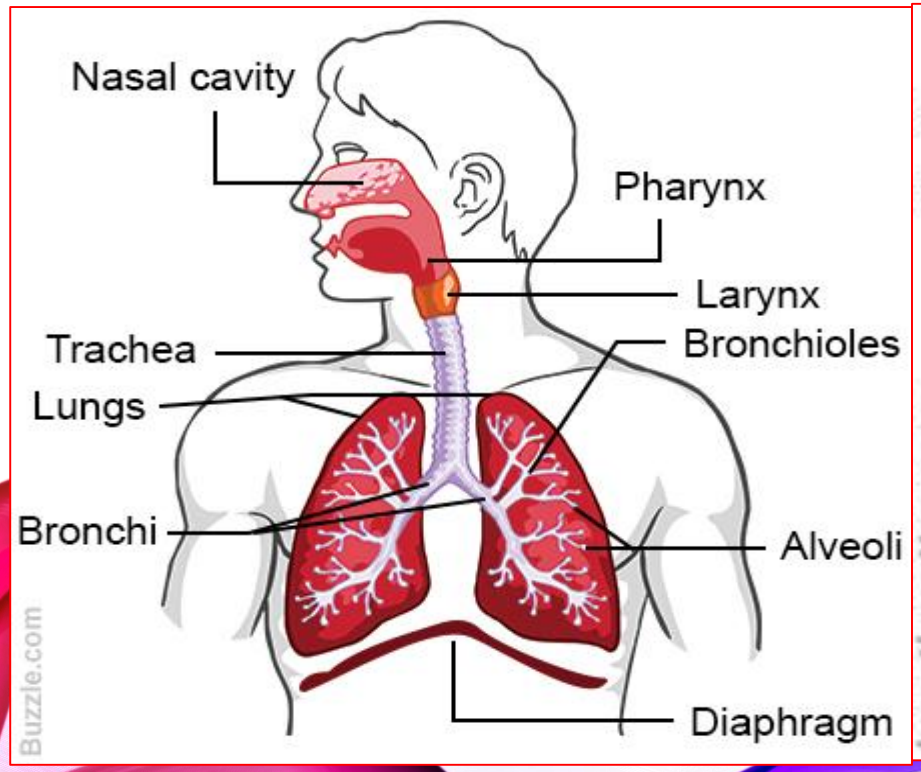
Caption lorem ipsum

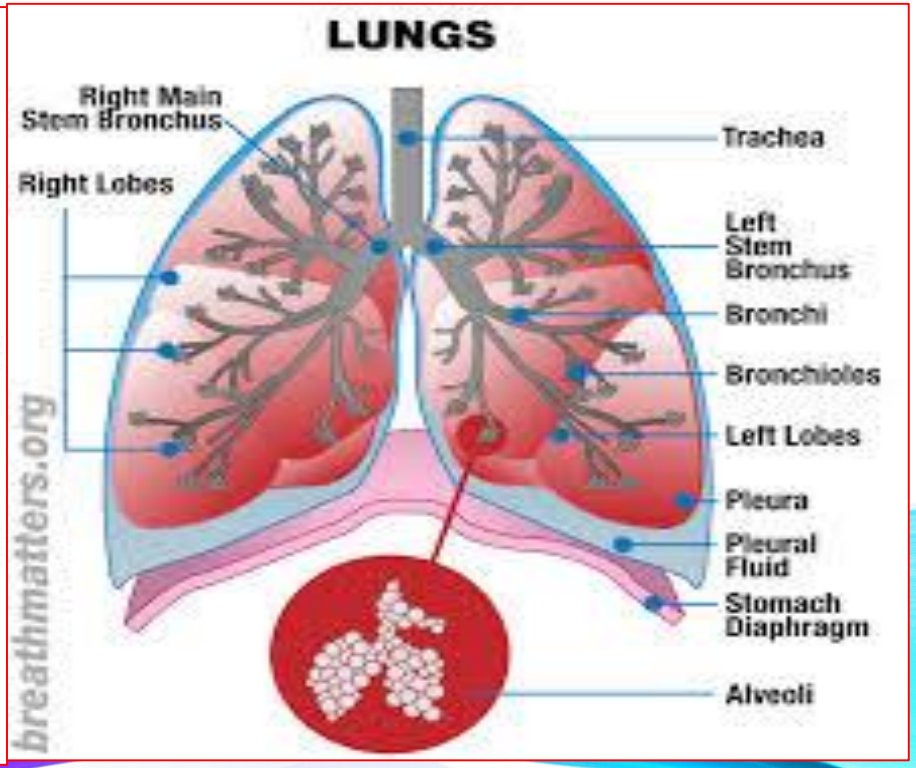
Safa Hameed Mohsin

27/2/2024

DRUG-INDUCED PULMONARY TOXICITY

ASSIST. LECTURER:
SAFA HAMEED MOHSIN





INTRODUCTION

- The respiratory system has elaborate defense mechanisms against damage from exposure to potentially hazardous particles and gases.

- Particles of **1-2 Mm** are the optimal size for reaching the alveoli.
- The **large** particles **get trapped** in nasal hairs and never enter the lower respiratory tract, or they are removed by **coughing or sneezing**.

- The **Smaller** particles (**2 Mm**) enter the trachea but land on the airway surfaces and stick to the surface mucus.
- The **finest** particles settle less efficiently and are usually exhaled.

- In the alveoli, some material may **dissolve and be absorbed into the bloodstream** or **interstitial fluid**.

- Particles that do not dissolve may be **phagocytized by macrophages** and the phagocytic cells are either swept up the tracheobronchial tree on the mucous blanket or they migrate to the interstitial fluid.

- **Some insoluble particles may remain sequestered in the lung**.

The immune system plays an important role in protecting the lungs:

Exposure to many substances, particularly those containing protein of animal or vegetable origin, sensitizes immune system cells which respond with a complex variety of reactions to destroy or immobilize the inhaled substance (acute response).

These process, often accompanied by inflammation of the surrounding tissues, which is part of the repair process necessary to restore normal function. Repeated exposure and inflammation is thought to result in serious and permanent tissue damage (chronic response).

MECHANISM OF PULMONARY INJURY

Pulmonary toxicity secondary to drugs or toxicants may be due to a variety of mechanisms:

1- Oxidant injury.

2- Pulmonary vascular damage.

3- Deposition of phospholipids within cells.

4- Immune system–mediated injury.

5- CNS depression.

6- Direct toxic effect.

1- **Oxidant Injury**

Oxidant molecules (**oxygen, hydrogen peroxide, hypochlorous acid**) that are formed within phagocytic cells (monocytes, macrophages and neutrophils) may participate in redox reactions resulting in fatty-acid oxidation that lead to membrane instability and perhaps autologous cytotoxicity.

Antioxidant defense mechanisms (**superoxide dismutase, glutathione peroxidase, alpha tocopherol**) provide the necessary balance to counteract the oxidant effects.

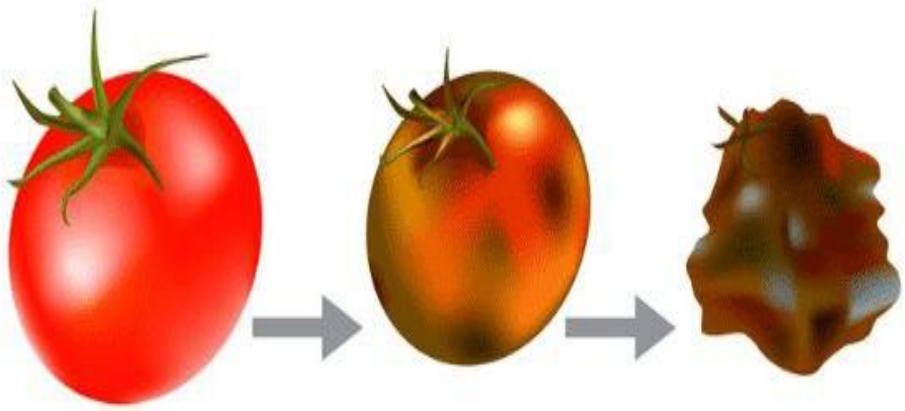
Examples of drug-mediated oxidant injury are:

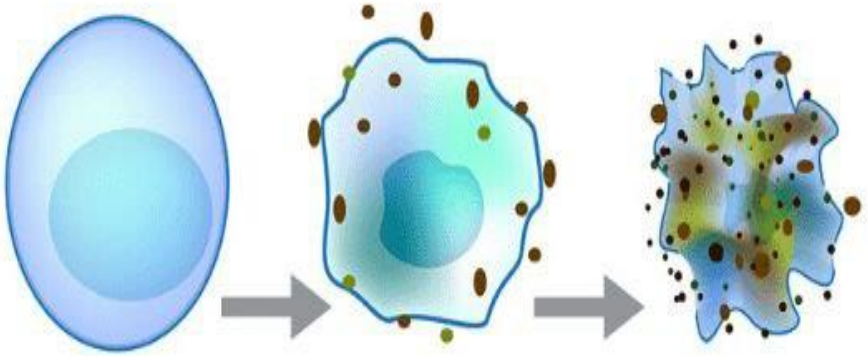
-chronic reactions to **nitrofurantoin**

-**chemotherapeutic** drug-induced pulmonary injuries.

- **Nitrofurantoin** may produce pulmonary fibrosis by accelerating the generation of oxygen radicals within lung cells, overwhelming the normal antioxidant protective mechanisms, this, in turn, stimulates an inflammatory and fibrotic reaction.

- **Antineoplastic drugs** may disturb oxidant/antioxidant system homeostasis, resulting in pulmonary injury.

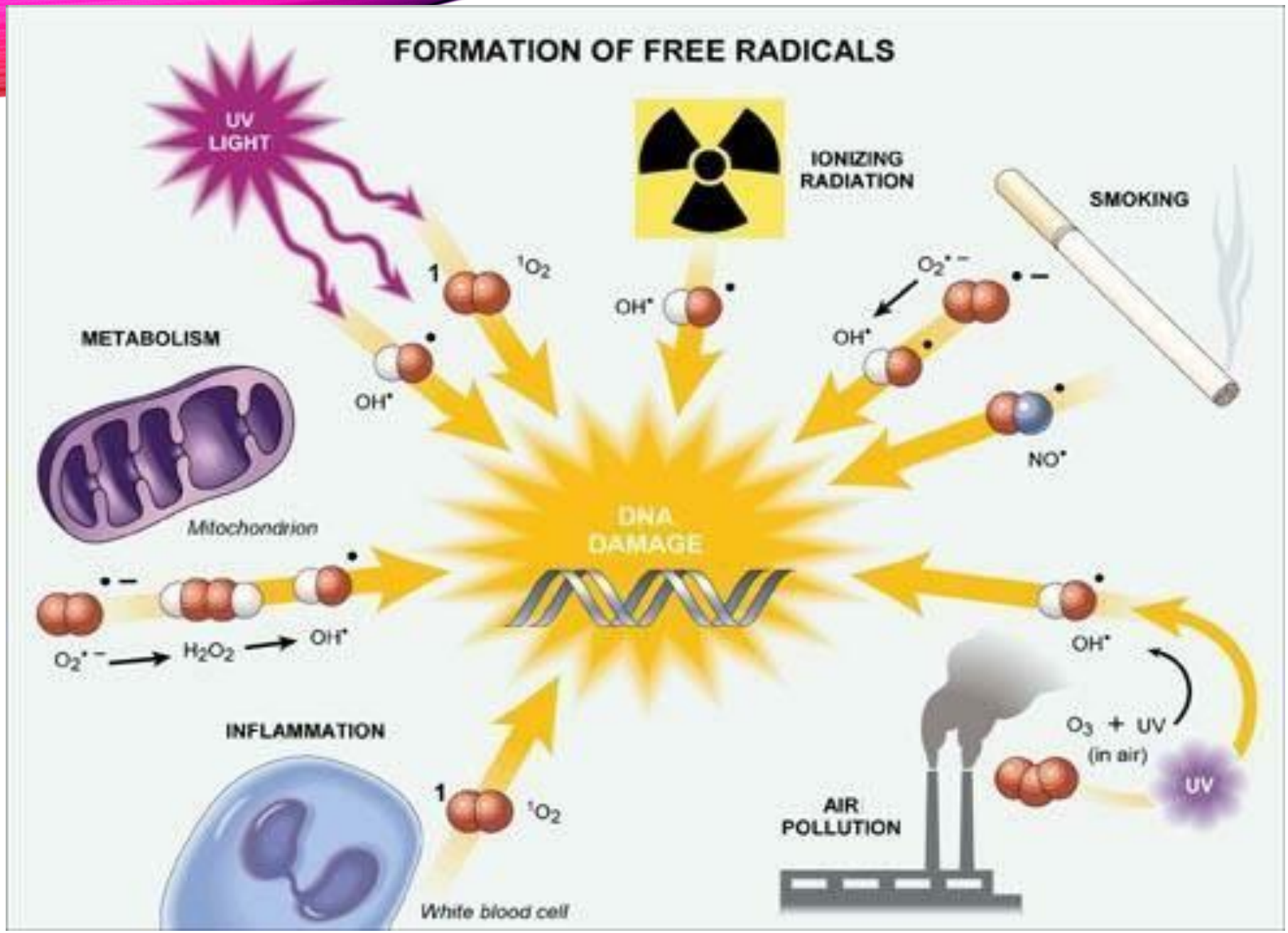




ecosh

OXIDATIVE STRESS CAN CAUSE:

- Cancer
- Vision loss
- Heart disease
- Arthritis
- Stroke
- Respiratory diseases
- Immune deficiency
- Emphysema
- Parkinson's or Alzheimer's disease
- Fast aging
- Obesity
- Hair loss
- Other inflammatory or ischemic conditions


FORMATION OF FREE RADICALS
UV LIGHT
IONIZING RADIATION
SMOKING
METABOLISM
Mitochondrion
DNA DAMAGE
INFLAMMATION
White blood cell
AIR POLLUTION
(in air)
UV

2- Pulmonary vascular damage

Clinically manifests as:

acute pulmonary edema

diffuse interstitial lung disease

pulmonary vascular occlusion

pulmonary hypertension or hemorrhage.

The proposed mechanisms of lung vascular damage are:

1- Increased microvascular hydrostatic pressure.

2- Increased permeability of the vascular endothelium.

3- Vascular occlusion by direct activation of inflammatory and immune mechanisms or indirectly by stimulating intravascular coagulation (pulmonary thromboembolism)

4- Impaired homeostasis.

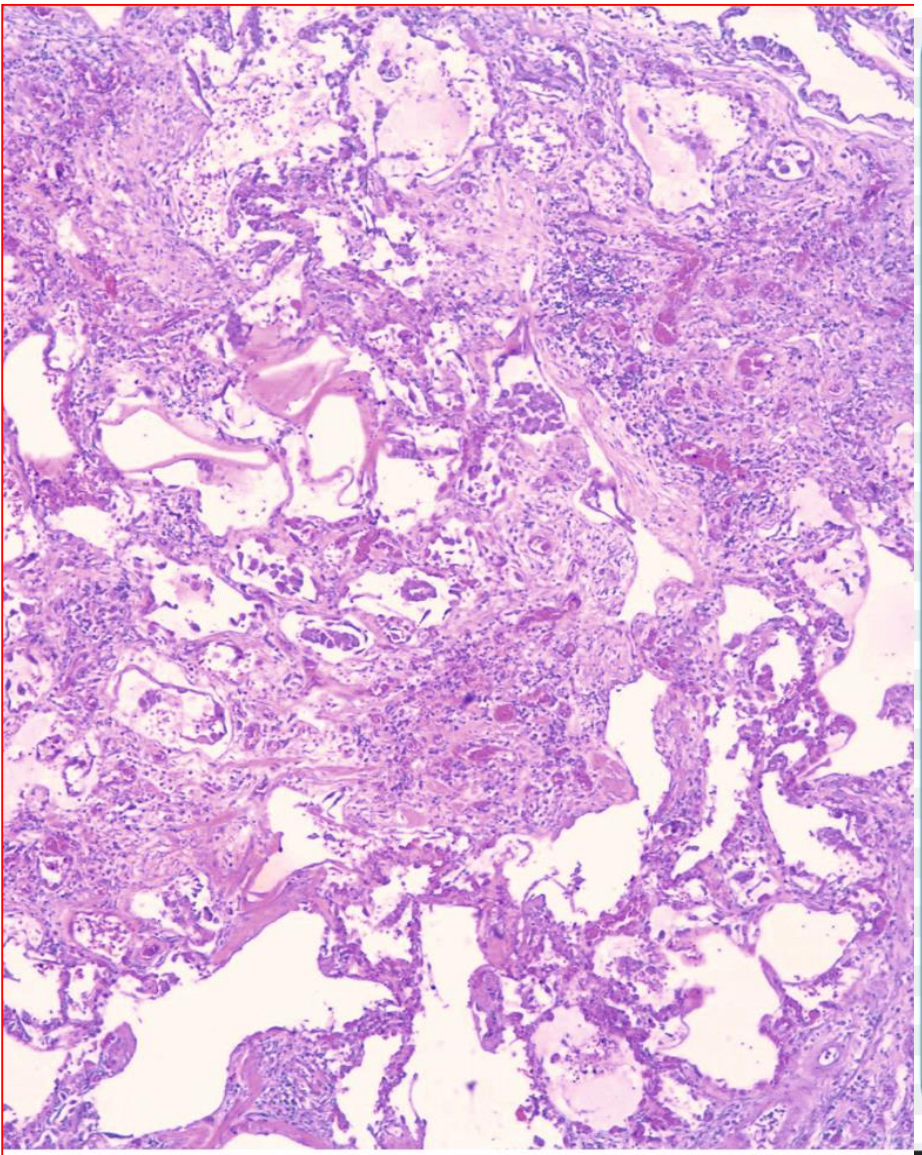
- **Oral contraceptives**: **estrogens** are well known to increase platelet adhesiveness and decrease venous tone and can cause a pro-coagulant effect.

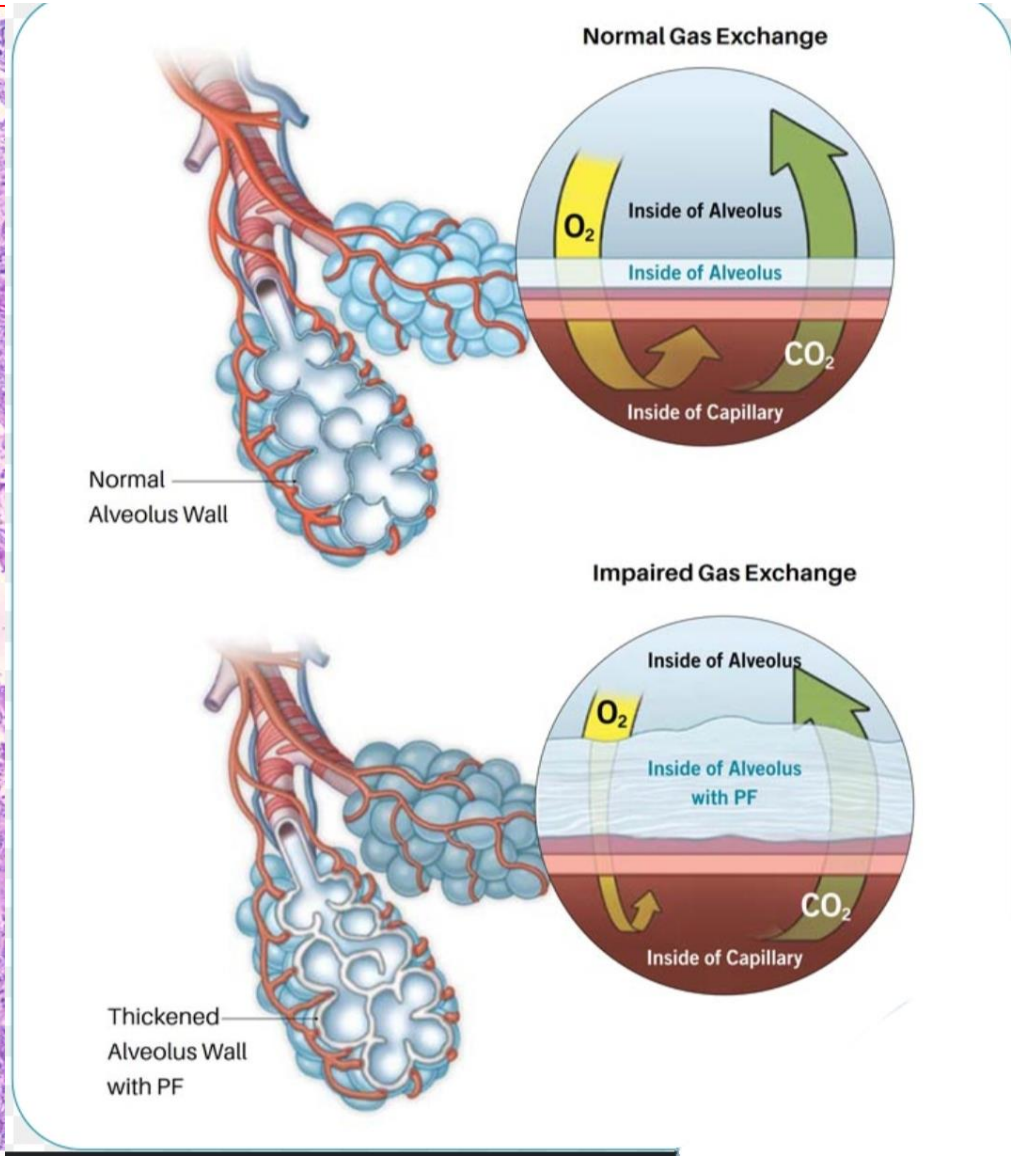
- **Appetite suppressants: (amphetamines,fenfluramine)** are associated with an increased risk of pulmonary hypertension.

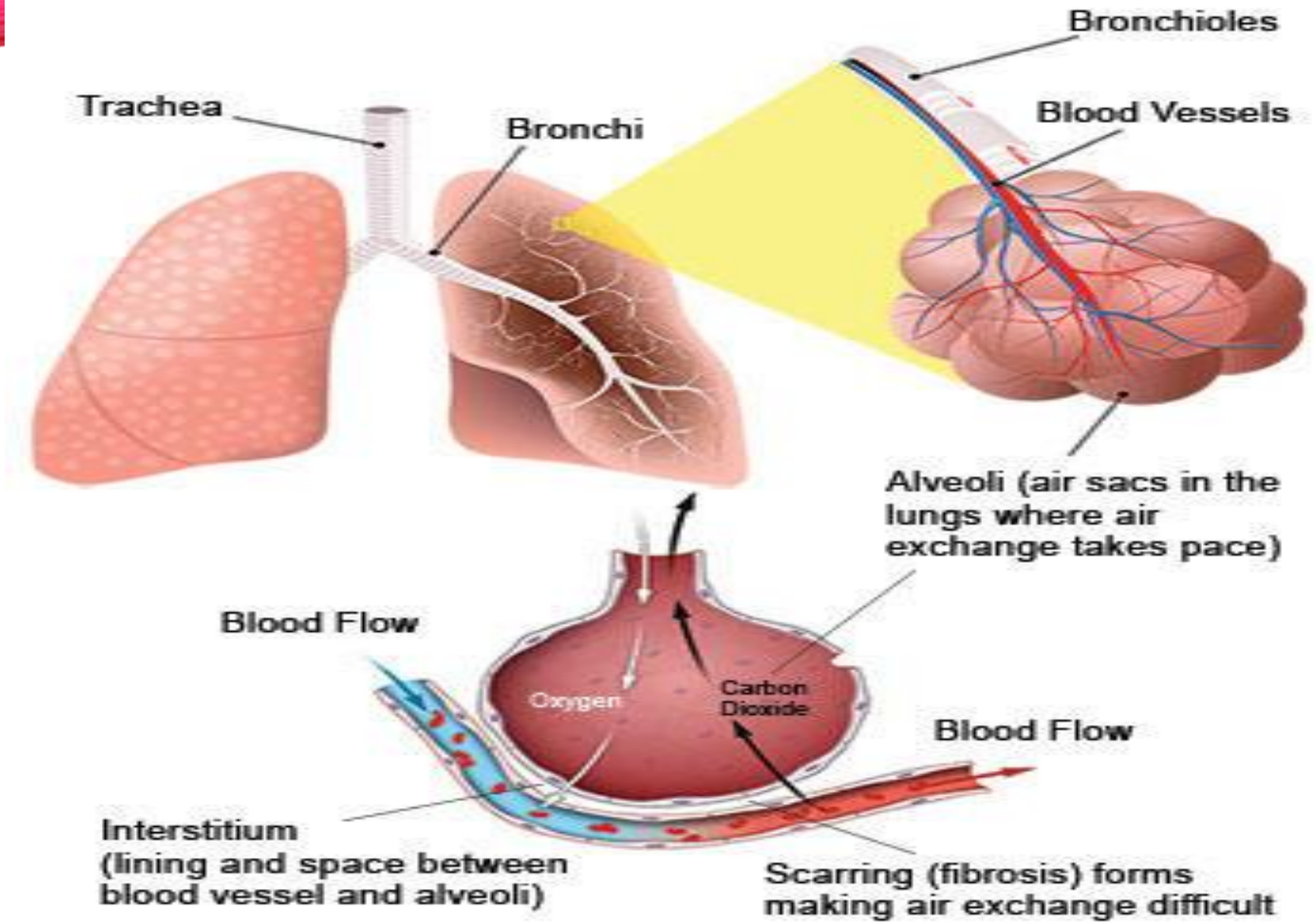
- **Pulmonary vasculitis** (is a form of hypersensitivity pneumonitis), caused by nitrofurantoin, sulfonamides, penicillins, phenytoin.

- **Several anticoagulants (heparin & warfarin) & Anti leukemia& lymphoma (cytarabine)** can produce **diffuse alveolar hemorrhage (DAH). Also cocaine** may cause DAH

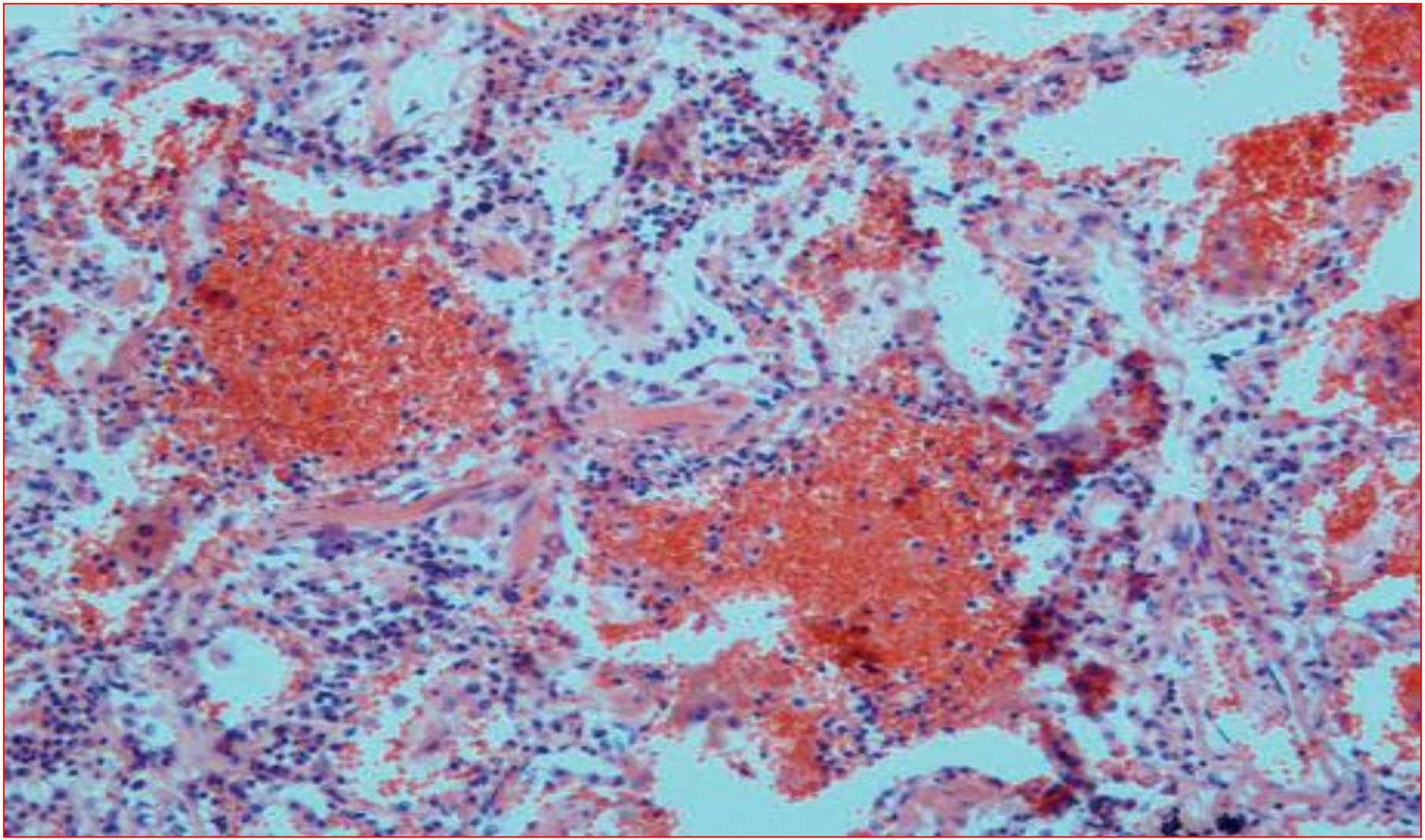
Severe interstitial fibrosis



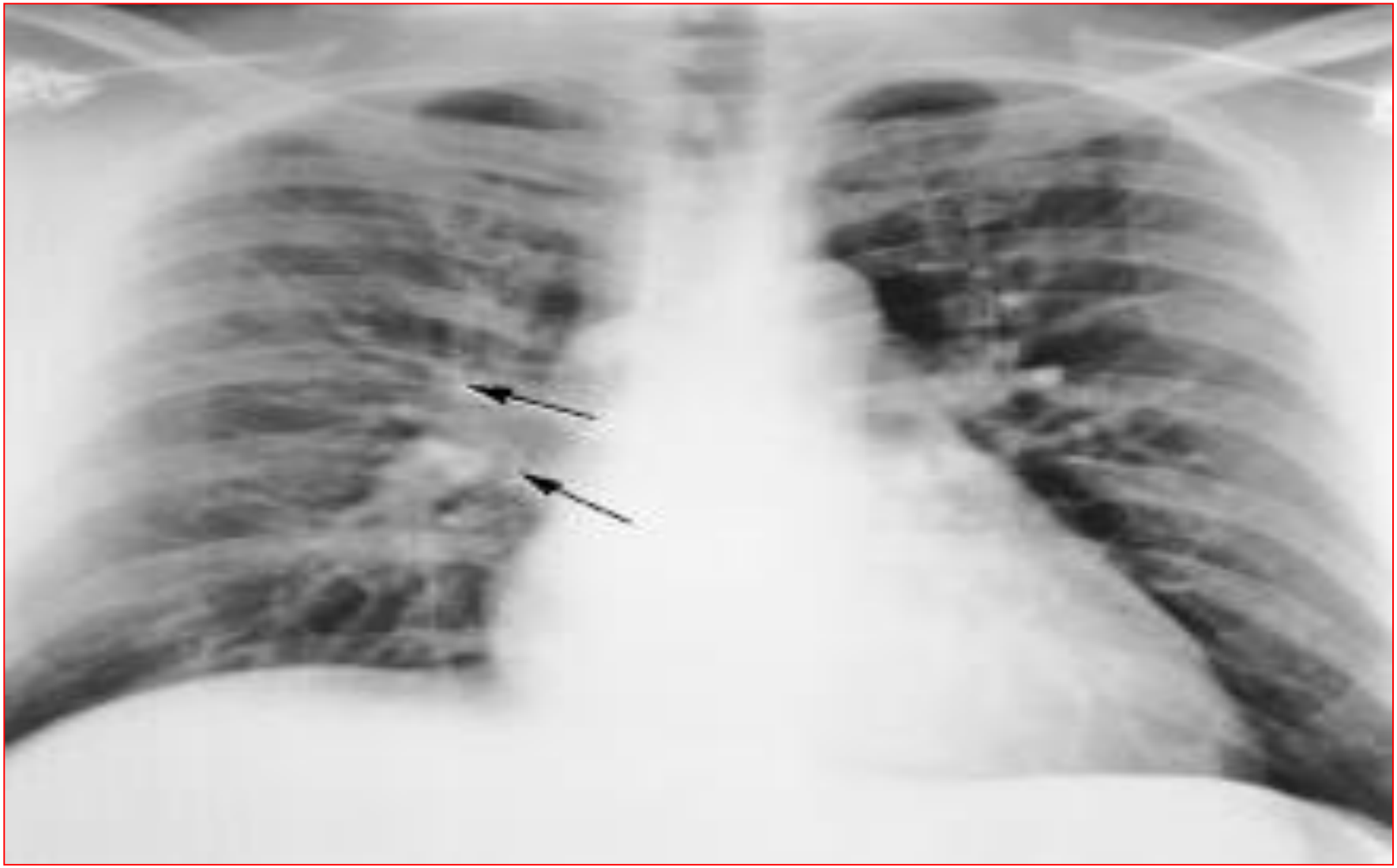


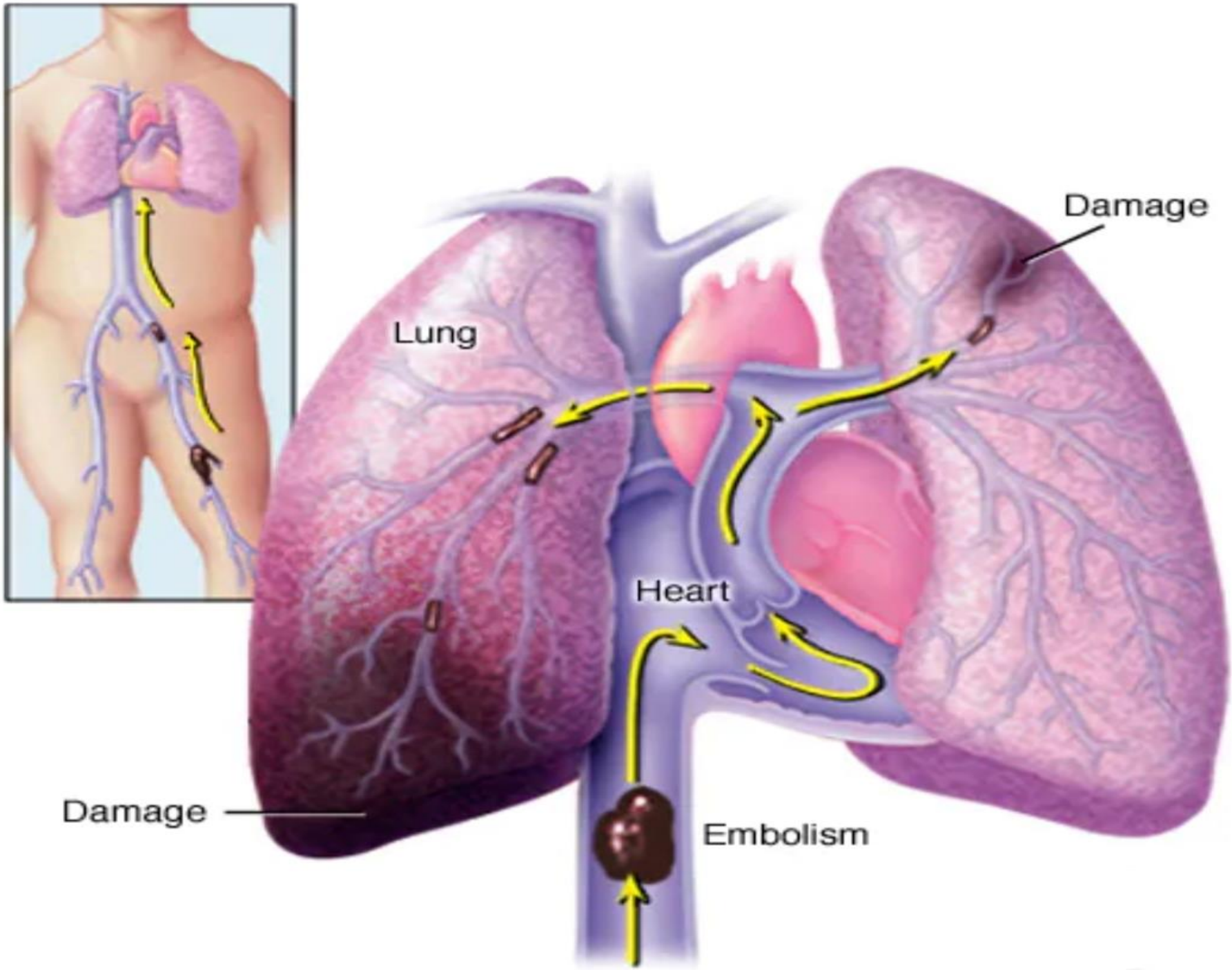

Bronchioles
Trachea
Bronchi
Blood Vessels
Alveoli (air sacs in the lungs where air exchange takes pace)
Blood Flow
Oxygen
Carbon Dioxide
Blood Flow
Interstitium
(lining and space between blood vessel and alveoli)
Scarring (fibrosis) forms making air exchange difficult

Pulmonary hemorrhage



Pulmonary Edema with increased capillary hydrostatic pressure.



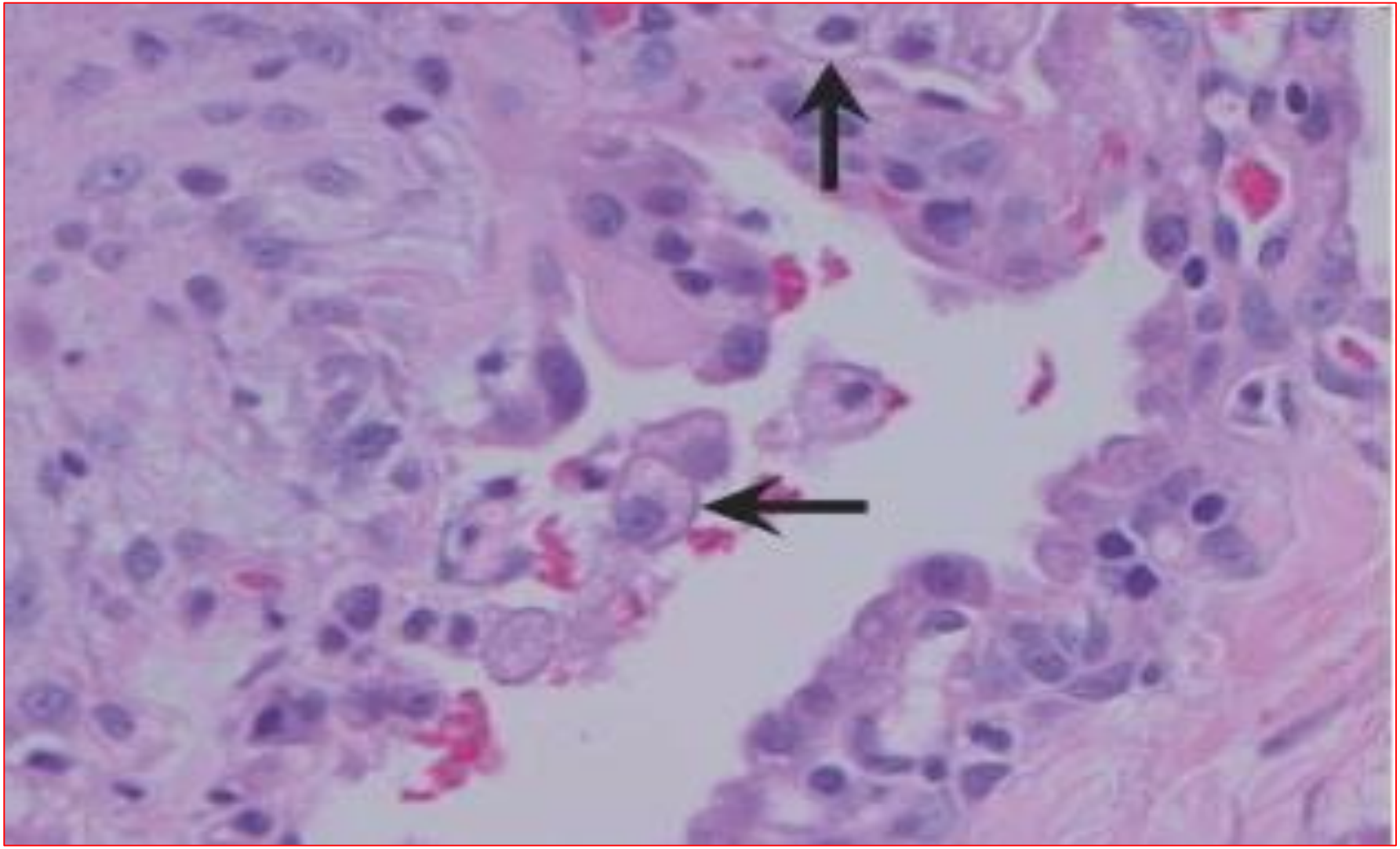

Damage
Lung
Heart
Damage
Embolism

3- DEPOSITION OF PHOSPHOLIPIDS WITHIN CELLS

- **Amiodarone** can cause an accumulation of phospholipids within lysosomes in the lung cells, owing to the inhibition of phospholipase A.
- **Amiodarone** has been demonstrated to produce phospholipidosis in alveolar macrophages and in type 2 cells. The process is reversible with discontinuation of the drug.

- Phospholipidosis: is a lysosomal storage disorder characterized by excessive accumulation of intracellular phospholipids in tissue; lung, liver & kidney.

Deposition of phospholipid in cell



4- IMMUNE -MEDIATED LUNG INJURY

- Drugs can act as potential antigens or haptens, inducing an immune cascade that can lead to immune-mediated lung toxicity. Deposition of antigen-antibody complexes may trigger an inflammatory response, leading **to pulmonary edema** and **interstitial lung disease**.

- Drug-induced systemic lupus erythematosus is an example of this injury
- Multiple mechanisms may be responsible for drug-induced cytotoxic pulmonary injury: reactive oxygen species (ROS), impairment of alveolar repair mechanisms & release of various cytokines.

- e.g. cytotoxic drugs: bleomycin, Methotreaxate, cyclophosphamide

  non-cytotoxic drugs: nitrofurantoin, sulfasalazine & amiodarone.

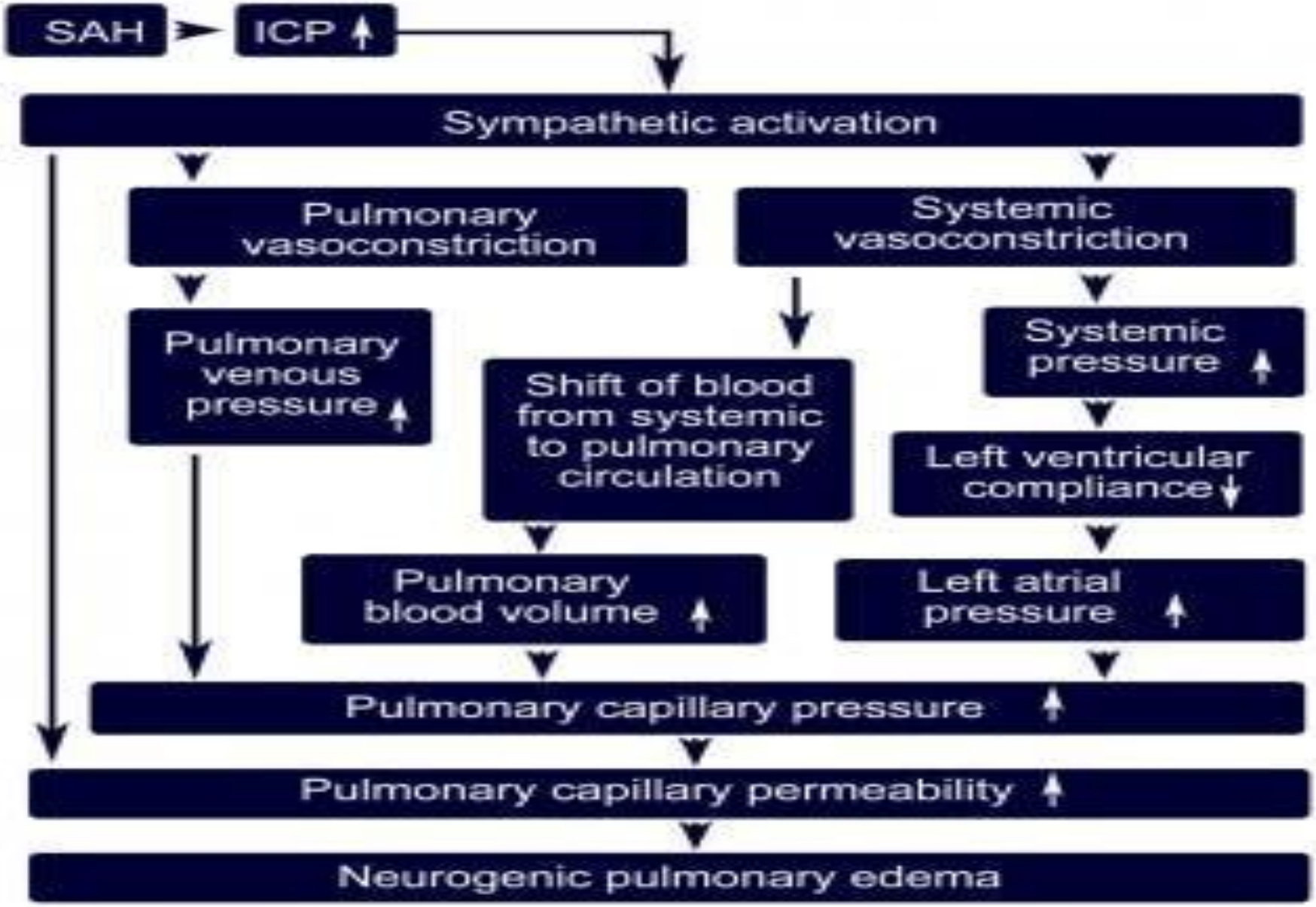
5- CNS DEPRESSION

The medulla is believed to activate sympathetic components of the autonomic nervous system.

Acute neurological crisis, accompanied by a marked increase in intracranial pressure, may stimulate the hypothalamus and the vasomotor centers of the medulla. Thus initiates a massive autonomic discharge, leading to **neurogenic pulmonary edema**.

- Acute NCPE (Non-Cardiogenic Pulmonary Edema) can occur after administration of a number of drugs:

Naloxone Heroin All-trans-retinoic acid
Contrast media Intrathecal methotrexate (MTX) Cytarabine

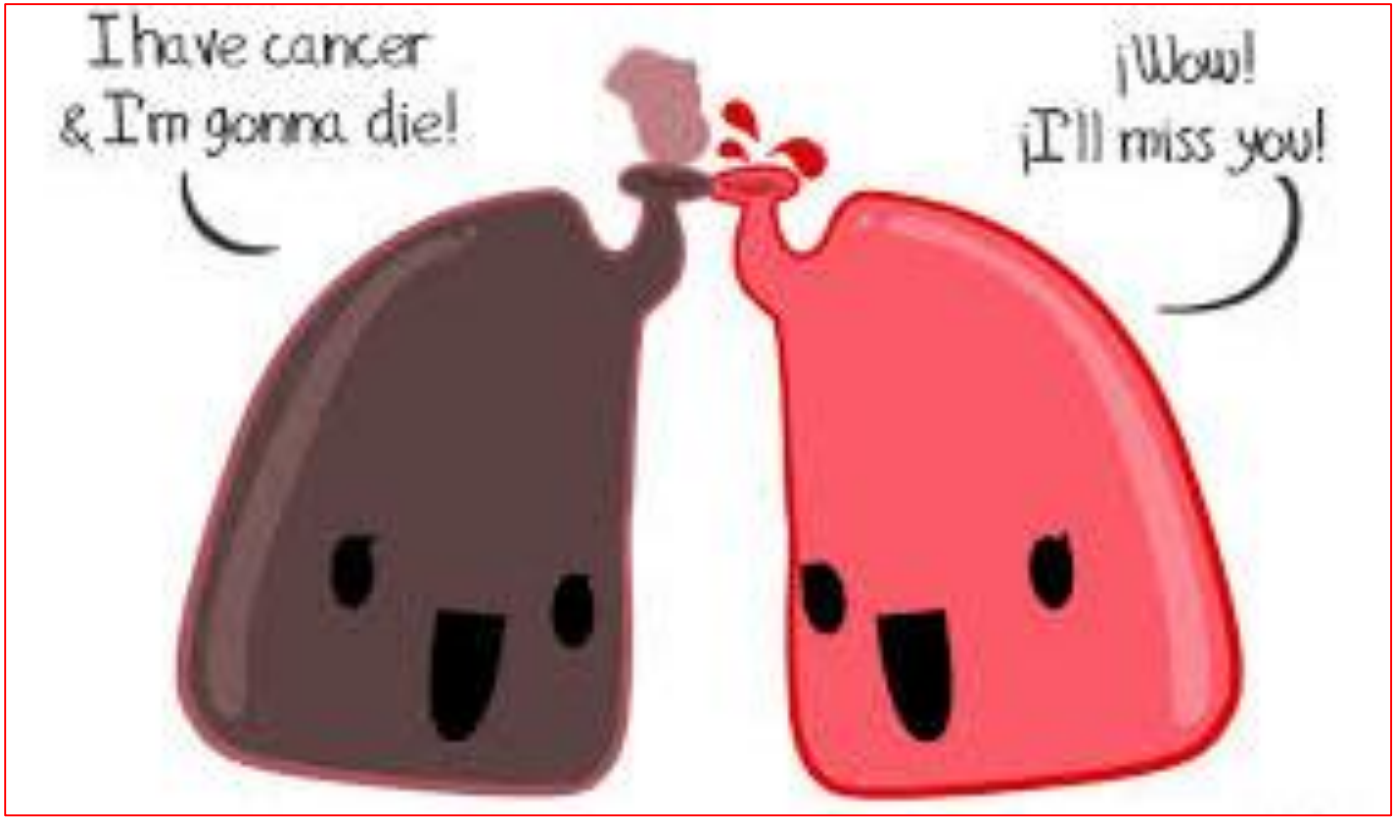

SAH
ICP
Sympathetic activation
Pulmonary vasoconstriction
Systemic vasoconstriction
Pulmonary venous pressure
Shift of blood from systemic to pulmonary circulation
Systemic pressure
Left ventricular compliance
Pulmonary blood volume
Left atrial pressure
Pulmonary capillary pressure
Pulmonary capillary permeability
Neurogenic pulmonary edema

6- DIRECT PNEUMOTOXIC TOXICANTS

Chemotherapeutic drugs can cause a direct toxic reaction.

The acute pulmonary toxicity of **bleomycin** has been attributed to DNA strand damage with resulting chromosomal injury.

Animal studies confirm that more **chronic bleomycin injury** occurs predominantly in the lungs, which have very low levels of bleomycin hydrolase activity.



THANKS FOR LISTENING