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Biochemistry of environmental pollution (649 ch)

for premaster students of biochemistry

LECTURES 6, 7 , 8 & 9

Drug abuse, Paints toxicity, Ammonia toxicity & Benzene toxicity.

Drug abuse

Presented by :

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Under supervision of :

Prof . dr. Elshahat Toson

- Different types of drugs affect your body in different ways, and the effects associated with drugs can vary from person to person.
- How a drug effects an individual is dependent on a variety of factors including :

- **body size**
- **general health**
- **the amount and strength of the drug**
- **whether any other drugs are in the system at the same time**.

- It is important to remember that illegal drugs are not controlled substances, and therefore the quality and strength may differ from one batch to another.
- Drugs can have short-term and long-term effects. These effects can be physical and psychological , and can also affect your work and social life.

- As explained in an article from the National Institute on Drug Abuse (NIDA), drug abuse over long periods of time makes changes to the brain and body that can have negative effects on a person’s overall health and well being, both physically and mentally. The pathways through which drugs of abuse deliver a “high” are the same mechanisms that can cause damage to the body’s various functional systems, having a negative effect to health in the long-term.

Risk factors for drug-related harm

- **The effects of a drug, and how long they last, depend on a number of factors:**

- The type and strength of drugs .
- Your physical characteristics (including height, weight, age, body fat and metabolism) .
- The dose that you take .
- How often and for how long you have been using drugs .
- How you ingest the drug (by inhalation, by injection or orally). Compared with swallowing a drug, inhalation and injection are more likely to lead to overdose and dependence. If you are injecting drugs, sharing injecting equipment will increase your risk of contracting serious diseases such as hepatitis and HIV. It will also increase your risk of serious infection.
- How the drug was made substances manufactured in home labs may contain bacteria, dangerous chemicals and other unsafe substances.

Physical harms from drug use

- Drug use can affect short- and long-term health outcomes. Some of these health outcomes can be serious, and possibly irreversible.
- **Drug use can lead to risky or out of character behaviour. When affected by drugs:**

➢ You are more likely to have an accident (at home, in a car, or wherever you are).

➢ pregnancy and sexually transmitted infection.

➢ You could commit a violent act.

➢ You may find it hard to sleep, think, reason, remember and solve problems.

Effects of Drug Abuse on Long-Term Health

1. Harm to organs and systems in your body, such as your throat, stomach, lungs, liver, pancreas, heart , brain, nervous system .
2. Cancer (such as lung cancer from inhaling drugs) infectious disease, from shared injecting equipment and increased incidence of risk-taking behaviors.
3. Harm to your baby, if you are pregnant.
4. Acne, or skin lesions if the drug you are taking causes you to pick or scratch at your skin.
5. Needle marks and collapsed veins, if you inject regularly.
6. Baldness.
7. Male pattern hair growth in women, such as facial hair.
8. Mood swings and erratic behavior.
9. Addiction.
10. Psychosis (losing touch with reality).
11. Higher risk of mental illness, depression, suicide and death.

Drugs affect your body's central nervous system

- They affect how you think, feel and behave. The three main types are **depressants, hallucinogens and stimulants:**

1. **Depressants** slow or 'depress' the function of the central nervous system. They slow the messages going to and from your brain. In small quantities depressants can cause a person to feel relaxed and less inhibited. In large amounts they may cause vomiting, unconsciousness and death. Depressants affect your concentration and coordination, and slow your ability to respond to situations.

- Alcohol, cannabis, GHB, heroin, morphine, codeine and benzodiazepines are examples of depressants.

Drugs affect your body's central nervous system

2. Hallucinogens distort your sense of reality. You may see or hear things that are not really there, or see things in a distorted way.

- Other effects can include : jaw clenching, panic, paranoia, gastric upset and nausea.
- Ketamine, magic mushrooms and cannabis are examples of hallucinogens.

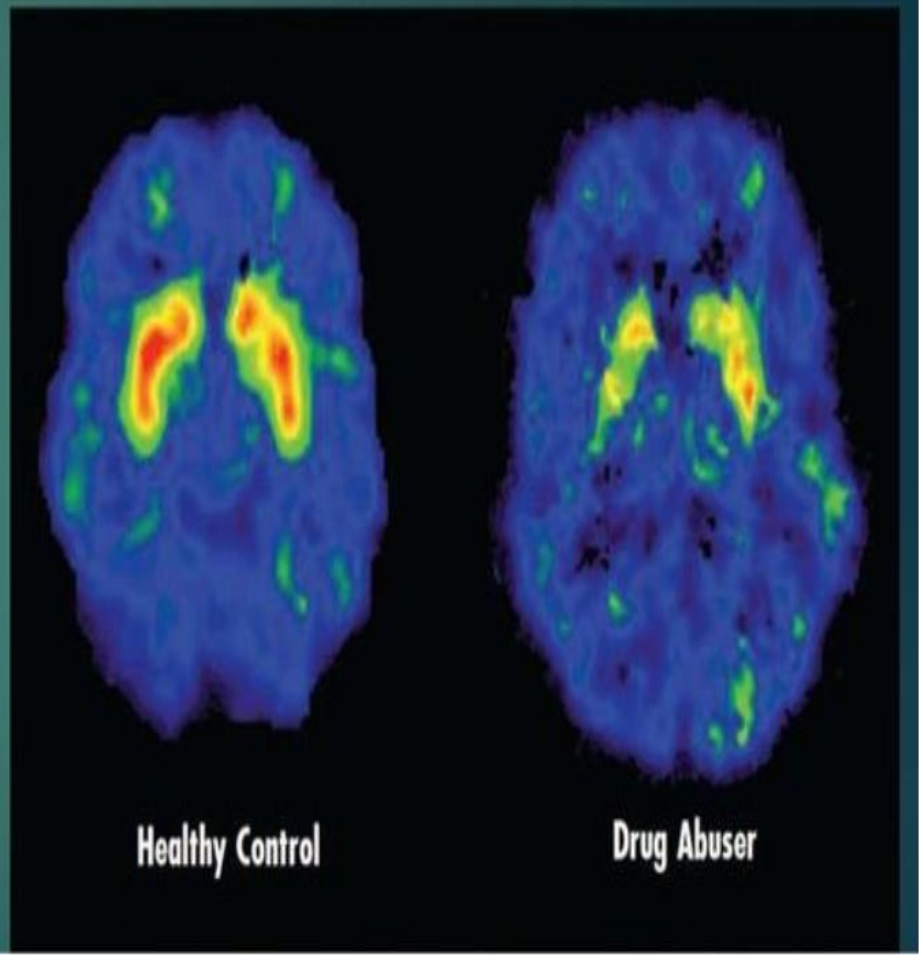
Drugs affect your body's central nervous system

3. Stimulants speed or 'stimulate' the central nervous system. They speed up messaging to and from the brain, making you feel more alert and confident. This can cause increased heart rate, blood pressure and body temperature, reduced appetite, agitation and sleeplessness. In large amounts stimulants may cause anxiety, panic, stomach cramps and paranoia.

- Caffeine, nicotine, amphetamines (speed and Ice), cocaine and ecstasy (MDMA) are examples of stimulants.

Effects of Drugs of Abuse on the Brain

- All drugs that are addicting can activate the brain's pleasure circuit. Drug addiction is a biological, pathological process that alters the way in which the pleasure center, as well as other parts of the brain, functions.
- Prolonged drug use changes the brain in fundamental and long-lasting ways. These long-lasting changes are a major component of the addiction itself.



Health Effects of Drug Abuse during Pregnancy

The health effects of drug abuse are not just a concern for the individual using drugs. In the case of a woman who is abusing drugs while pregnant, the long-term health of the child can be affected as well. A study from Pediatrics reports that babies born to women who abuse drugs during pregnancy may have physical, emotional, and mental health issues during childhood and even throughout their lives, including:

1. Slowed or impeded physical growth.
2. Delayed development of language abilities.
3. Slowed cognitive development, learning disabilities, and decreased intellectual capabilities.
4. Increased risk of behavioral issues, including hyperactivity, attention deficit, and delinquency.
5. Increased risk of mental health disorders later in life, including substance abuse.

Effects of common drugs

1. Cannabis (marijuana):

- May cause relaxation .
- Can lead to increased heart rate and low blood pressure.
- Can make you feel relaxed and happy, but can also cause anxiety, paranoia, and psychosis in extreme cases. A history or family history of mental illness may increase the possibility of more extreme psychotic reactions.
- Is linked to mental health problems such as schizophrenia and, when smoked, to lung diseases such as asthma, chronic bronchitis and lung, throat, mouth and tongue cancer
- Affects how your brain works. Regular use can make it hard for you to concentrate, learn and retain information
- Reduces your fertility.
- When mixed with tobacco, is likely to increase the risk of heart disease and lung cancer.

2. Cocaine

1. Gives you increased energy .
2. Makes you feel happy, awake, confident and less inhibited, but has a nasty 'come down' that makes you feel depressed and unwell.
3. Can overstimulate the heart and nervous system and lead to a seizure, brain haemorrhage, stroke or heart attack (people have died from cocaine-induced heart failure).
4. Reduces your pain perception and may result in injury.
5. Carries greater risk if mixed with alcohol or other stimulants, especially if you have high blood pressure or if you have an existing heart condition.
6. Can harm your baby during pregnancy, and may cause miscarriage .
7. Can increase the risk of mental health issues such a s anxiety and paranoia .
8. Can cause damage to the lining of the nasal passage and nose.
9. If injected, can cause vein collapse and increased risk of HIV and hepatitis infection.

COCAINE mechanism of action

1.Block reuptake of biogenic amines: Dopamine, Nor-epinephrine,Epinephrine,Serotonin.

↑epinephrine→tachycardia

↑nor-epinephrine→hypertension

↑dopamine,serotonin→cocaine addiction

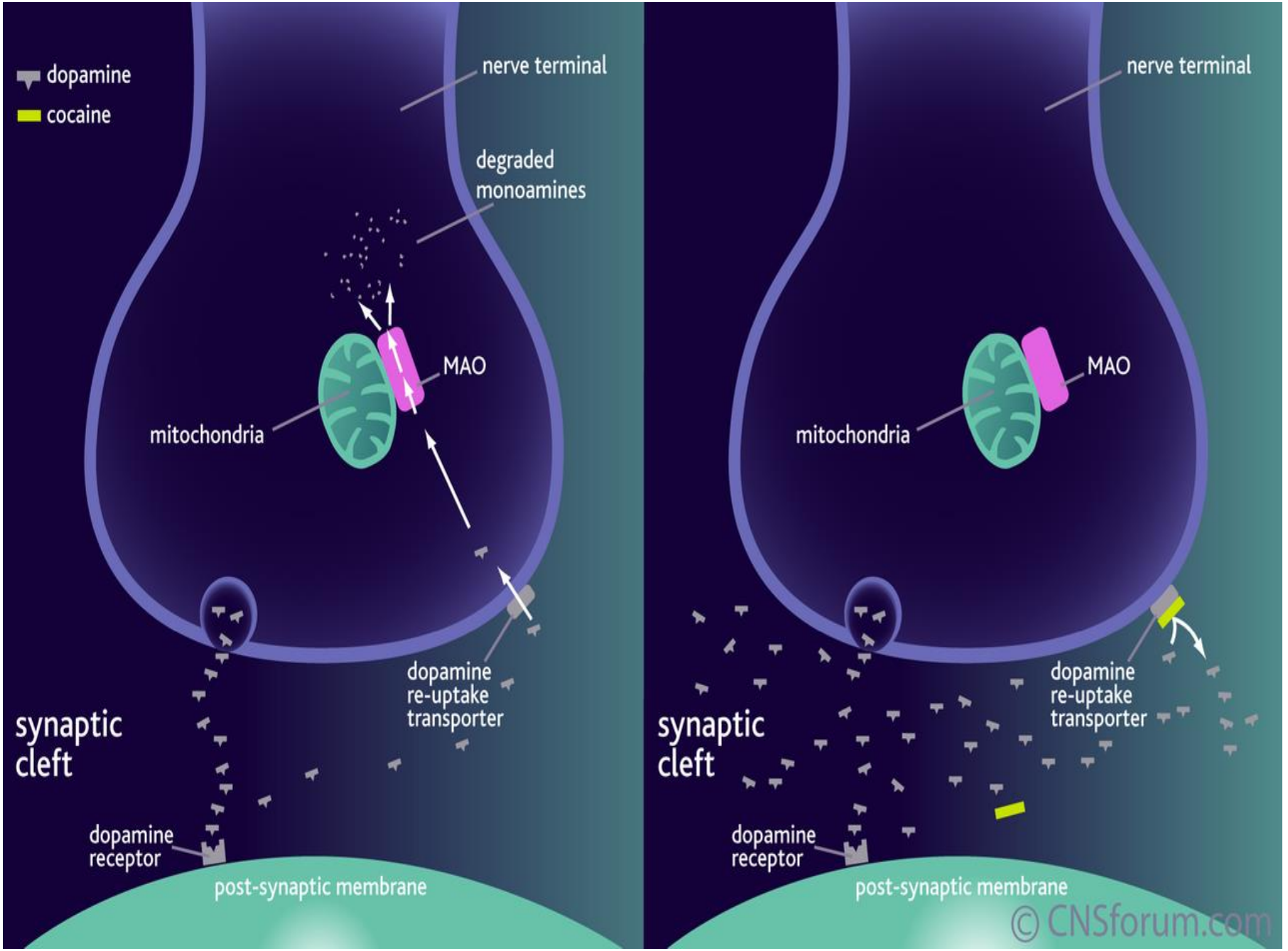
↑serotonin→seizures

2.Increses excitatory amino acid concentration in brain:

-psychomotor agitation

-hyperthermia

-seizures


dopamine
cocaine
nerve terminal
degraded
monoamines
MAO
mitochondria
dopamine
re-uptake
transporter
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cleft
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receptor
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nerve terminal
MAO
mitochondria
dopamine
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dopamine
receptor
post-synaptic membrane
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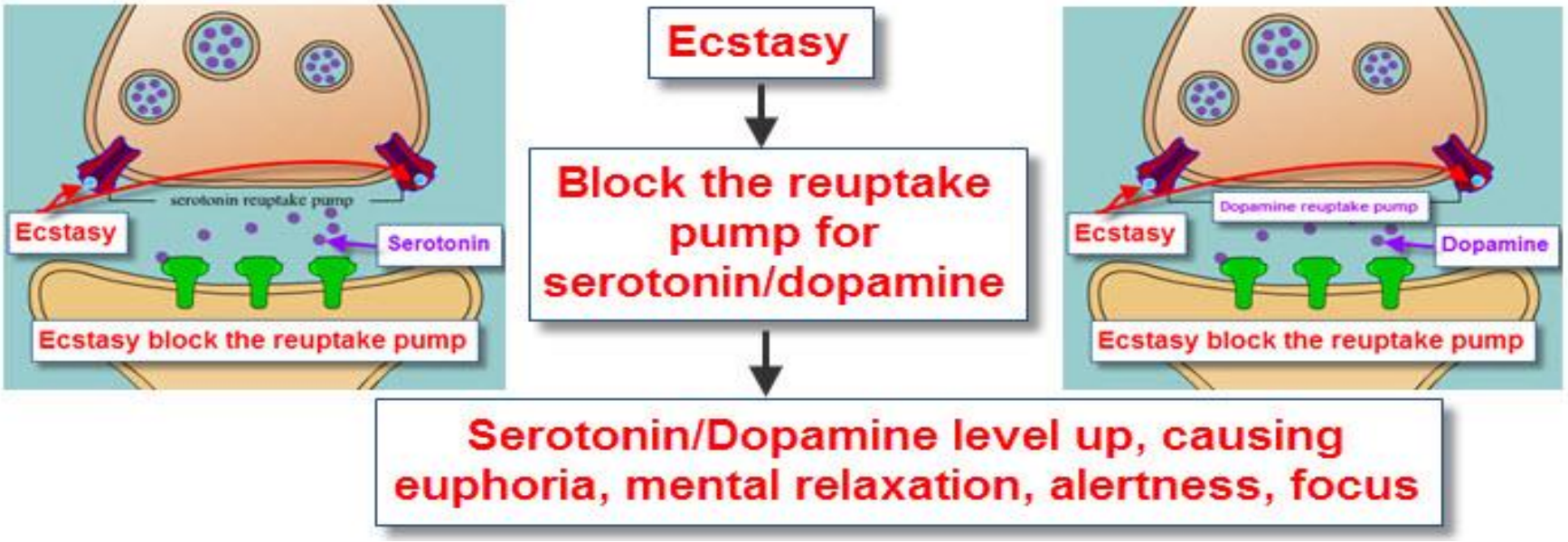
3.Mephedrone

1. Can induce feelings of happiness, euphoria and confidence, but can also cause anxiety and paranoia.
2. Causes vomiting, sweating and headaches in some users.
3. Can overstimulate your heart and nervous system.
4. Can cause periods of insomnia.
5. Can lead to fits and agitated and hallucinatory states.
6. If used in large amounts, can cause tingling of the hands and feet, seizure and respiratory failure.
7. If injected, can cause vein collapse and increases the risk of HIV and hepatitis infection.

4.Ecstasy (MDMA,pills)

1. Can make you feel alert, warm and chatty.
2. Can make sounds and colours seem more intense.
3. May cause anxiety, confusion, paranoia and even psychosis.
4. Is linked (in cases of long-term use) to memory loss, depression and anxiety.
5. Can lead to overheating and dehydration.
6. Tends to stop your body producing enough urine, so your body retains fluid.

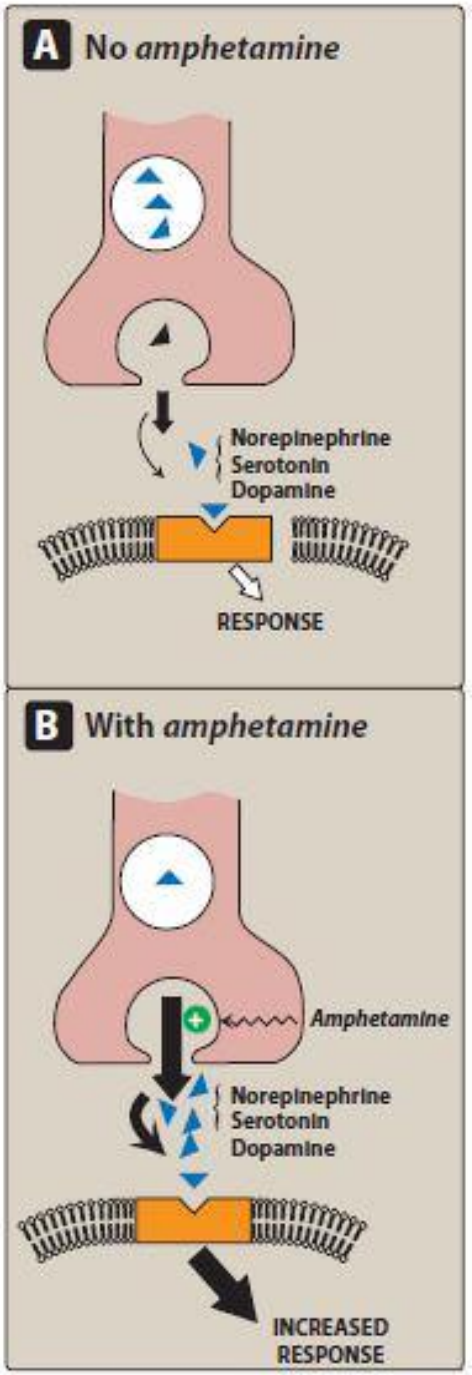


5.Speed (amphetamine, billy, whizz)

1. Can make you feel alert, confident and energetic.
2. Can reduce appetite.
3. May make you agitated and aggressive.
4. May cause confusion, paranoia and even psychosis.
5. Can make you very depressed and lethargic for hours or days, when used a lot.

Amphetamines

- Releases intracellular stores of catecholamines (norepinephrine, serotonin, dopamine)
- Inhibits MAO
- Dextroamphetamine (similar to amphetamine)
- Methamphetamine
- Actions
  - CNS stimulant, increase alertness, reduce fatigue, depress appetite
  - Activate the sympathetic nervous system
- Can cause dependence (limit their use)



6.Heroin

- Long-term heroin use causes damage to the brain, not only in the dopamine pathway that it directly affects, but also to the brain’s white matter, which is nerve tissue that helps in coordinating communication between the different regions of the brain. This results in psychological difficulties, such as having trouble making decisions and being unable to control behavior or manage stress.
- One of heroin’s immediate effects is to suppress the respiratory system. With continued use, this can result in a condition called hypoxia, or a lack of oxygen to the brain. This can also result in permanent brain damage, coma, or even death.

6.Heroin

- **According to NIDA, other health issues that can develop with heroin use include:**

- Bacterial infections in the circulatory system and collapsed veins
- Lung disease, including pneumonia and tuberculosis
- Diseases transmitted by injection, such as HIV or hepatitis
- Liver or kidney disease

7.Prescription Opioids

1. Restlessness
2. Muscle and bone pain
3. Insomnia
4. Diarrhea
5. Vomiting
6. Cold flashes with goose bumps
7. Leg movements

8.Steroids

1. Mood swings
2. Tiredness
3. Restlessness
4. Loss of appetite
5. Insomnia
6. Lowered sex drive
7. Depression

Paints Toxicity

prepared by:

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Prof.Dr.ElShahat Toson

Paints definition

- Paint is any pigmented liquid, liquefiable, or solid mastic composition that, after application to a substrate in a thin layer, converts to a solid film.

The first ideas to explain the mechanism of the neurotoxic effects of solvents

- The major component of thinner is toluene, a well-known neurotoxic agent. Acute and chronic effects of toluene on neurons have been well documented. The first ideas to explain the mechanism of the neurotoxic effects of solvents such as toluene were based on the lipid hypothesis, which proposed that perturbation of the lipid bilayer would result in dysfunctional membrane proteins.
- Solvents were thought act on lipids in the cell membrane, because toluene and other solvents have lipophilic properties that allow them to reach high concentrations in the CNS. Lipid changes were observed in rat brain exposed to toluene (320 ppm) for 30 days. Total phospholipids were reduced in the cerebral cortex, where a slight increase in phosphatidic acid was also observed.

The first ideas to explain the mechanism of the neurotoxic effects of solvents

- No changes were observed in the brainstem. The mechanism for these changes is uncertain.
- The authors proposed a specific toluene-phospholipid interaction in synaptosomes that resulted in altered membrane composition and fluidity. The same authors showed later that toluene increased phospholipid methylation and stimulated Na and K adenosine triphosphatase (ATPase) activity in synaptosomes both *in vivo* and *in vitro*.
- Inhibition of the integral enzymes acetylcholinesterase (AChE) and ATPase of rat synaptosomal membrane after incubation with 3 mM toluene was observed *in vitro*.

OXIDATIVE STRESS

- Oxidative stress is a cellular state characterized by an excess of oxidants (reactive oxygen and nitrogen species) that overwhelms the antioxidant capacity. Oxidants are constituted by free radical species containing reactive oxygen and nitrogen species.
- The presence of unpaired electrons makes them unstable and highly reactive. DNA, RNA, proteins, and lipids are the targets of these radicals. Reactive oxygen species (ROS) include oxygen-derived free radicals: the superoxide anion radical and the hydroxyl radical or its derivates, such as hydrogen peroxide. ROS are the result of the aerobic environment, and the superoxide anion radical arises during mitochondrial respiration. Coenzyme Q (CoQ) sporadically loses an electron in the transfer of reducing equivalents through the electron chain.

OXIDATIVE STRESS

- This electron is transferred to dissolve O_2 producing superoxide. It is estimated that 1-2% of the O_2 consumed by mitochondria is converted to the superoxide anion radical. Oxidativee stress induces oxidation of lipids, proteins, and DNA in cells and a response of a variety of cellular detoxification systems: superoxide dismutase (SOD), glutathione peroxidase (GPX), and glutathione (GSH).

OXIDATIVE STRESS

- Thinner inhalation induces oxidative stress. Activation of free radical processes underlies the effect of many toxic substances like: ethanol, toluene, ionizing radiation, lead, arsenate, etc. In the case of thinner, there are some proposed mechanisms:

1. One of them is the oxidative metabolism of benzene, toluene, xylene, ethanol, acetone, and tri-methylbenzene which generates cytosolic NADH. NADH is oxidized indirectly by mitochondria electron transport depending on hydrogen shuttling mechanism that involve carriers in the mitochondrial inner membrane. This condition that increases mitochondrial NADH and enhance the reducing pressure on the electron transport chain without increasing the rate of respiration promotes the formation of O_2 in the electron transport chain.

OXIDATIVE STRESS

2. The production of quinones by cytochrome P450, particularly during toluene, and benzene metabolism is another mechanism proposed. These quinones are able to establish a futile redox cycle (quinones and semiquinone radicals), during which cytotoxic ROS are accumulated.
3. Another mechanism is non-mitochondrial which increase ROS formation. Metabolism of thinner's components results in activation of cytochrome P450 isoforms like CYP2E1 which is prone to radical formation.
4. In addition, toxic substances exposures cause inflammation. In the case of thinner, inhalation induces inflammatory response in lungs.

OXIDATIVE STRESS

Considerable evidence supports a role of inflammatory mediators released by phagocytic leukocytes and infiltrating macrophages in the generation of reactive oxygen and nitrogen species in lung. Macrophages produce NO (nitric oxide) via an inducible form of the enzyme, NO synthase. This enzyme is up-regulated by inflammatory mediators such as cytokines like tumor necrosis factor alpha (TNF-α). Moreover, rapid and persistent activation of nuclear factor κB (NF- κB) in alveolar macrophages induce the expression of an inducible form of the enzyme NO synthase (iNOS) and the TNF-α receptor.

OXIDATIVE STRESS

- The highly reactive O_2-(superoxide anion) is released by stimulated leukocytes including monocytes, macrophages, and polymorphonuclear leukocytes by the action of NADPH oxidase. There are many different methods to evaluate oxidative stress. The indices based on the composition of various biological specimens are the most used. Most publications used at least two methods to assay oxidative stress, evaluation of promoters and peroxidation products induced by oxidative, oxidized proteins, and DNA oxidation.

Signs and symptoms

- Nausea, vomiting, diarrhoea, abdominal pain, can also lead to haematemesis. Aspiration lead to coughing, choking and gasping. Bronchospasm may develop, resulting in mismatch of ventillation and perfusion resulting in hypoxia and CNS depression. Hemoptysis may also occur. Acute effects include coma and seizures. It may produce initial euphoria, agitation, hallucinations. Hepatic and renal damage may be seen leading to hematuria, albuminuria, oliguria, and dysuria and DIC can also be seen. Myocardial injury, cardiac arrhythmias and myoglobinuria can be seen. Parenteral injection causes hypoxemia and non cardiogenic pulmonary edema, cellulitis and a sterile abscess at the injection site

Varnish poisoning

- Varnish is a clear liquid that is used as coating on woodwork and other products. Varnish poisoning occurs when someone swallows varnish. It is a member of a class of compounds known as hydrocarbons. It consists of hurmful resins and solvents that are lipophilic substances with ability to penetrate the cells or tissues. Exposure to hydrocarbons, both intentional and unintentional, is a common problem, resulting in thousands of calls to poison control centers every year.

Symptoms

- Symptoms has been expanded.
- Below are symptoms of varnish poisoning in different parts of the body.
- **EYES, EARS, NOSE, AND THROAT**
- Loss of vision
- Severe pain in the throat
- Severe pain or burning in the nose, eyes, ears, lips, or tongue
- **KIDNEYS AND BLADDER**
- Blood in the urine
- Kidneys stop working (kidney failure(
- **LUNGS AND AIRWAYS**
- Breathing difficulty
- Throat swelling (which may also cause breathing difficulty(

Symptoms

- **HEART AND BLOOD**
- Collapse
- Low blood pressure that develops rapidly
- **NERVOUS SYSTEM**
- Coma (decreased level of consciousness and lack of responsiveness(
- Dizziness
- Impaired memory
- Irritability
- Loss of coordination
- Sensation of being drunk
- Severe brain damage
- Sleepiness
- Stupor (decreased level of consciousness(
- Walking difficulties

Symptoms

- **SKIN**
- Burns
- Irritation
- **STOMACH AND INTESTINES**
- Blood in the stool
- Burns in the esophagus
- Severe abdominal pain
- Vomiting
- Vomiting blood

Symptoms

- Delayed injury may occur, including a hole forming in the throat, esophagus, or stomach. This can lead to severe bleeding and infection. Surgical procedures may be needed to treat these complications.
- If varnish gets in the eye, ulcers may develop in the cornea, the clear part of the eye. This can cause blindness.

Thinner Poisoning

- 26 year old male was admitted to the emergency with alleged history of accidental ingestion of thinner. He had consumed about 200–250 ml of thinner, mistaking it for water in the darkness of the night. He was brought within half an hour of thinner ingestion with complaints of vomiting, headache, weakness and dizziness.

Continued...

- On examination, the patient was conscious, with a dusky discoloration of tongue and nails along with tachycardia and mild tachypnoea. Other vital parameters and systemic examination were within normal limits.

Clinical findings

- Blood withdrawn for investigations was found to be chocolate brown in color. Because of the color of the blood, severe unexplained cyanosis and alleged history of thinner consumption, a clinical diagnosis of methemoglobinemia was made.

Continued....

- Blood investigations revealed Hb = 15.5 gm%, platelet count = 2.1 lac/mm3, blood sugar = 112 mg%, blood urea = 18 mg%, serum creatinine = 1.0 mg%, serum bilirubin = 1.1 mg%, S. Na+ = 143 mEq/L and S. K+ = 3.6

Home Care

- If the varnish is on the skin or in the eyes, flush with lots of water for at least 15 minutes.
- If the person swallowed the varnish, give them water or milk right away, unless a provider tells you not to. DO NOT give anything to drink if the person has symptoms that make it hard to swallow. These include vomiting, convulsions, or a decreased level of alertness. If the person breathed in varnish fumes, move them to fresh air right away.

Mechanism of action

Schematic diagram showed the possible mechanisms of GFNs cytotoxicity. GFNs get into cells through different ways, which induce in ROS generation, LDH and MDA increase, and Ca2+ release. Subsequently, GFNs cause kinds of cell injury, for instance, cell membrane damage, inflammation, DNA damage, mitochondrial disorders, apoptosis or necrosis

Ammonia

Introduced by :

Samar Helal

under Supervision of :

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What is ammonia?

- Ammonia is an essential mammalian metabolite for DNA, RNA, and protein synthesis and is necessary for maintaining acid-base balance.
- Ammonia is produced and used endogenously in all mammalian species. It exists naturally in humans and in the environment.
- It has been estimated that up to 17 grams of ammonia are produced in humans daily.
- Of these 17 grams, approximately 4 grams are produced in the gut by intestinal bacteria, where it enters the portal circulation and is metabolized rapidly in the liver to urea.

- Ammonia (NH_3) is one of the most commonly produced industrial chemicals .
- Ammonia is essential for many biological processes and serves as a precursor for amino acid and nucleotide synthesis.
- In the environment, ammonia is part of the nitrogen cycle and is produced in soil from bacterial processes. Ammonia is also produced naturally from decomposition of organic matter, including plants, animals and animal wastes.

- Ammonia is excreted primarily as urea and urinary ammonium compounds through the kidneys.
- Levels of ammonia in the blood from healthy humans range from 0.7 to 2 mg/L.

Production of ammonia [endogenous sources[

- Ammonia is a major byproduct of systemic and cerebral nitrogen metabolism and is generated in at least 20 enzymatic reactions within the major organs of the body.
- Ammonia is thought to be generated in the gastrointestinal tract by the action of bacteria on nitrogenous substrates and by deamidation of glutamine in the large and small intestine.
- Substantial amounts of ammonia are generated in the liver from glutamate and in the kidney by deamidation of glutamine

- The principal fate of systemic blood ammonia, in the brain and other organs, is incor-poration into glutamine (amide).
- The glutamine derived from brain, muscle and other tissues acts as an energy source for the gut and at the same time releases ammonia for urea synthesis. Thus, ultimately, most extrahepatic ammonia is incorporated into urea by temporary storage in glutamine (amide).

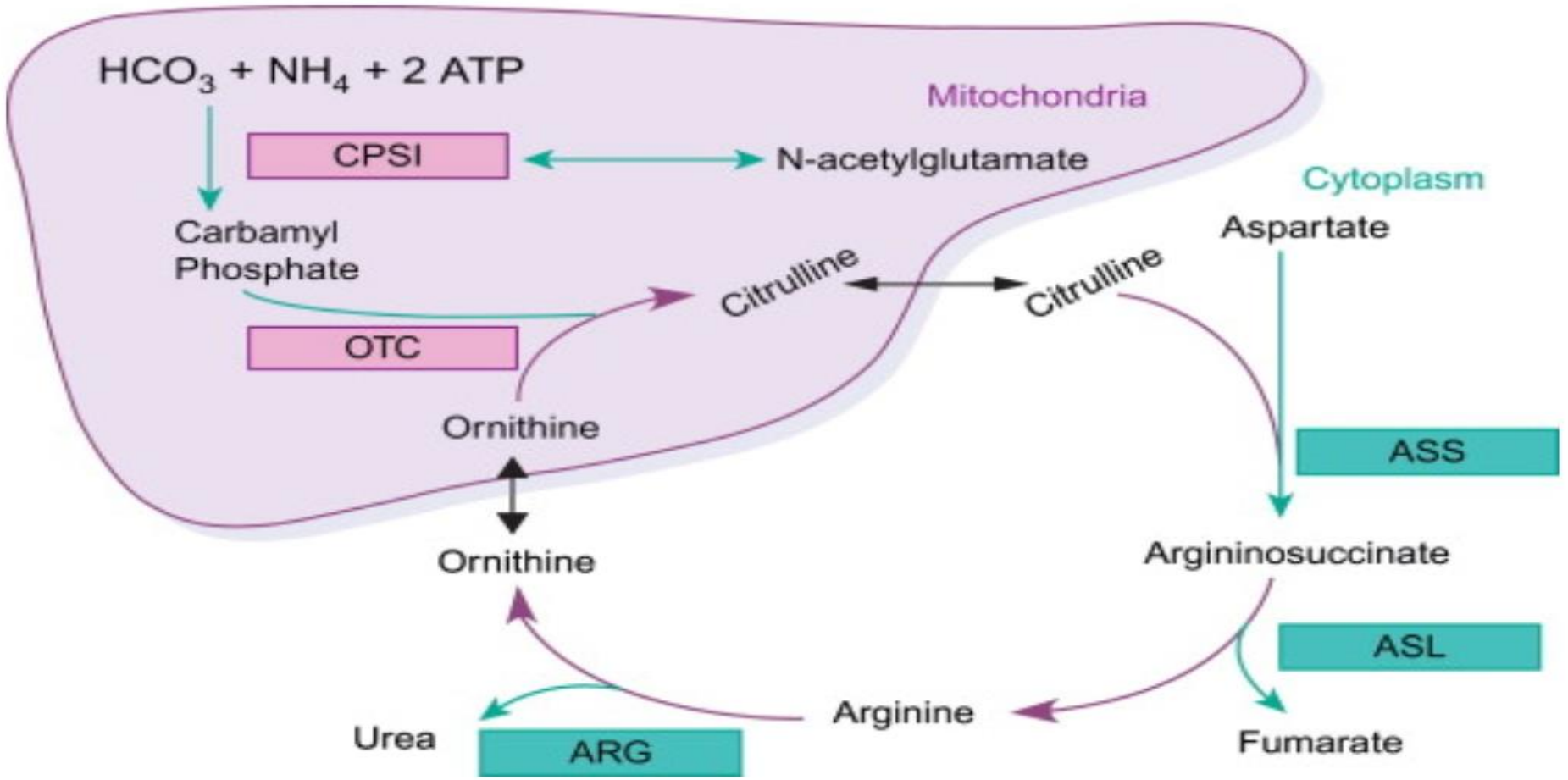


Figure. The urea cycle.

How is ammonia used ?
Exogenous sources

- About 80% of the ammonia produced by industry is used in agriculture as fertilizer.
- a refrigerant gas,
- for purification of water supplies,
- in the manufacture of plastics, explosives, textiles, pesticides, dyes and other chemicals.

How can people be exposed to ammonia?

- Most people are exposed to ammonia from inhalation of the gas or vapors.
- Since ammonia exists naturally and is also present in cleaning products,
- exposure may occur from these sources.
- The widespread use of ammonia on farms and in industrial and commercial locations also means that exposure can occur from an accidental release or from a deliberate terrorist attack.

What is ammonia's mechanism of action?

- Ammonia interacts immediately upon contact with available moisture in the skin, eyes, oral cavity, respiratory tract, and particularly mucous surfaces to form the very caustic ammonium hydroxide.
- Ammonium hydroxide causes the necrosis of tissues through disruption of cell membrane lipids (saponification) leading to cellular destruction.
- As cell proteins break down, water is extracted, resulting in an inflammatory response that causes further damage.

What are the immediate health effects of ammonia exposure?

Inhalation:

- Ammonia is irritating and corrosive. Exposure to high concentrations of ammonia in air causes immediate burning of the nose, throat and respiratory tract. This can cause bronchiolar and alveolar edema, and airway destruction resulting in respiratory distress or failure.
- Inhalation of lower concentrations can cause coughing, and nose and throat irritation. Ammonia's odor provides adequate early warning of its presence, but ammonia also causes olfactory fatigue or adaptation, reducing awareness of one's prolonged exposure at

Skin or eye contact:

- Exposure to low concentrations of ammonia in air or solution may produce rapid skin or eye irritation.
- Higher concentrations of ammonia may cause severe injury and burns.
- Contact with concentrated ammonia solutions such as industrial cleaners may cause corrosive injury including skin burns, permanent eye damage or blindness.
- The full extent of eye injury may not be apparent for up to a week after the exposure.
- Contact with liquefied ammonia can also cause frostbite injury.

Ocular Effects.

symptoms progress as follows:

- inflamed eyes,
- lacrimation,
- swelling of the eyelids,
- hyperemic conjunctiva,
- blurred vision,
- possible transient blindness,
- corneal abrasions, and sustained corneal damage.

Ingestion:

- Exposure to high concentrations of ammonia from swallowing ammonia solution results in corrosive damage to the mouth, throat and stomach.
- Ingestion of ammonia does not normally result in systemic poisoning.

Respiratory Effects.

- Ammonia is an upper respiratory irritant in humans.
- Exposures to levels exceeding 50 ppm result in immediate irritation to the nose and throat; however, tolerance appears to develop with repeated exposure.

Neurological Effects.

- Neurological effects in humans following inhalation or dermal exposure to ammonia are usually limited to blurred vision, most likely due to direct contact, but more severe exposures, which result in significant elevation of blood ammonia levels (hyperammonemia), can result in diffuse nonspecific encephalopathy, muscle weakness, decreased deep tendon reflexes, and loss of consciousness.
- Hyperammonemia in humans can result from certain disease states such as cirrhosis of the liver, acute liver failure, and congenital deficiencies of any of the urea cycle enzymes; hyperammonemia may lead to encephalopathy.

- Some have suggested that ammonia may be involved in the generation of the symptomatology and progression of Alzheimer's disease as a result of pathological ammonia metabolism in the brain.
- Cerebral edema and herniation and intracranial hypertension have been noted in animal models of hyperammonemia.

The effect on immune system

- The date showed that ammonia exposure could induce intracellular reactive oxygen species (ROS), interrupt intracellular Ca(2+) (cf-Ca(2+)) homeostasis, and subsequently lead to DNA damage and cell apoptosis. To test the apoptotic pathway, the expression patterns of some key apoptotic related genes including P53, Bax Bcl2, Caspase 9, Caspase 8 and Caspase 3 in the liver were examined.

- The results showed that ammonia stress could change these genes transcription, associated with increasing of cell apoptosis, suggesting that the P53-Bax-Bcl2 pathway and caspase-dependent apoptotic pathway could be involved in cell apoptosis induced by ammonia stress. In addition, ammonia stress could induced up-regulation of inflammatory cytokines (BAFF, TNF-α, IL-6 and IL-12) transcription, indicating that innate immune system play important roles in ammonia-induced toxicity in fish. Furthermore, the gene expressions of antioxidant enzymes (Mn-SOD, CAT, GPx, and GR) and heat shock proteins (HSP90 and HSP70) in the liver were induced by ammonia stress, suggesting that antioxidant system and heat shock proteins tried to protect cells from oxidative stress and apoptosis induced by ammonia stress.

How is ammonia exposure treated?

- There is no antidote for ammonia poisoning, but ammonia's effects can be treated, and most people recover.
- Immediate decontamination of skin and eyes with copious amounts of water is very important.
- Treatment consists of supportive measures and can include administration of humidified oxygen, bronchodilators and airway management.
- Ingested ammonia is diluted with milk or water.

Ammonia test

- **Why Get Tested?**

To detect an elevated level of ammonia in the blood that may be caused by severe liver disease, kidney failure, or certain rare genetic urea cycle disorders; to help investigate the cause of changes in behavior and consciousness; to support the diagnosis of hepatic encephalopathyor Reye syndrome

When To Get Tested?

- When someone with liver disease or kidney failure experiences mental changes or lapses into a coma;
- when a newborn experiences frequent vomiting and increased lethargy or when a child has continuous vomiting and unusual sleepiness about a week after a viralillness, such as the flu or chickenpox

Sample Required?

- A blood sample drawn from a vein in your arm

Test Preparation Needed?

- You should not smoke cigarettes prior to collection of the specimen.

Test results

- In infants, an extremely high level is associated with an inherited urea cycle enzyme deficiency.

- An increased ammonia level and decreased glucose level may indicate the presence of Reye syndrome in symptomatic children and teens. An increased concentration may also indicate a previously undiagnosed enzymatic defect of the urea cycle.
- The underlying problem with the use of aspirin during a viral illness is an inhibition of fatty acid metabolism (oxidative phosphorylation and b-oxidation) in the liver.

- normal blood ammonia level may mean that a person's signs and symptoms are due to a cause other than excess ammonia. However, normal concentrations of ammonia do not rule out hepatic encephalopathy.
- A decreased level of ammonia may be seen with some types of hypertension.
- Decreased levels of ammonia may be seen with the use of some antibiotics, such as neomycin.

hepatic encephalopathy (HE).

Loss of brain function occurs when the liver is unable to remove toxins from the blood. This is called hepatic encephalopathy (HE).

Causes

An important function of the liver is to make toxic substances in the body harmless. These substances may be made by the body (ammonia), or substances that you take in (medicines).

When the liver is damaged, these "poisons" can build up in the bloodstream and affect the function of the nervous system. The result may be HE.

HE can occur suddenly and you may become ill very quickly. Causes of HE may include:

1. Hepatitis A or B infection (uncommon to occur this way)
2. Blockage of blood supply to the liver
3. Poisoning by different toxins or medicines
4. Constipation
5. Upper gastrointestinal bleeding

- People with severe liver damage often suffer from HE. The end result of chronic liver damage is cirrhosis. Common causes of chronic liver disease are:

1. Severe hepatitis B or C infection
2. Alcohol abuse
3. Autoimmune hepatitis
4. Bile duct disorders
5. Some medicines
6. Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH)

Once you have liver damage, episodes of worsening brain function may be triggered by:

- Less body fluids (dehydration)
- Eating too much protein
- Low potassium or sodium levels
- Bleeding from the intestines, stomach, or food pipe (esophagus)
- Infections
- Kidney problems

Disorders that can appear similar to HE may include:

- Alcohol withdrawal
- Bleeding under the skull
- Brain disorder caused by lack of vitamin B1

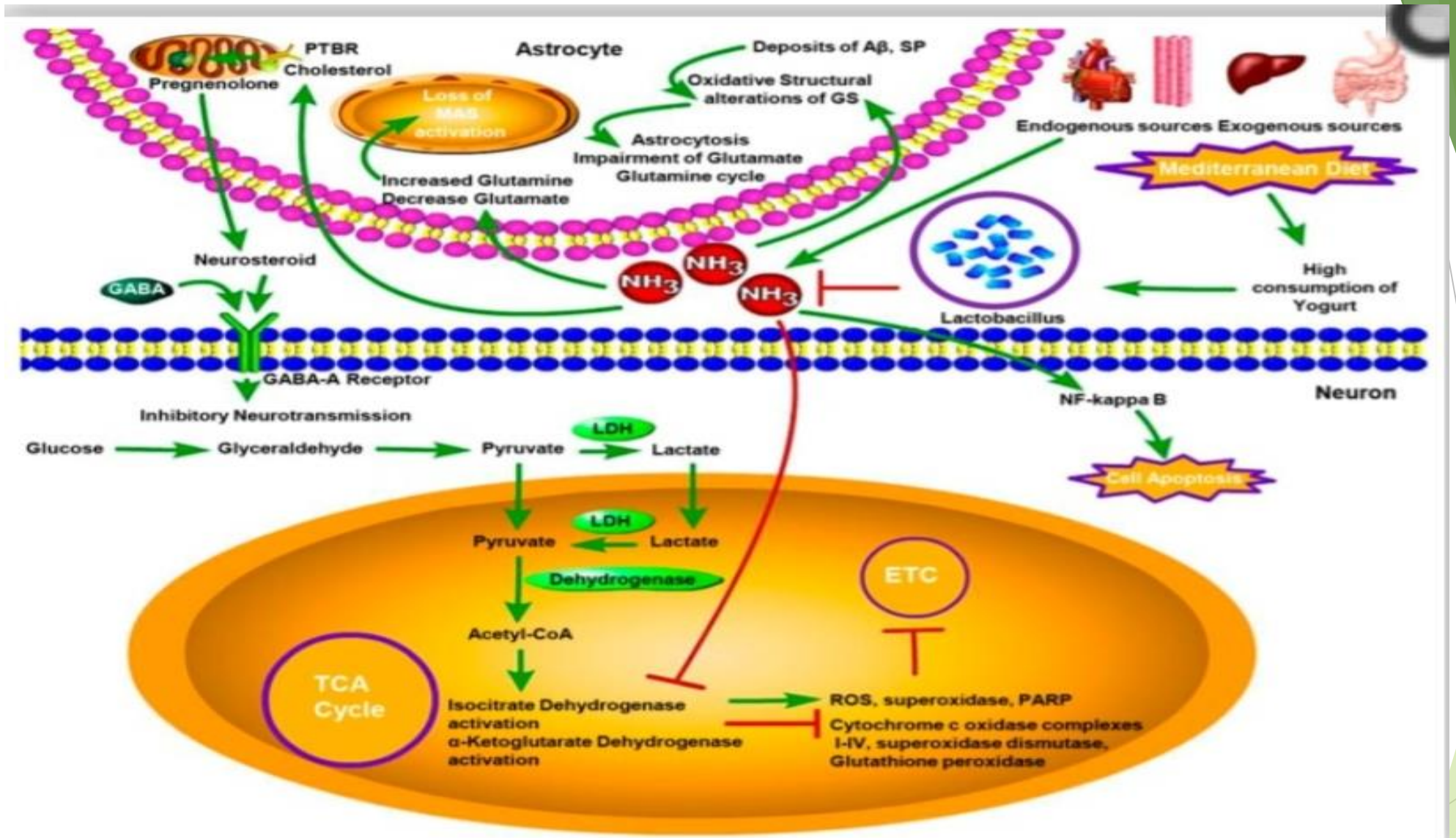
In some cases, HE is a short-term problem that can be corrected. It may also occur as part of a long-term (chronic) problem from liver disease that gets worse over time.

Mechanism of hepatic encephalopathy and Alzheimer's including ammonia

- Ammonia significantly disrupts mitochondrial function and cerebral energy metabolism. High ammonia concentration suppresses the activities of alpha-ketoglutarate dehydrogenase and isocitrate dehydrogenase to increase the activity of ROS, superoxidase and Poly ADP-Ribose polymerase (PARP) in AD brain mitochondria [37]. This can also decrease the activity of cytochrome c oxidase, complexes I–IV, superoxidase dismutase and glutathione peroxidase to inhibit mitochondrial electron transport chain (ETC) [38,39].

- Consequentially, the ammonia-induced stress condition contributes to the changes in mitochondria morphology.
- Besides mitochondrial dysfunction, energy metabolism is affected in AD brain. The reduction in glycolytic process was observed by comparing the enzymatic activity of glucose transporters, pyruvate dehydrogenase (PDH) , hexokinase and enzymes of the tricarboxylic acid (TCA) cycle between AD group and control group.

- In addition, ammonia-induced inhibition of the TCA cycle in brain was observed along with the demonstration of how the increased astrocytic glutamine reduces glutamate concentration, leading to the loss of malate-asparate shuttle (MAS) activity to result in the reduction of pyruvate/lactate ratio. Unrelated to MAS activity, hyperammonemia inhibits PDH via regulating decarboxylation of alpha-ketoglutarate .


Astrocyte
PTBR
Cholesterol
Pregnenolone
Loss of MAS activation
Deposits of Aβ, SP
Oxidative Structural alterations of GS
Astrocytosis
Impairment of Glutamate Glutamine cycle
Increased Glutamine Decrease Glutamate
Endogenous sources Exogenous sources
Mediterranean Diet
High consumption of Yogurt
Lactobacillus
Neurosteroid
GABA
NH3
NH3
NH3
GABA-A Receptor
Neuron
NF-kappa B
Cell Apoptosis
Inhibitory Neurotransmission
Glucose
Glyceraldehyde
Pyruvate
LDH
Lactate
Pyruvate
LDH
Lactate
Dehydrogenase
ETC
Acetyl-CoA
TCA Cycle
Isocitrate Dehydrogenase activation
α-Ketoglutarate Dehydrogenase activation
ROS, superoxidase, PARP
Cytochrome c oxidase complexes I-IV, superoxidase dismutase, Glutathione peroxidase


Thanks!

Benzene Toxicological

WHAT IS BENZENE?

Benzene, also known as benzol, is a colorless liquid with a sweet odor. Benzene evaporates into air very quickly and dissolves slightly in water. Benzene is highly flammable. Benzene is found in air, water, and soil. Benzene comes from both industrial and natural sources.

Long-term exposure to benzene can cause cancer of the blood-forming organs. This condition is called leukemia. Exposure to benzene has been associated with development of a particular type of leukemia called acute myeloid leukemia (AML). The Department of Health and Human Services has determined that benzene is a known carcinogen

HOW CAN BENZENE ENTER AND LEAVE MY BODY?

Route of adminstration:

Benzene can enter your body through your lungs, gastrointestinal tract, and across your skin. When you are exposed to high levels of benzene in air, about half of the benzene you breathe in passes through the lining of your lungs and enters your bloodstream. When you are exposed to benzene in food or drink, most of the benzene you take in by mouth passes through the lining of your gastrointestinal tract and enters your bloodstream. A small amount will enter your body by passing through your skin and into your bloodstream during skin contact with benzene or benzene-containing products. Once in the bloodstream, benzene travels throughout your body and can be temporarily stored in the bone marrow and fat. Benzene is converted to products, called metabolites, in the liver and bone marrow. Some of the harmful effects of benzene exposure are caused by these metabolites. Most of the metabolites of benzene leave the body in the urine within 48 hours after exposure.

Distribution

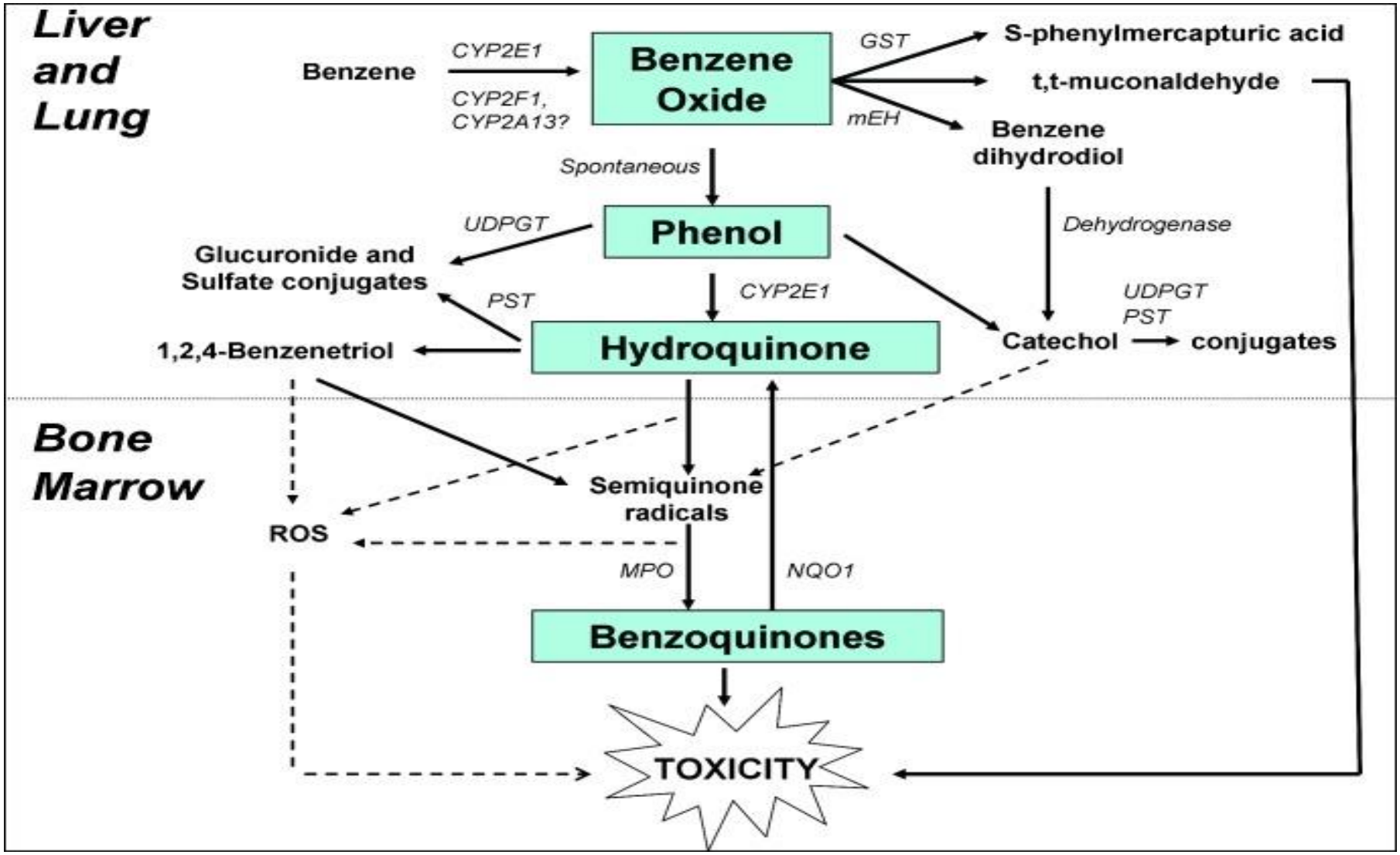
benzene is lipophilic, a high distribution to fatty tissue .Benzene is expected to readily bind to plasma proteins. benzene metabolites have been found to form covalent adducts with proteins from blood in humans. The relatively widespread distribution of benzene and its metabolites to other tissues and organs.

benzene, parent compound and its metabolites were found to be present in lipid-rich tissues, such as brain and fat, and in well-perfused tissues, such as liver and kidney. Benzene was also found in the placenta and fetuses immediately following inhalation of benzene . Benzene was also distributed to the kidney, lung, liver, brain, and spleen. The benzene metabolites phenol, catechol, and hydroquinone were detected in blood and bone marrow following 6 hours of exposure to benzene, with levels in bone marrow exceeding the respective levels in blood. The levels of
phenol in blood and bone marrow decreased much more rapidly after exposure ceased than did those of catechol or hydroquinone, suggesting the possibility of accumulation of the latter two compounds.

Fat, bone marrow, and urine contained about 20 times the concentration of benzene in blood; benzene levels in muscles and organs were 1–3 times that in blood; and erythrocytes contained about twice the amount of benzene found in Plasma benzene was stored longer (and eliminated more slowly) in female and male rats with higher body fat content than in leaner Animals.

Benzene was detected in the liver, lung, and blood of rats and mice examined immediately following a 6-hour exposure to benzene vapors at a concentration of 50 ppm .

Metabolism


Liver and Lung
Benzene
CYP2E1
CYP2F1, CYP2A13?
Benzene Oxide
GST
S-phenylmercapturic acid
t,t-muconaldehyde
mEH
Benzene dihydrodiol
Spontaneous
Phenol
UDPGT
Glucuronide and Sulfate conjugates
Dehydrogenase
PST
CYP2E1
UDPGT
PST
1,2,4-Benzenetriol
Hydroquinone
Catechol
conjugates
Bone Marrow
Semiquinone radicals
ROS
MPO
NQO1
Benzoquinones
TOXICITY

Although the metabolism of benzene has been studied extensively, the steps leading to benzene toxicity are not yet fully understood. It is generally understood that both cancer and noncancer effects are caused by one or more reactive metabolites of benzene. Available data indicate that metabolites produced in the liver are carried to the bone marrow where benzene toxicity is expressed. Benzene metabolism may occur, at least in part, in the bone marrow. Benzene is excreted both unchanged via the lungs and as metabolites (but also as parent compound in small amounts) in the urine. The rate and percentage of excretion via the lungs are dependent on exposure dose and route.

Metabolic Pathways for Benzene

Each of the phenolic metabolites of benzene (**phenol, catechol, hydroquinone, and 1,2,4-benzenetriol**) can undergo **sulfonic or glucuronic conjugation** the conjugates of phenol and hydroquinone are major urinary metabolites of benzene .Other pathways of benzene oxide metabolism include: reaction with glutathione (GSH) to form S-phenylmercapturic acid ironcatalyzed ring-opening conversion to *trans,trans-muconic acid*

A number of investigators have suggested that covalent binding of benzene metabolites to cellular macromolecules is related to benzene's mechanism of toxicity, although the relationship between adduct formation and toxicity is not clear. Benzene metabolites have been found to form covalent adducts with proteins from blood in humans . Benzene metabolites form covalent adducts with nucleic acids and proteins in covalently bind to proteins in liver, bone marrow, kidney, spleen, blood, and muscle bind to proteins in bone marrow and in liver DNA *and bind to DNA*

Exposure-related increases in blood levels of albumin adducts of benzene oxide and 1,4-benzoquinone were noted among workers occupationally exposed to benzene air concentrations ranging from 0.07 to 46.6 ppm Several reactive metabolites of benzene have been proposed as agents of benzene **hematotoxic** and **leukemogenic effects**. These metabolites include benzene oxide, reactive products of the phenol pathway (catechol, hydroquinone, and 1,4-benzoquinone), and *trans,trans-muconaldehyde*..

Elimination and Excretion

Available human data indicate that following inhalation exposure to benzene, the major route for elimination of un metabolized benzene is via exhalation. Absorbed benzene is also excreted in humans via metabolism to **phenol** and **muconic acid** followed by urinary excretion of conjugated derivatives (sulfates and glucuronides).The rate of excretion of benzene was the greatest during the first hour. The study also showed that only 0.07–0.2% of the retained benzene was excreted in the **urine**. Other studies suggest that **benzene in the urine may be a useful biomarker of occupational exposure of benzene**

MECHANISMS OF ACTION

Benzene is readily absorbed via all natural routes of exposure (**inhalation, oral, and dermal**) and distributed throughout the body via the blood. Based on physical properties such as slight water solubility, high lipid solubility, and nonpolarity, benzene is expected to enter the blood via passive diffusion from gut, lungs, and skin.Benzene is expected to readily bind to **plasma proteins** .Being moderately lipophilic, benzene tends to accumulate in fatty tissues. However, benzene metabolism is relatively rapid and required for **hematopoietic and leukemogenic effects** to be expressed. Multiple reactive metabolites appear to be involved in benzene toxicity.

It is generally believed that reactive **hepatic metabolites** of benzene are transported to the major toxicity **target (bone marrow).** Additional metabolism likely occurs in bone marrow. Phenolic metabolites (**phenol, hydroquinone, catechol, 1,2,4-benzenetriol, and 1,2- and 1,4-benzoquinone)** appear to play a major role in benzene toxicity. Smith noted that the phenolic metabolites can be **metabolized by bone marrow peroxidases, such as myeloperoxidase (MPO),** to highly reactive semiquinone radicals and quinones that stimulate the production of **reactive oxygen species**. These steps lead to **damage to histone proteins, topoisomerase II**, other **DNA associated proteins**, and **DNA itself (clastogenic effects such as strand breakage, mitotic recombination, chromosome translocations, and aneuploidy).** Damage to **stem or early progenitor cells would be expressed as hematopoietic and leukemogenic effects**. Results of several mechanistic studies demonstrate that benzene hematotoxicity is dependent upon metabolism. Inhibition of benzene metabolism reduced its toxicity .**Partial hepatectomy decreased both benzene metabolism and toxicity**

Biomarkers Used to Identify or Quantify Exposure to Benzene

Several biomarkers of exposure to benzene the metabolized of benzene can be detected in **urine** of humans exposed to benzene. **Urinary phenol** measurements have routinely been used for monitoring occupational exposure to benzene and correlated with exposure levels. **Urinary *trans,trans-muconic acid*** *has been widely biomarker of exposure to benzene* ***phenylmercapturic acid*** *levels have also been correlated with occupational exposure to benzene*

Hemoglobin and albumin adducts of the benzene metabolites, benzene oxide and 1,4-benzoquinone, have been used as biomarkers of exposure to benzene .DNA adducts with benzene metabolites have been found after benzene exposure. **Early biomarkers of exposure** to relatively **low** levels of numbers of one or more of the circulating blood cell types

Acute-Duration Exposure

There are reports on the health effects resulting from acute exposure of humans and animals to benzene via the inhalation, oral, and dermal routes. The primary target organs for acute exposure are the **hematopoietic system, nervous**, **immunsystem** and **Neurotoxicity**

However, there are acute inhalation data that characterize the effects of benzene on the hematological system in humans and animals. Data regarding effects on the human hematological system following acute inhalation exposure to benzene are scant, but indicate leukopenia, **anemia**, and **thrombocytopenia** after more than 2 days of exposure to more than 60 ppm benzene

Chronic-Duration Exposure and Cancer

Benzene is a multiple site **carcinogen** following inhalation exposure and oral exposure inducing lymphomas and other neoplasms in numerous tissues. How benzene causes cancer, particularly the mechanism of benzene leukemogenesis. The exact mechanism of benzene carcinogenicity is not known, but it has been postulated that some benzene metabolites are capable of forming **adducts with DNA** and are responsible for **reduced immune function** which could potentially lead to cancer. The clastogenic properties of benzene may play a role in its carcinogenicity. DNA adduct formation could occur with both inhalation and oral exposures. the mechanism of benzene carcinogenesis include how benzene metabolites produce greater-than-additive effects, determination of the critical target genes, whether **aplastic anemia** is essential to the development of **leukemia**, and determination of the role of cytokines and growth factor pathways in benzene toxicity

Hematological Effects

All of the major types of blood cells are susceptible (**erythrocytes, leukocytes, and platelets**). In the less severe cases of toxicity, specific deficiencies occur in individual types of blood elements. A more severe effect occurs when there is hypoplasia of the bone marrow, or hypercellular marrow exhibiting ineffective **hematopoiesis** so that all types of blood cells are found in reduced numbers. This is known as **pancytopenia**. A biphasic response (i.e., a hyperplastic effect in addition to destruction of the bone marrow cells) has been observed. Severe damage to the bone marrow involving cellular aplasia is known as **aplastic anemia** and can occur with prolonged exposure to benzene. This condition can lead to **leukemia**.

Significantly **reduced counts for all three blood factors** (white blood cells [WBCs], red blood cells [RBCs], and platelets); and other evidence of adverse effects on blood-forming units (reduced bone marrow cellularity, bone marrow hyperplasia and hypoplasia, granulocytic hyperplasia, decreased number of colony-forming granulopoietic stem cells and erythroid progenitor cells, damaged erythrocytes and erythroblast-forming cells) have been observed in animals at benzene concentrations in the range of **10–300 ppm**.

Deficiencies in various types of blood cells lead to other disorders, such as **hemorrhagic conditions from a lack of platelets**, **susceptibility to infection from the lack of leukocytes**, and **increased cardiac output from the lack of erythrocytes**

Genotoxicity

benzene exposure and the appearance of structural and numerical **chromosome aberrations** in human lymphocytes suggests that benzene can be considered a human clastogen. Benzene-induced cytogenetic effects, including chromosome and chromatid aberrations, sister **chromatid exchanges**, and micronuclei, have been consistently found in *in vivo animal studies*

Binding of benzene and/or its metabolites to DNA, RNA, and
proteins has been consistently observed. Inhalation exposure has yielded identifiable benzene-derived hemoglobin adducts have shown that intermediate-duration exposure to benzene by inhalation **induce gene mutations in the lymphocytes**. benzene's genotoxicity is derived primarily from its metabolites activators that causes **DNA breaks** and affect on human **topoisomerases** (enzymes involved in DNA replication and repair

Reproductive Toxicity

There are data on gonadal effects (e.g. **degeneration, decrease in spermatozoa, moderate increases in abnormal sperm forms**)

Exposure to benzene may be harmful to the reproductive organs. Some women workers who breathed high levels of benzene for many months had **irregular menstrual periods**. When examined, these women showed a **decrease in the size of their ovaries**. However, exact exposure levels were unknown, and the studies of these women did not prove that benzene caused these effects. It is not known what effects exposure to benzene might have on the developing fetus in pregnant women or on fertility in men. Studies with pregnant animals show that breathing benzene has harmful effects on the developing fetus. These effects include **low birth weight**, **delayed bone formation**, and **bone marrow damage**.

Immunotoxicity

.Benzene has been shown to have adverse immunological effects in humans following inhalation exposure for intermediate and chronic durations. Adverse immunological effects in animals occur following both inhalation and oral exposure for acute, intermediate, and chronic durations. The effects include **damage to both humoral (antibody) and cellular (leukocyte) responses**. Human studies of intermediate and chronic duration have shown that benzene causes **decreases in the levels of circulating leukocytes in workers at low levels (30 ppm)** of exposure and **decreases in levels of circulating antibodies** in workers exposed to benzene at 3–7 ppm. Other studies have shown **decreases in human lymphocytes and other blood elements** after exposure; these effects have been seen at occupational exposure levels as low as 1 ppm or less. Animal data support these findings. Both humans and rats have shown **increases in leukocyte alkaline phosphatase activity**..

Animal studies have also shown that benzene **decreases circulating leukocytes and decreases the ability of lymphoid tissue** to produce the mature lymphocytes necessary to form antibodies. This has been demonstrated in animals exposed for acute, intermediate, or chronic periods via the inhalation route. This **decrease in lymphocyte** numbers is reflected in impaired cell-mediated immune functions in mice following intermediate inhalation exposure to **100 ppm of benzene** Humans after inhalation, oral, or dermal exposure, since absorption of benzene through any route of exposure would **increase the risk of damage to the immunological system.** Studies show that the immunological system is susceptible to chronic exposure at low levels, so people living in and around hazardous waste sites who may be exposed to contaminated air, drinking water, soil, or food may be at an **increased risk for adverse immunological effects**.

Neurological Effects

In humans, results of occupational studies indicate that there is a cause-and effect relationship between acute inhalation of very high concentrations of benzene and symptoms indicative of central nervous system toxicity. These symptoms, observed following both acute nonlethal and lethal exposures, include **drowsiness**, **dizziness**, **headache**, **vertigo**, **tremor**, **delirium**, and **loss of consciousness**. These symptoms are reversible when symptomatic workers are transferred from the problem area. Comparable toxicity in humans has been reported following ingestion of benzene at doses of 125 mg/kg and above. Occupational exposure to benzene has also been reported to produce neurological abnormalities in humans. Electromyographical and motor conduction velocity examinations were conducted on six patients with **aplastic anemia**, all of whom worked in environments where adhesives containing benzene were used (in one case, air concentrations bracketed around 210 ppm). Abnormalities in motor conduction velocity were noted in four of the six **pancytopenic** individuals and were thought to result from a direct effect of benzene on the **peripheral nerves and/or spinal cord**.
In its acute stages, benzene toxicity appears to be due primarily to the direct effects of benzene on the **central nervous system**

In addition, because benzene may induce **an increase in brain catecholamines,** it may also have a secondary effect on the immune system via the hypothalamus-pituitary-adrenal axis**. Increased metabolism of catecholamines** can result in **increased adrenal corticosteroid levels**,

Respiratory Effects

Respiratory effects have been reported in humans after acute exposure to benzene vapors .Fifteen male workers employed in removing residual fuel from shipyard tanks were evaluated for benzene exposure . After exposure to benzene vapors on a chemical for only minutes, autopsy reports on three victims revealed hemorrhagic, edematous lungs. Acute granular tracheitis, laryngitis, bronchitis, and massive hemorrhages of the lungs were observed at autopsy of an 18-year-old male who died of benzene poisoning after intentional inhalation of *benzene* .

Cardiovascular Effects

The effects of acute inhalation exposure to high concentrations of benzene vapor on the heart muscle. Information from the electrocardiograms indicated that exposure to benzene vapor caused extra systoles and ventricular tachycardia of the prefibrillation type. Animals that had their adrenals and stellate ganglias removed did not exhibit extra systoles or ventricular tachycardia. These findings suggest that the arrhythmias were caused by catecholamine release and sympathetic discharge. This study is limited in that exact levels of exposure are not available. An additional study investigated the influence of benzene inhalation on ventricular arrhythmia .

Gastrointestinal Effects

Very few data are available describing gastrointestinal effects in humans after inhalation exposure to benzene. In a case study involving the death of an 18-year-old boy who intentionally inhaled benzene, the autopsy revealed congestive gastritis