TOXICOLOGY OF SOLVENTS

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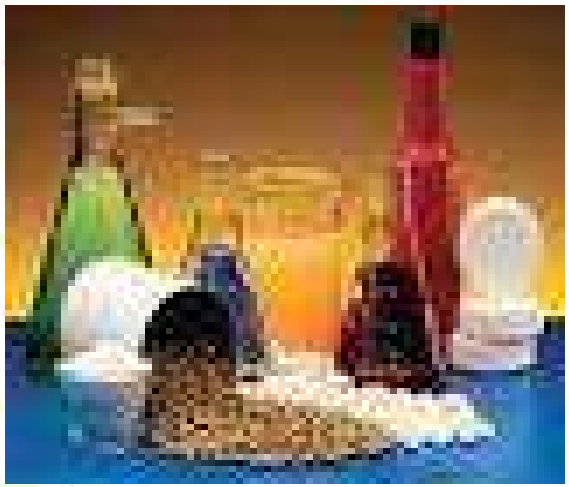


General characteristic of solvents

- The **solvents** are **organic compounds,** which belong to the group of **CNS depression (narcosis) - inducing compounds.**
- They have the potential on acute high-level vapor exposure to **cause narcosis** and **death**.
- appreciable **volatility** and high **lipid solubility**.

The **solvents** can be grouped into **four chemical categories**:

1. **Aliphatic hydrocarbons** which are commonly derived from petroleum;
2. **Aromatic hydrocarbons** which are found in coal products;
3. **Halogenated hydrocarbons**, containing **chlorine or fluorine**;
4. **Others** - alcohols, aldehydes, ethers, esters, ketons, carbon disulfide, etc.;

I. Sources and use

The solvents are used:

- as **solubilizer, dispersants** and **diluents** of **paints, varnishes, gums**;
- for **synthesis** of **medicines, pesticides, synthetic rubber, plastics**, etc.;
- as **fuel** for the **transport**;

The solvents used **in the industry** are usually chemical mixtures of organic compounds. They have different **trade names** but frequently contain **similar chemicals**.

II. Mechanism of action

- The **major route** of exposure is **the respiratory system**.
- The **ability** of solvent vapor to enter the bloodstream depends of their **lipid solubility**, since **lipoprotein cell membranes** must be traversed.
- **A second major** potential route of exposure is **the skin**. Frequent contacts with lipid soluble solvents can lead to **defatting of skin or to skin irritation**.
- Some solvents may penetrate skin barriers (by absorption from both liquid and vapor phases) and enter the bloodstream.

II. Mechanism of action

- **The toxic effects** of solvents are both **general and specific**.
- These effects depend on **many factors including:**
  - ✓ **solvent structure**
  - ✓ **exposure levels**
  - ✓ **frequency** of **exposure**
  - ✓ **individual sensitivity**.

1. General effects

Persons exposed to **high concentration** solvents show signs of **central nervous system disturbance**.

- ✓ **disorientation**
- ✓ **euphoria**
- ✓ **paralysis**
- ✓ **confusion**
- ✓ **unconsciousness**
- ✓ **convulsions**
- ✓ **death** from **respiratory** or **cardiovascular arrest**

More detailed **neurological effects of solvents** may be grouped as follow:

a) Sensory - **paresthesias**, **visual** or **auditory deficits**

b) Cognitive – memory disturbances (both short-term and long-term), **confusion, disorientation**

c) Affective - **nervousness, irritability, depression, apathy, compulsive behavior**

d) Motor - **weakness in hands, incoordination, fatigue, tremor**

2. Specific effects

Specific organ toxicity which is associated with solvents includes:

- **haematopoietic** toxicity of **benzene**;
- **CNS depression** effects of **alkyl benzene**;
- **hepatotoxicity** of certain **chlorinated hydrocarbons**;
- **ocular toxicity of methanol**;
- **hepatotoxicity and CNS depression** effects of **ethanol**;
- **neurotoxicity of n-hexane** and certain **deketons**;
- **reproductive toxicity** of **ethylene glycol ethers**;
- **carcinogenicity of dioxine**;

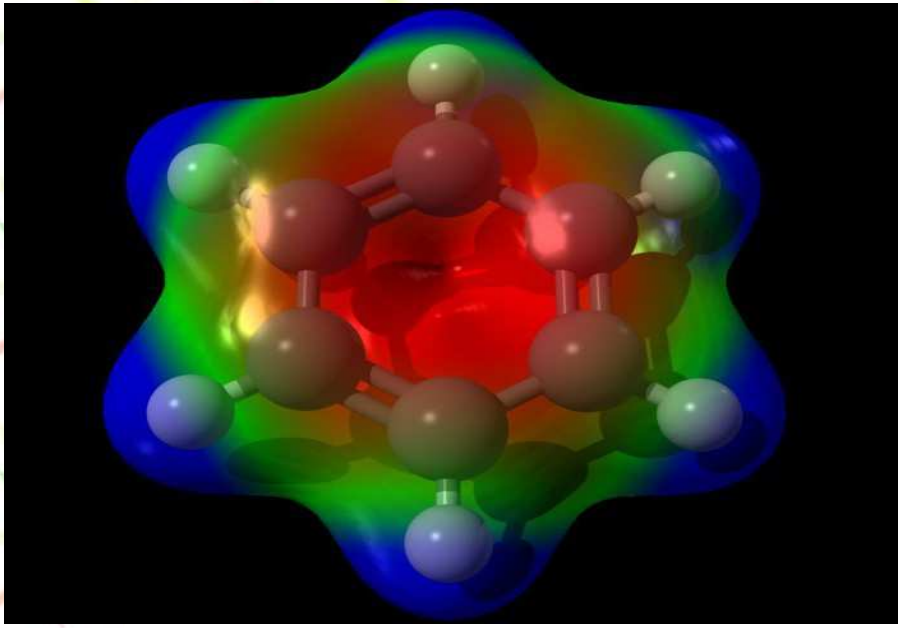
III. Metabolism of solvents

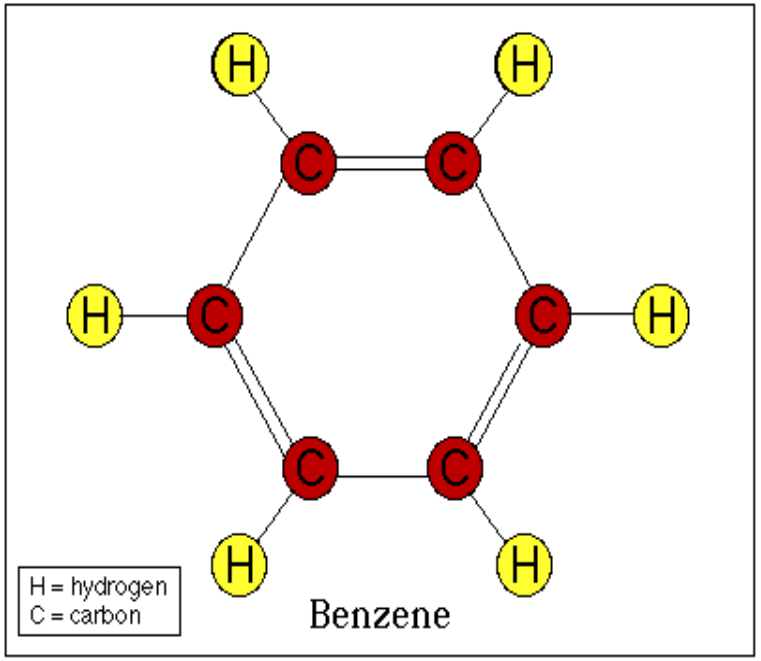
Specific toxicity of solvents is directly **related to its toxic metabolites**:

- The **cytochrome P-450 dependent mixed function oxidizes** largely **mediate the biotransformation** of these solvents.
- As a result of this process, an **oxygen is introduced** into any **chemical** that contains **favorable positioned bands**: C-H, N-H, S-H, or C-X (X - halogen).

IV. Treatment

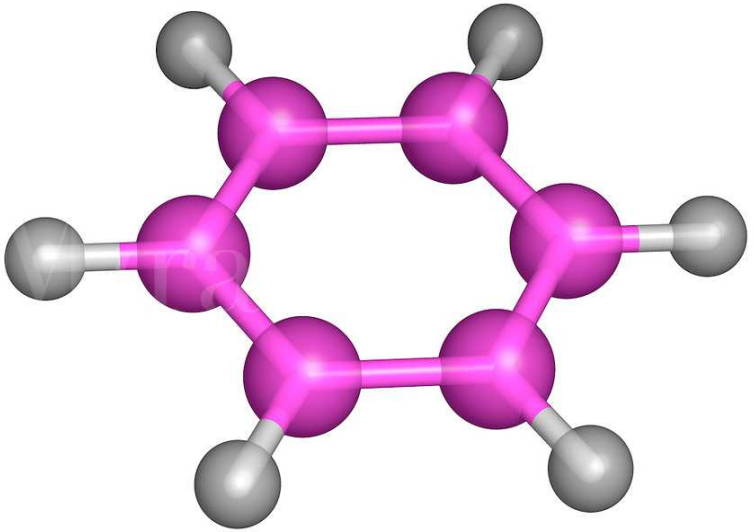
- There **are not any antidotes** for the solvents.
- The treatment is primarily:
  - ✓ **symptomatic**
  - ✓ **pathogenetic**
  - ✓ **organoprotective (liver, kidney and CNS).**





TOXICOLOGY OF BENZENE (C_6H_6)

I.Use



- Use in the industry:
  - ✓ first as a volatile solvent;
  - ✓ later as a starting material for the synthesis of other chemicals;
- Benzene has a high vapor pressure at ambient temperatures. For this reason in occupational and disaster condition usually causes intoxication via inhalation.
  - ✓ The liquid benzene penetrates partially by the skin.

II.Metabolism of benzene.

- **The benzene toxicity is produced by one or more metabolites** of benzene.
- **There are two metabolic pathways for biotransformation of benzene:**

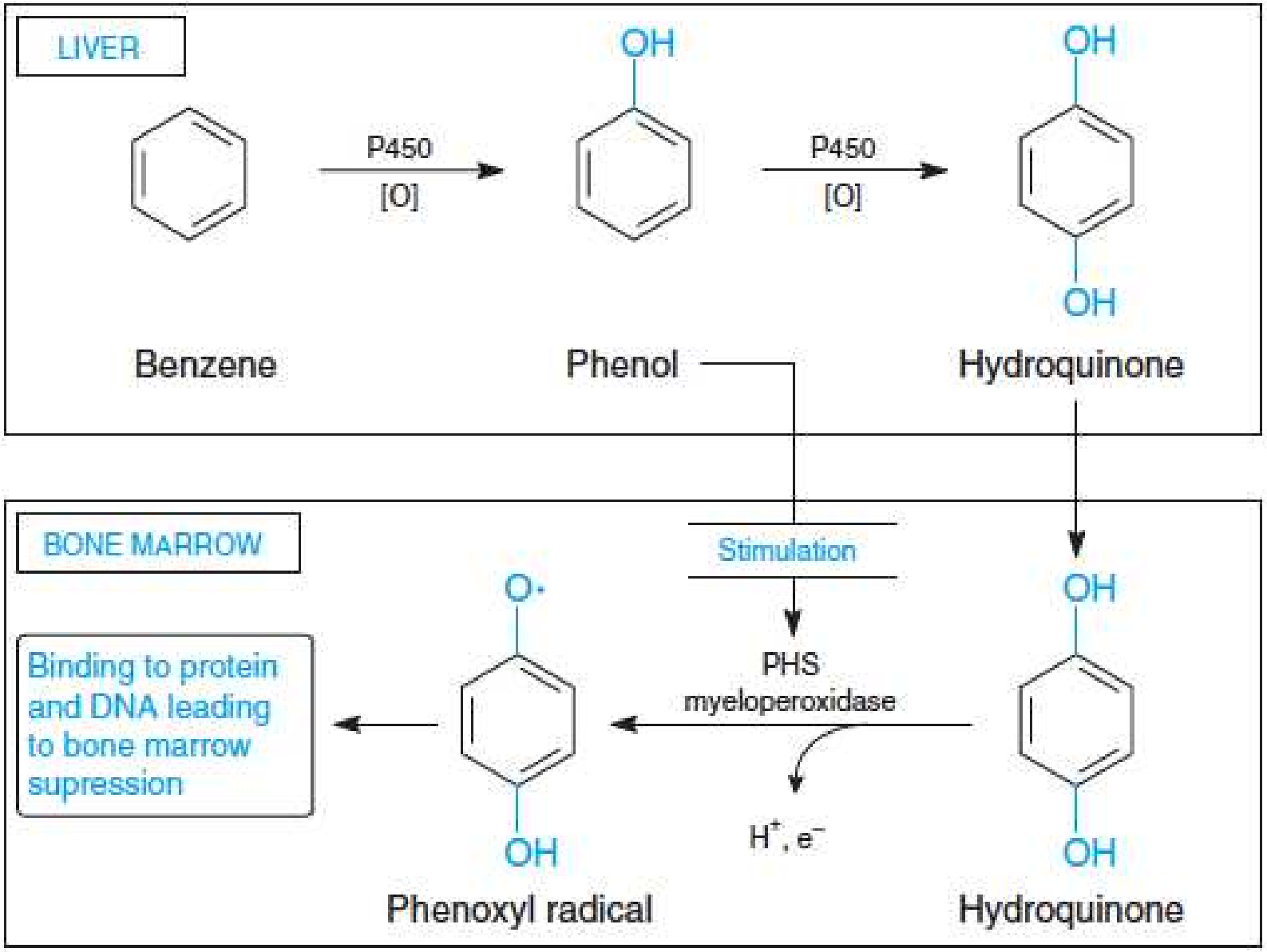
1. Benzene is converted to **benzene oxide** by **the hepatic microsomal mixed function oxidizes**. This **benzene oxide may rearrange nonenzymatically** to form:

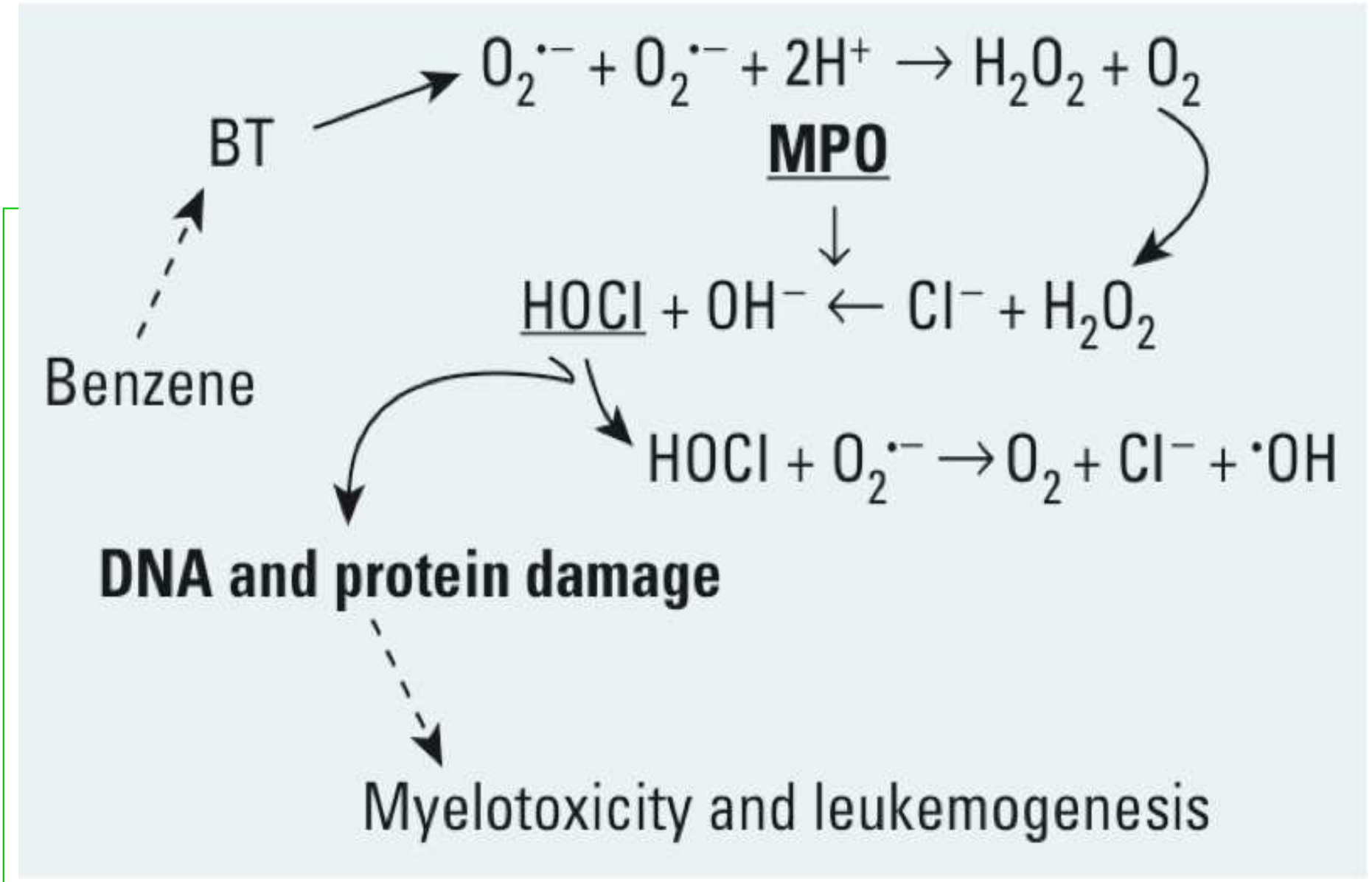
- ✓ **phenol**, which is **main benzene metabolite** (50 - 90% of absorbed benzene);
- ✓ **hydroquinone**
- ✓ **catechol**.

II.Metabolism of benzene.

2. **Second mechanism is opening the benzene ring to yield muconaldehyde**, a potential toxic metabolite. The muconaldehyde is subsequently converted to **muconic acid**.

- **The final benzene metabolites** that appear in the urine are:
  - ✓ **etheral sulfates** and **glucuronides** of the **phenol**
  - ✓ **muconic acid**
  - ✓ **mercapturic acids** resulting from glutathione conjugation


LIVER
OH
P450
[O]
P450
[O]
OH
OH
Benzene
Phenol
Hydroquinone
BONE MARROW
Stimulation
O·
OH
PHS
myeloperoxidase
Binding to protein and DNA leading to bone marrow supression
H^+, e^-
OH
OH
Phenoxyl radical
Hydroquinone


$O_2^{\bullet-} + O_2^{\bullet-} + 2H^+ \rightarrow H_2O_2 + O_2$
BT
MPO
HOCl + OH^- ← Cl^- + H_2O_2
Benzene
$HOCl + O_2^{\bullet-} \rightarrow O_2 + Cl^- + {}^{\bullet}OH$
DNA and protein damage
Myelotoxicity and leukemogenesis

III. Mechanism of toxic effects

- The **benzene toxicity and carcinogenesis** is related to:
  - the **covalent binding** of the **benzene metabolites (phenol, hydroquinone, etc.) to cellular macromolecules** (**proteins in liver, bone marrow, kidney, spleen and muscles**)
  - the **covalent binding of benzene metabolites to DNA** leading to **inhibition of cell replication** or to initiation of **leukemia**
  - inhibition of **specific enzymes** by the benzene metabolites

IV.Clinical presentation

a)Acute poisoning

The exposure to high concentration of benzene causes:

- ✓ **euphoria**
- ✓ **cephalgia**
- ✓ **confusion**
- ✓ **unconsciousness**
- ✓ **convulsions**

Very **high concentration** of benzene may kill by:

- ✓ **depressing the central nervous system** (the respiration);
- ✓ producing **fatal cardiac arrhythmia**;

IV.Clinical presentation

b) Chronic poisoning

Chronic exposure to low levels of benzene is associated with **blood disorders:**

- **a progressive decrease in each of the circulating elements of the blood;**
- first, the **leucocytes;**
- second, the **thrombocytes**;
- third, the **erythrocytes**;
- finally, **pancytopenia**, when all three-cell types are sufficiently depressed;

In case of pancytopenia, morphologically is observed **necrosis and fatty replacement of bone marrow.**

c) leukemia - the most commonly is the acute myelogenous leukemia. It is characterized by an increased number of cells, morphologically similar to the myeloblasts.

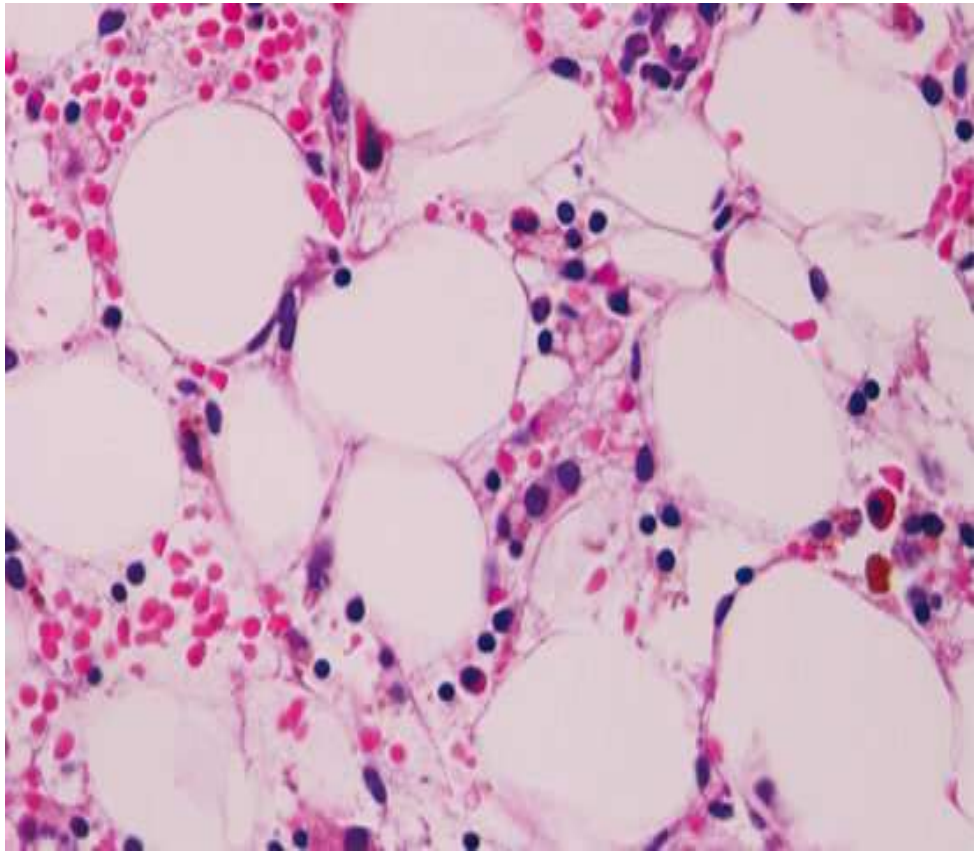
Haematological diseases of chronic benzene exposure

Aplastic Anemia

(**bone marrow aplasia**)

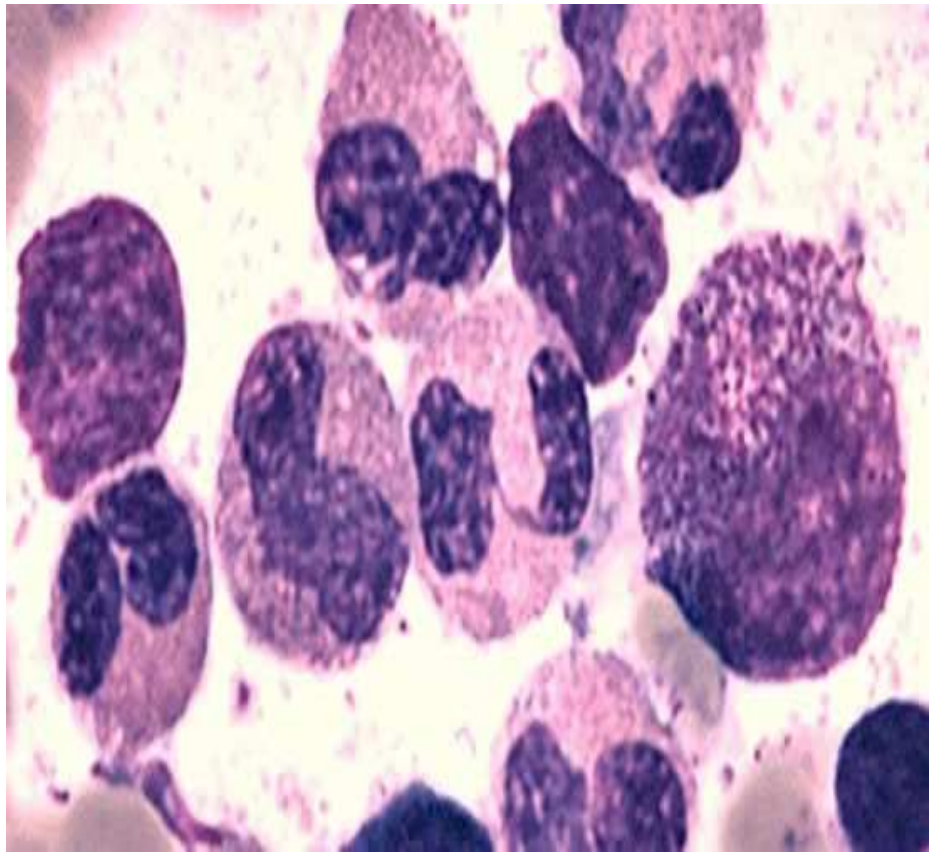
Strong reduction in the number of blood cells.

infection bleeding



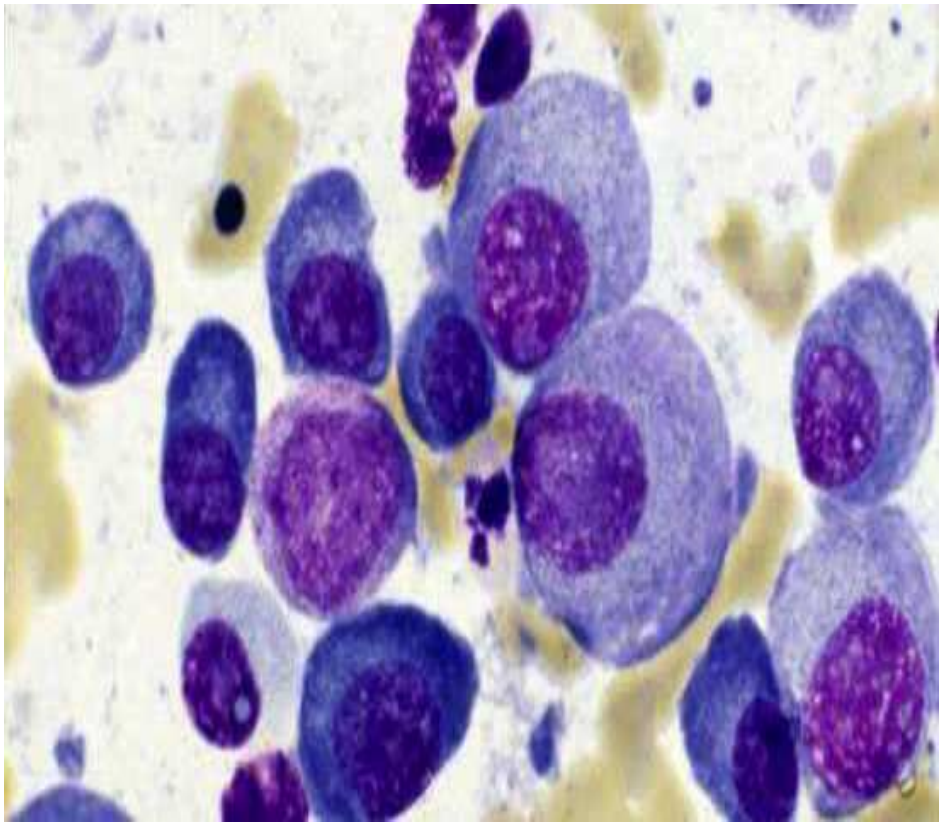
Myelodysplastic Syndromes (MDS)

MDS are clonal diseases of stem cells characterized by single or multilinease cytopenia and various bone marrow abnormalities. Up to 35% of MDS patients progress of Acute myeloid Leukemia (AML) within a few months of initial diagnosis and the MDS has sometimes been haracterized as a preleukemic condition or simply preleukemia."



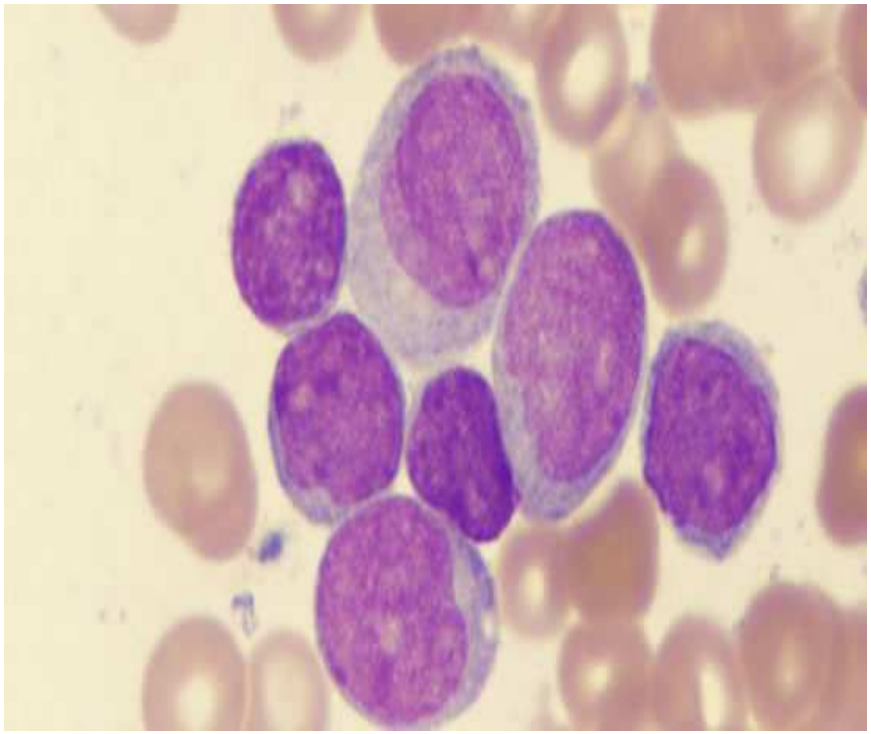
Multiple Myeloma (Kahler's disease, subtype of non-Hodgkin's lymphoma)

It is a cancer of the **plasma cells**. Multiple myeloma has been reported in workers exposed to petrochemicals, especially those occupationally exposed to benzene. Elevated risks of multiple myeloma have been reported among farmers and others engaged in agricultural operations, metal workers, rubber manufacturing workers and painters. **Benzene** is the chemical most strongly associated with multiple myeloma.

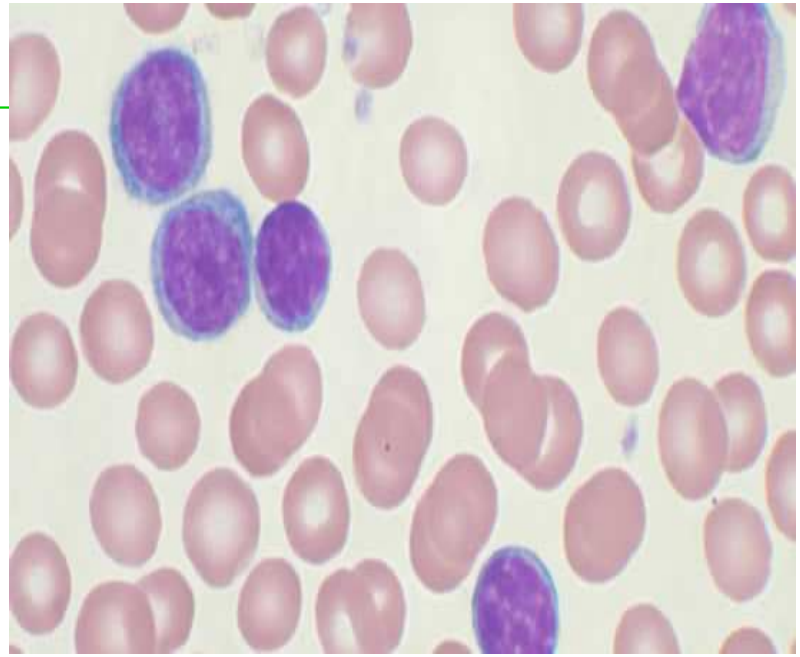


Acute Myelogenous Leukemia (AML)

AML is an aggressive cancer of the blood. There are many types of leukemia. However, AML is the type of leukemia that is most strongly associated with benzene exposure.



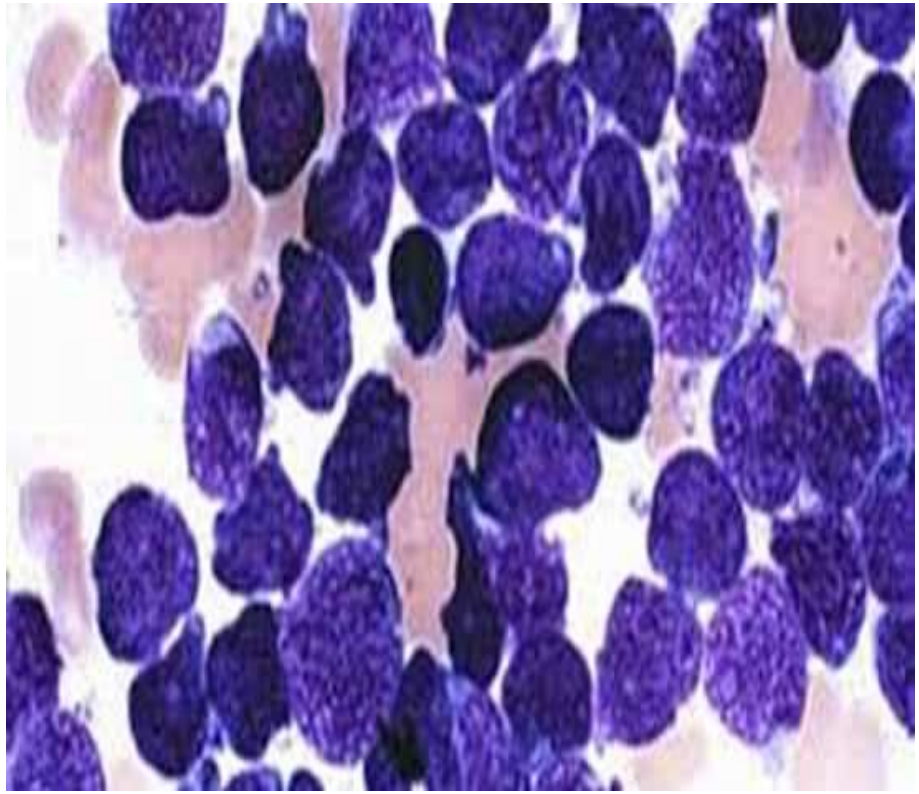
Chronic Lymphocytic Leukemia (CLL)



CLL has been reported in workers exposed to pure benzene and benzene containing chemicals such as gasoline, crude oil, toluene, naphtha, xylene and other solvents.Benzene is the chemical most strongly associated with CLL.
CLL is a form of leukemia that starts from lymphocytes in the bone marrow but then go into the blood.

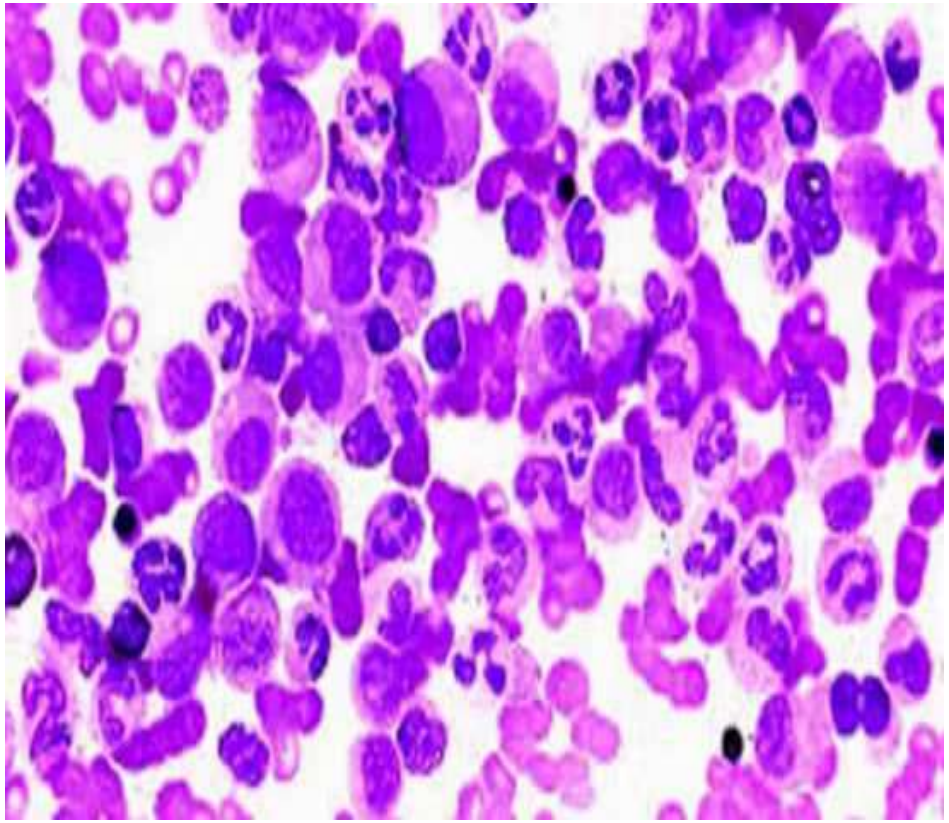
Acute Lymphocytic (Lymphoblastic) Leukemia (ALL)

Benzene is the chemical most strongly associated with ALL.

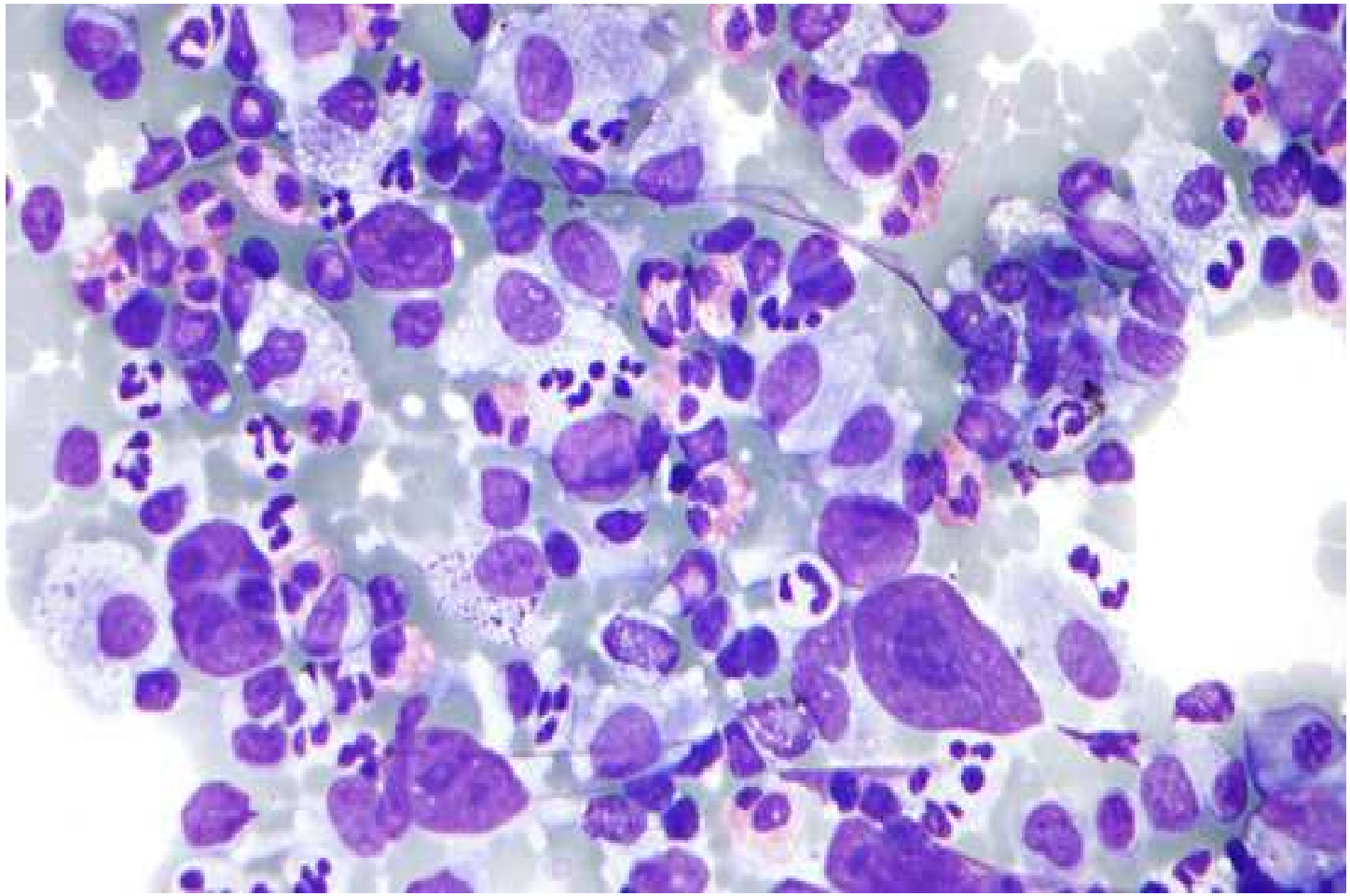


Chronic Myeloid (Myelogenous) Leukemia (CML)

CML is a slow growing leukemia, but it can also change into a fast-growing acute leukemia. CML has been reported in workers exposed to pure benzene and benzene containing chemicals. Benzene is the chemical most strongly associated with CML.



Non-Hodgkin's Lymphoma



V.Treatment

There is not any specific anti-benzene antidotes.

The treatment is:

- **symptomatic**
- **pathogenetic** (convulsion, coma, respiration and cardiac disorders)
- **organoprptective** (liver, CNS)

CHLORINATED HYDROCARBONS

General Structure

– H of hydrocarbon replaced by F, Cl, Br, I

Names

– Halogen named as substituent group

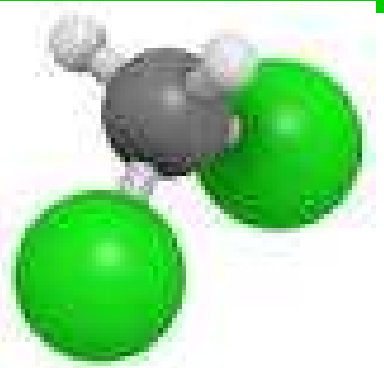
F –fluoro Cl - chloro

Br-bromo I - iodo

– Examples:

- **dichloromethane = CH2Cl2**
- **1,2-dibromoethane = CH2Br-CH2Br**

1. Dichloromethane

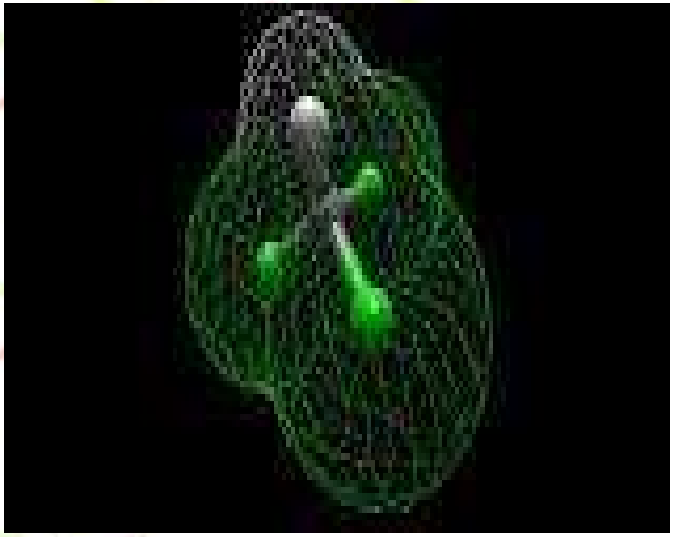


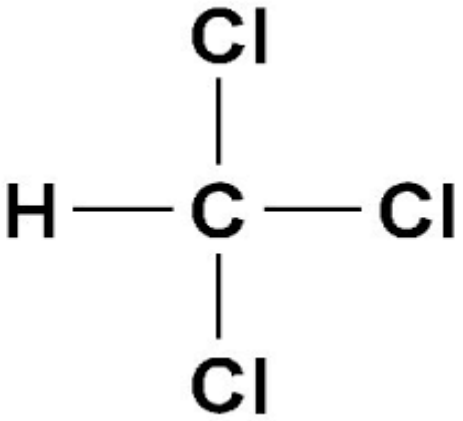
- **Dichloromethane** (**methylene chloride** – (CH_2Cl_2) is typical compound of the chlorinated hydrocarbons.
- **Dichloromethane is coloreless liquid with a chloroformic like odor.** It is **used** for:
  - ✓ **removing paint and degreasing;**
  - ✓ **extracting of foods** (e.g. for the removal at caffeine from coffee);
  - ✓ **manufacture of plastics**, etc.

1. Dichloromethane

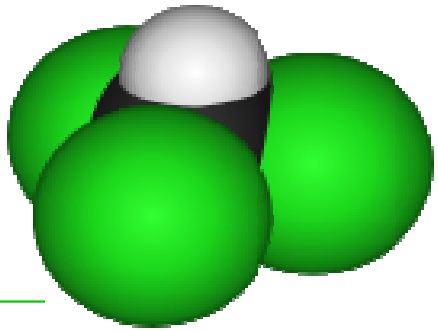
- The metabolism of the **dichloromethane** leads **to dehalogenation and the end product is carbon monoxide**. As a result an elevation in **carboxyhemoglobin** levels may be observed.
- The acute effects include:
- **eye and throat irritation**
- **cough**
- **fatigue**
- **decreased manual performance**
- **sensory and psychomotor disturbances**

Chronic exposure to low concentrations of dichloromethane **does not increase the cancer risk** or **chronic neurotoxicity**.



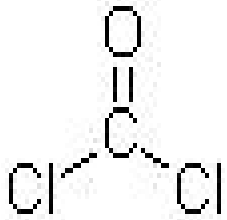


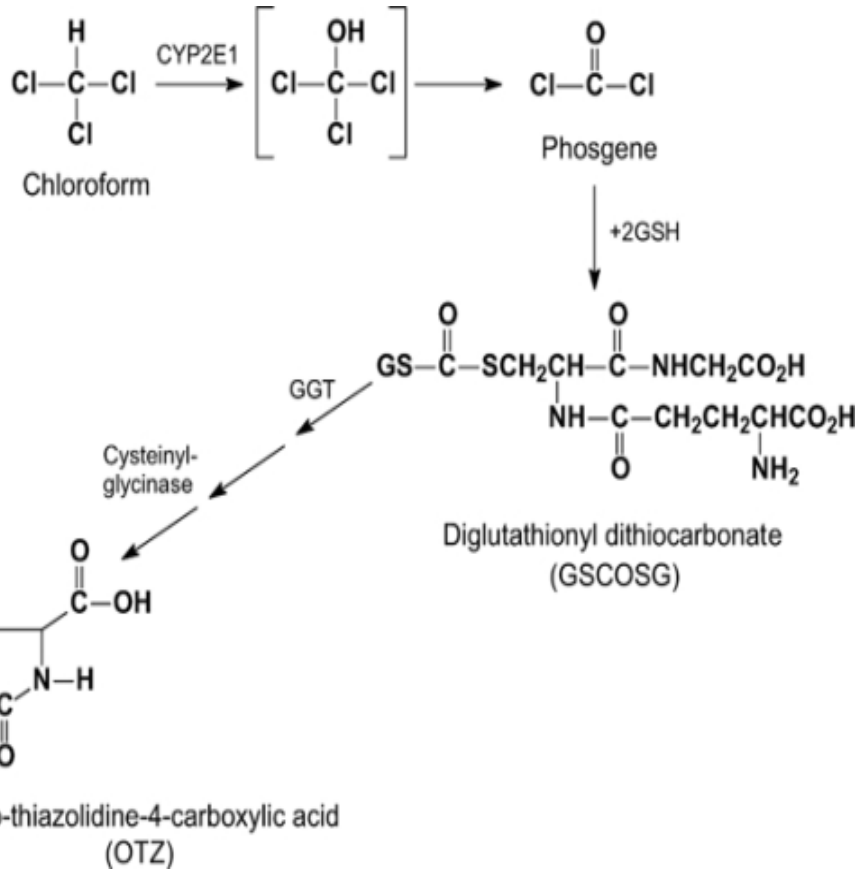
CHLOROFORM

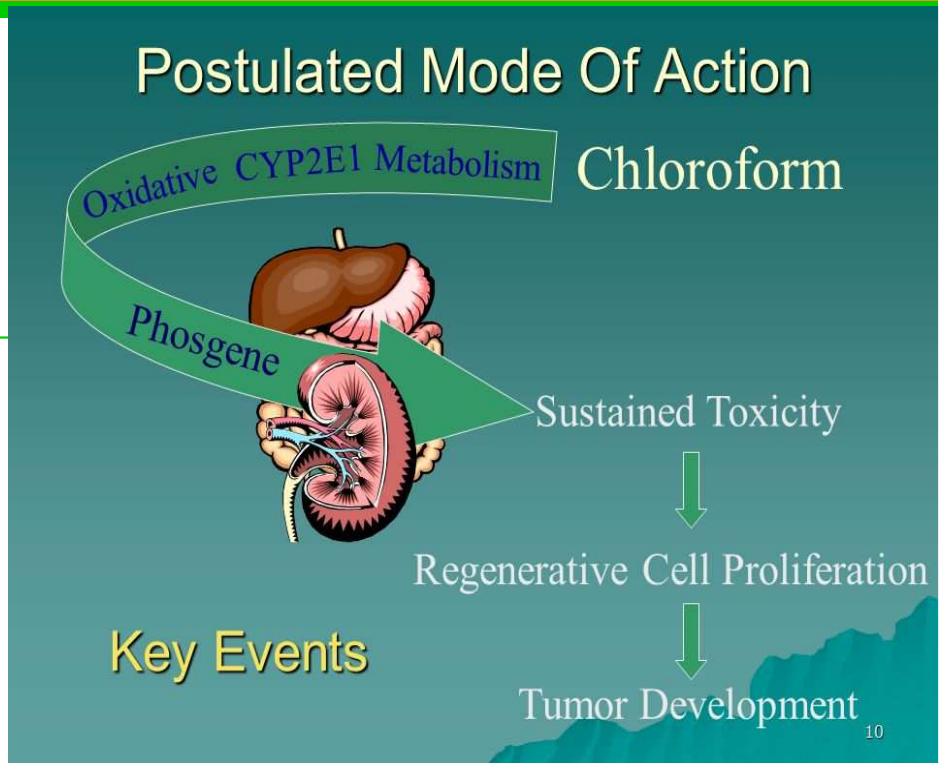


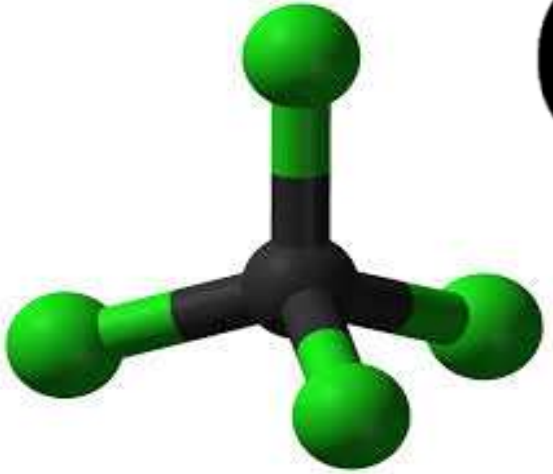
- The **primary toxic effect** of **high-level exposure** to **chloroform ($CHCl_3$)** is **depression (narcosis)** on the **CNS**.
- **Exposure** to **very high levels** of chloroform **can damage liver and kidney** and produce **cardiac arrhythmia.**
- **In humans** who have developed **liver failure following anesthesia**, symptoms were observed **within a few days** as follow:
  - ✓ **nausea**
  - ✓ **vomiting**
  - ✓ **jaundice**
  - ✓ **coma**
  - ✓ **upon autopsy: centrolobular necrosis** into **periportal areas**

- **Repeated exposure** to low, **subnarcotic levels** of chloroform can also cause **liver and kidney injury**.
- The **primary mechanism** of the chloroform toxicity is formation of **reactive metabolites that:**
  - ✓ **covalently bind to hepatic proteins**
  - ✓ **deplete the liver of glutathione**
  - ✓ **phosgene formation**

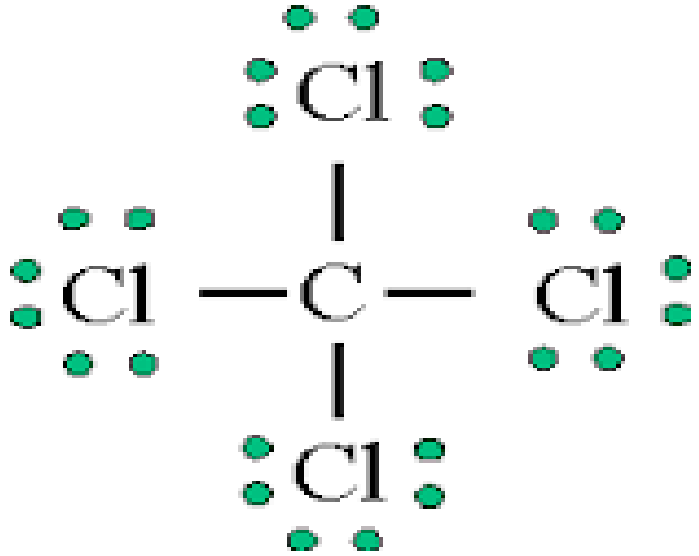



CYP2E1
Chloroform
Phosgene
+2GSH
GGT
Cysteinyl-
glycinase
Diglutathionyl dithiocarbonate
(GSCOSG)
2-Oxo-thiazolidine-4-carboxylic acid
(OTZ)

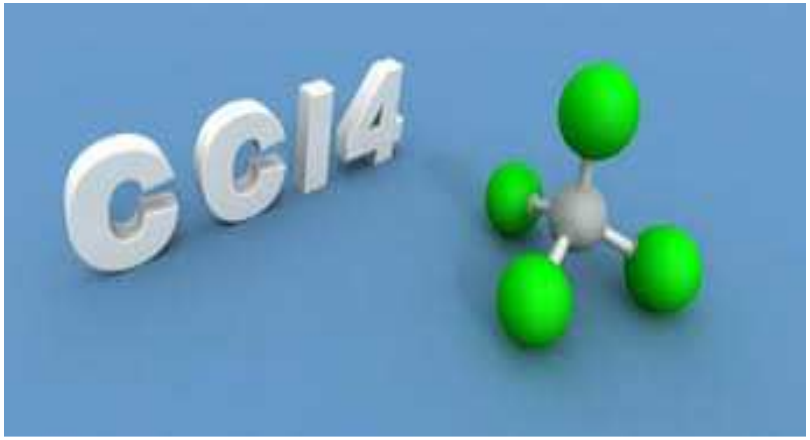

Postulated Mode Of Action
Oxidative CYP2E1 Metabolism
Chloroform
Phosgene
Sustained Toxicity
Regenerative Cell Proliferation
Key Events
Tumor Development
10

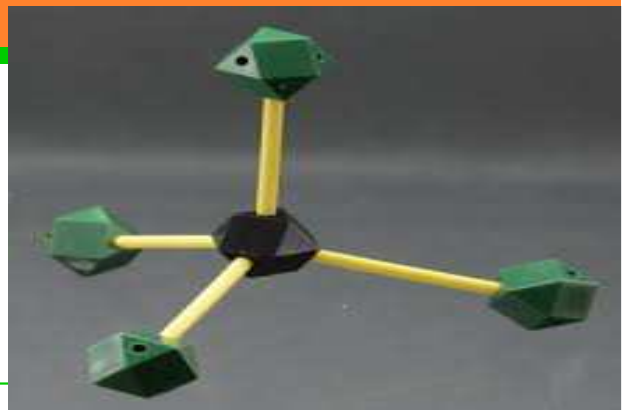


CCl_4



CARBON TETRACHLORIDE

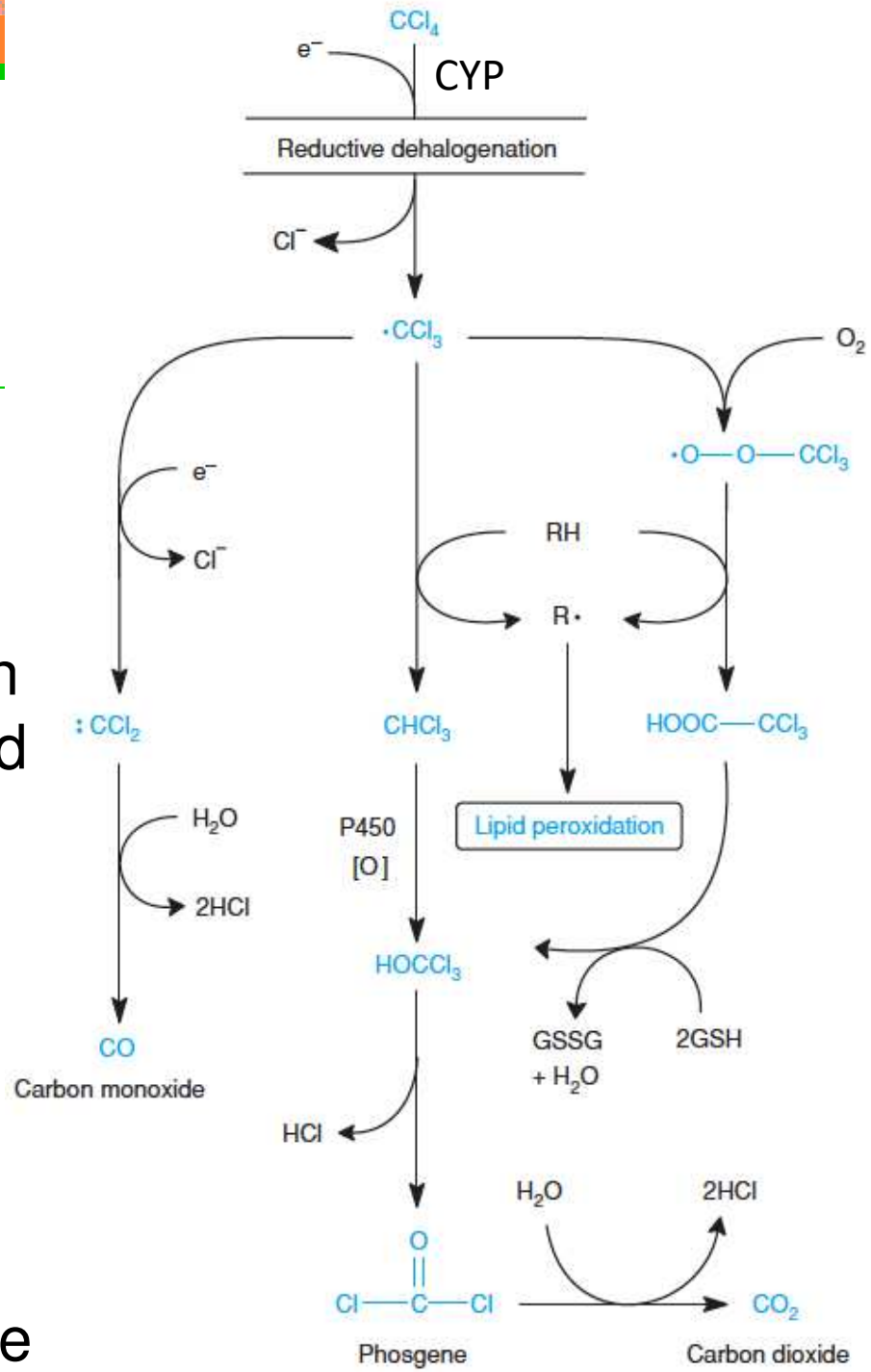




- **Carbon tetrachloride** (**CCl_4, tetrachloromethane**) causes severe form of **toxic hepatitis.**
- **A single application of toxic dose of carbon tetrachloride** leads to:
  - ✓ **centrolobular necrosis**
  - ✓ **increased activities** of **transaminases**, **lactic dehydrogenase and gamma glutamyl transpeptidase** and total content of **bilirubin** in serum.
- **The mechanism of** toxicity **involves:**
  - ✓ **first,** formation of **trichloromethyl** and **chlorine free radicals by cytochrome P-450.**
  - ✓ **second, attacks on the enoic fatty acids** in the **membranes** and the **enzymes** by the trichloromethyl free radical

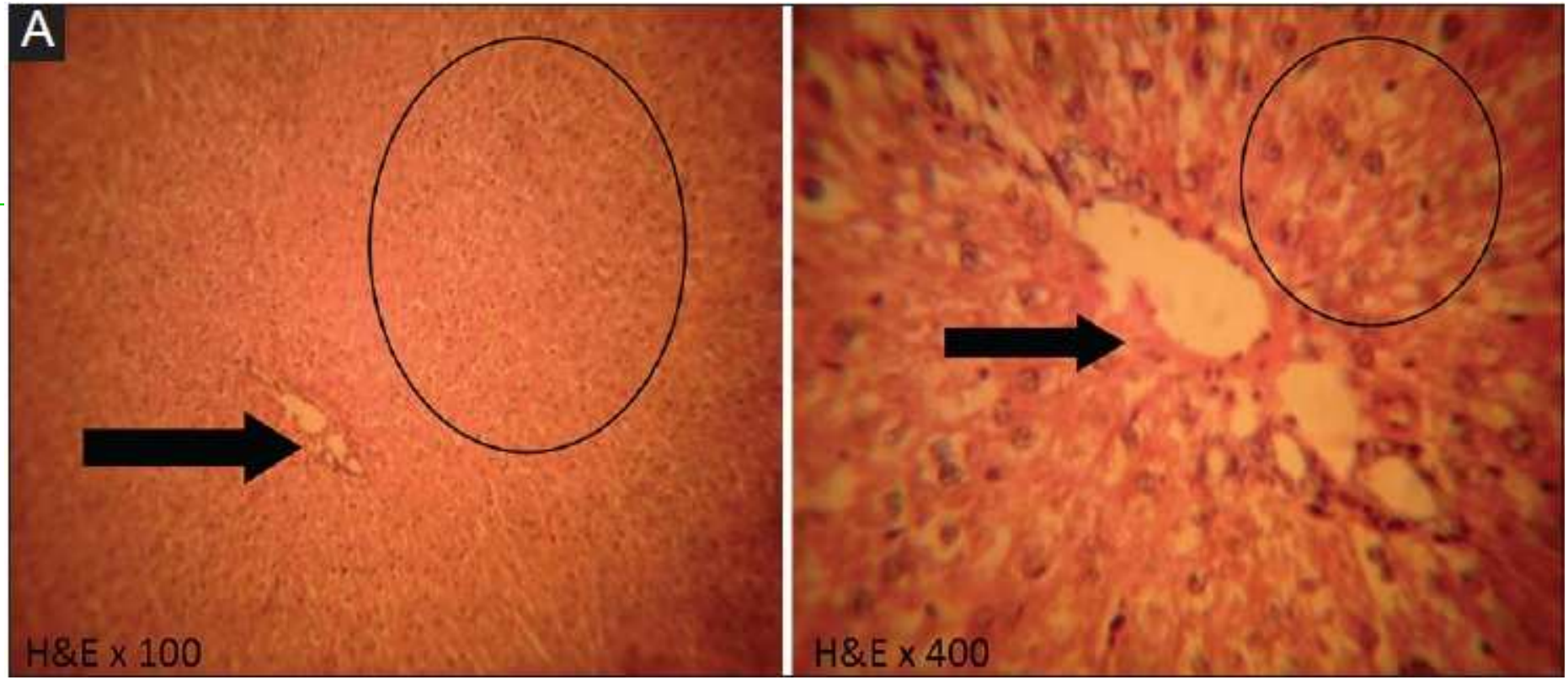
Carbon Tetrachloride

- One of the most potent hepatotoxins, also causes ozone depletion
- Causes liver necrosis, and can also affect nervous system and kidneys.
- Can cause liver cancer, liver fibrosis, liver damage, liver failure
- Replaced by **tetrachloroethylene**, also carcinogenic - similar mechanism to trichloroethylene

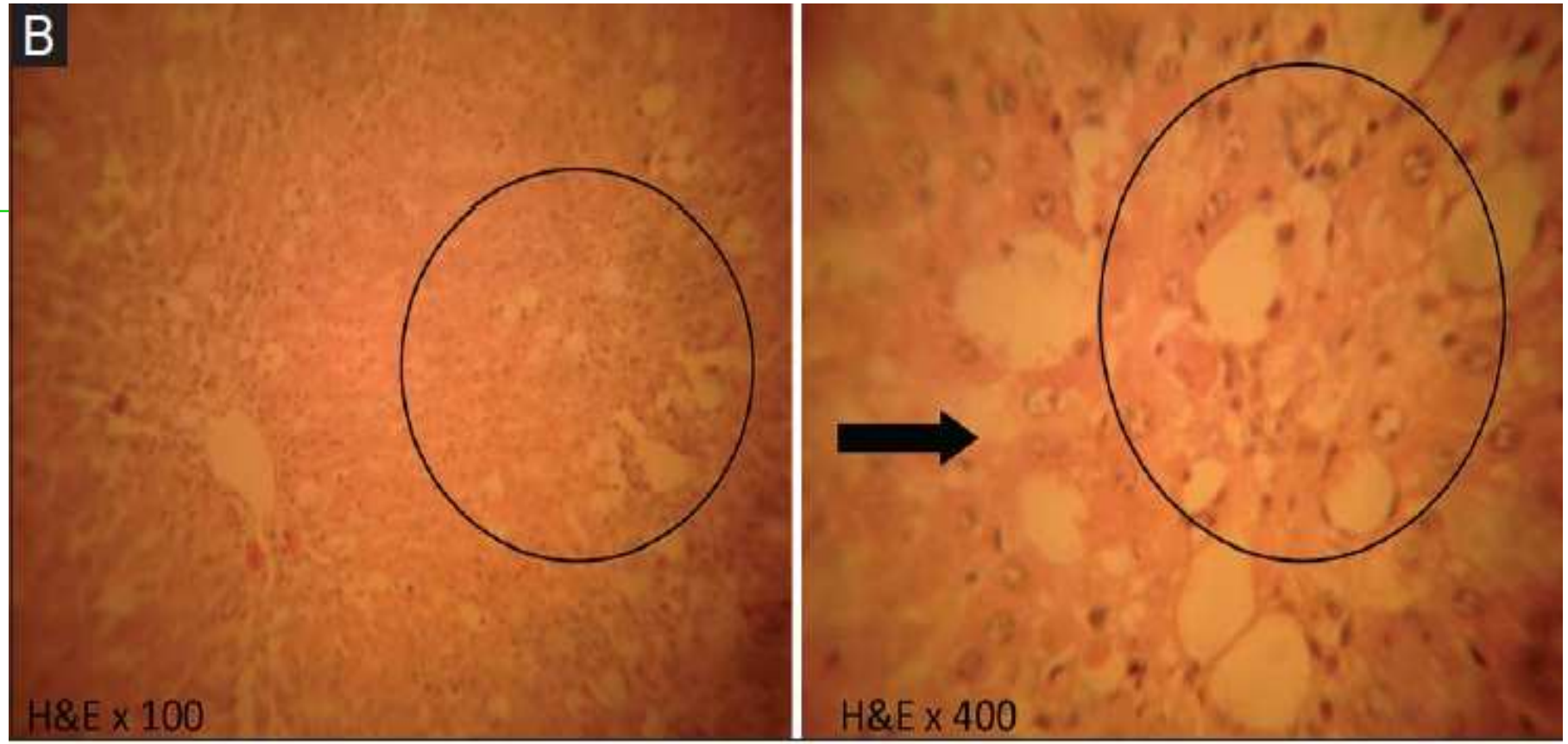


Inhibit microsomal ATP-ase activity within minutes.
Single cell necrosis 5-6 hr.
Maximal centrolobular necrosis 24-48 h.

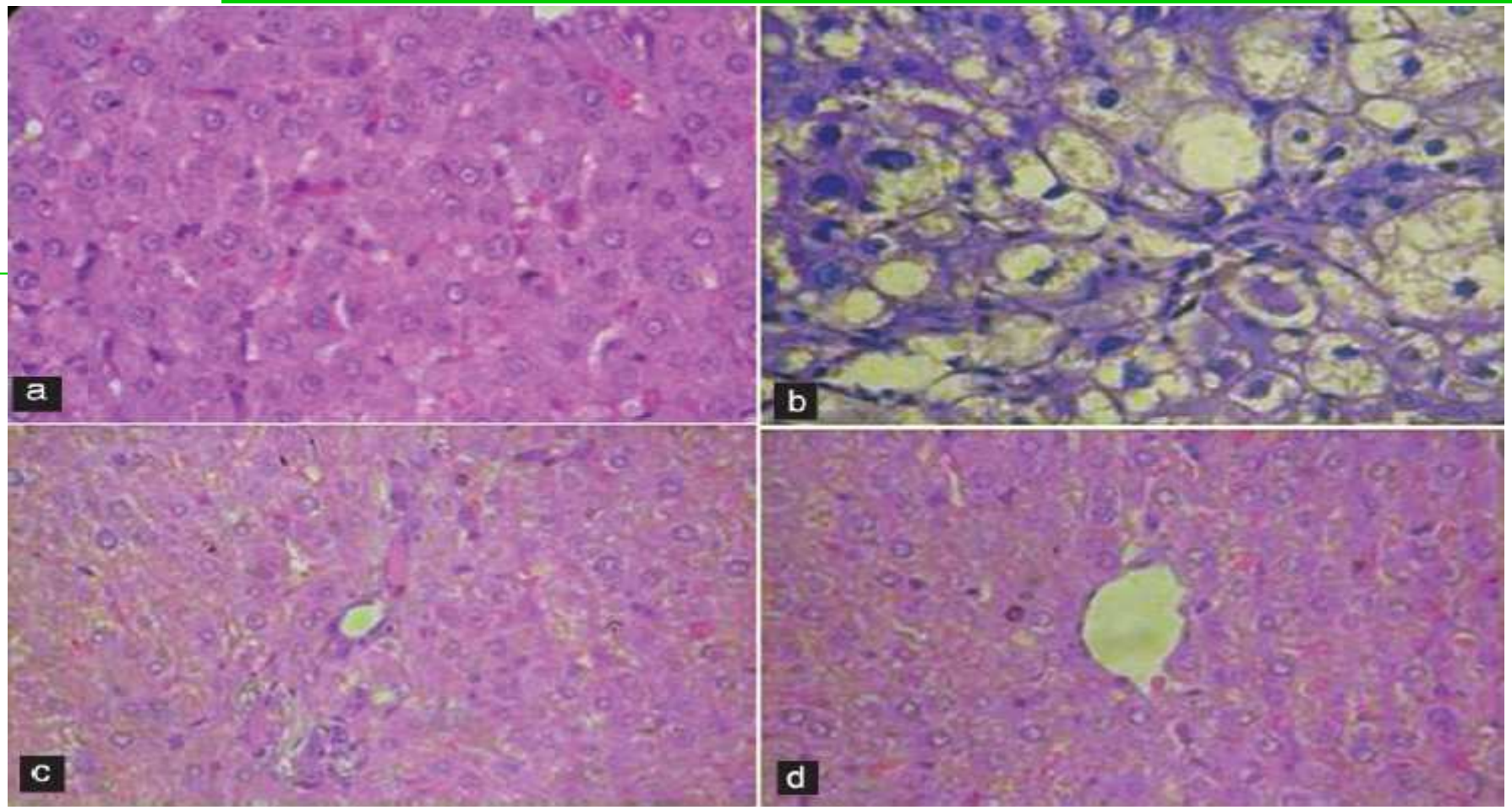
CYP2E1 inhibitors can prevent CCl4 toxicity



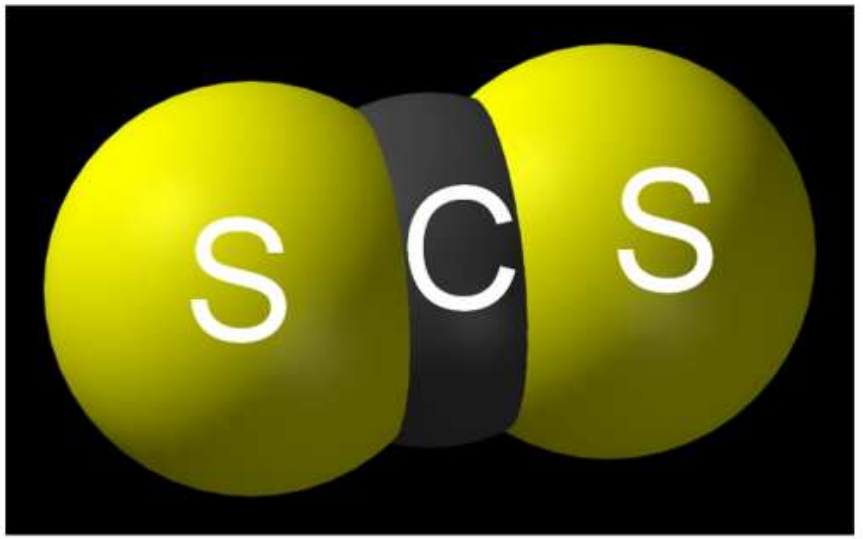
Liver tissue of control animals (Group A) showing a normal portal triad (arrow) and hepatocytes (circle)



Liver tissue of Group B (treated with Carbon tetrachloride). Cytoplasmic deposit of large fat globules (circle) and degeneration of hepatocyte (arrow)

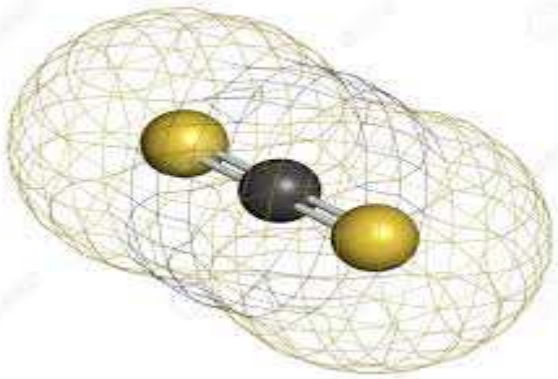


a) Histology of the liver sections of control animals - normal hepatic cells with well preserved cytoplasm, prominent nucleus, nucleolus and visible central veins;
b) The liver sections of CCl4-intoxicated rats - intense centrilobular necrosis, vacuolization, macrovesicular fatty changes showing massive fatty accumulation in the hepatocytes, and broad infiltration of the lymphocytes and the loss of cellular boundaries;



CS_2

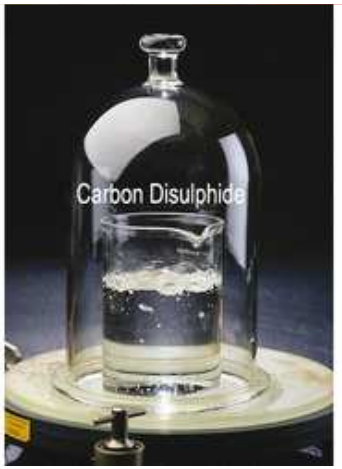
CARBON DISULFIDE



- **Carbon disulfide (CS_2)** is primarily used in:
  - ✓ production of **rayon** and **cellophane**
  - ✓ **manufacture of carbon tetrachloride**
  - ✓ as **a solvent for resins, rubber and fats**
  - ✓ **as a pesticide**
  - ✓ **as preservative** for fresh **fruit**
- **Metabolism**
  - ✓ following **exposure to carbon disulfide very little of the parent compound is excreted unchanged**;
  - ✓ **most of the absorbed dose** is excreted as **sulfur - containing urinary metabolites (dithiocarbamates);**

- The **mechanism of carbon disulfide** toxicity is not well studied.
  - **Carbon disulfide** reacts with **amine groups** of **cellular enzymes,** and thereby causing **cellular damage.**
  - **Dithiocarbamates** (the metabolites of carbon disulfide) are known to **chelate metal ions**, such **as copper and zinc** which are necessary for **neuronal enzyme function**.
- Toxic effects of human exposure to high levels carbon disulfide include:
  - **organic brain damage**
  - **peripheral nervous system injury**
  - **neurobehavioral dysfunction**
  - **ocular and auditory effects**

- Carbon disulfide-induced **encephalopathy** have the following symptoms:
  - **headache**
  - **sleep disturbance**
  - **general fatigue**
  - **emotional labiality**
  - **impairment of memory for recent events**
  - **“Parkinson" syndrome** (**in young subjects**)
- Carbon disulfide exposure also may **cause peripheral neuropathy (relatively mild)** including:
  - **muscle cramps**
  - **muscle pain**
  - **paresthesias**
  - **muscle weakness**
  - **tremor**



- **Ocular and auditory effects** of carbon disulfide:
  - ✓ **changes in the** fundal morphology, sensitivity and motility (of the eyes)
  - ✓ **hearing loss to high-frequency tones**
- **Postmortal findings** in case of very high level exposure **consist**:
  - ✓ **neuronal degeneration;**
  - ✓ **cell loss,** diffusely distributed over the **cerebral cortex, globus pallidus and putamen**;