Organic solvents

- Volatile, strongly lipophilic liquids.
- The basic structure is aliphatic, alicyclic or aromatic.
- The functional groups involved in their structure are halogens, alcohols, ketones, glycols, esters, ethers, carboxylic acids, amines and amides.
- Very wide use - they dissolve fats, also resins and waxes - both natural and synthetic.
- Used for chemical syntheses, also for degreasing metals, diluting adhesives and paints.
- Because of their flammability they are also used as fuels and because of their low flammability as a cartridge for fire extinguishers (formerly tetrachloromethane).
- According to toxicity they can be divided into two groups:
  1. **low toxicity'** - gasoline, diesel, trichloroethylene (frequent use, lethal dose to humans is in the hundreds of milliliters);
  2. **highly toxic'** - carbon disulfide, carbon tetrachloride, benzene, chloroform (lethal dose is in the range of a few millilitres).

Metabolism of organic solvents

- Most of them can be biotransformed by the human body, mainly by oxidation (e.g. toluene), their metabolites are then excreted in the urine.
- They can also be excreted unchanged.
- Metabolic processes often play a major role in toxicity or therapy.
- Toxic metabolites are formed, for example, in methyl alcohol, ethylene glycol.
- An important metabolic pathway is the enzymes **alcohol dehydrogenase and aldehyde dehydrogenase** - the human body metabolizes not only ethyl alcohol but also trichloroethylene, toluene, ethylene glycol or methyl alcohol - in poisoning of the latter two, therapy takes advantage of the fact that enzymes prefer ethyl alcohol and therefore it is the latter that is administered.
- Excretion occurs either in the urine or by exhalation unchanged (e.g. in the case of gasoline or ether).

Route of entry into the body

1. **Inhalation'** - is the main one for both professional exposure and abusive exposure.
2. **Percutaneous absorption** - water-soluble organic solvents (e.g. glycol ethers) are more readily absorbed through the skin, highly volatile substances evaporate rapidly, and are less readily absorbed through the skin.
3. **Oral absorption'** - rapid and effective, often by accident or abusage.

General effects of organic solvents

- *CNS'* - we distinguish between acute and chronic effects
  1. acute:
     - '**excitation'**: depression of inhibitory functions, corresponds to stage 1 anesthesia;
     - **depression'**: occurs at higher concentrations (somnolence to coma or respiratory arrest). The narcotic effects increase with hydrocarbon chain length, halogen or alcohol substitution, and the presence of double bonds.
  2. Chronic:
     - Grade 1: **Pseudoneurasthenic syndrome** - a set of symptoms that are reversible (disappear after withdrawal from exposure), characterized by mood swings, sleep disturbances, or feelings of fatigue;
     - Stage 2: **organic psychosyndrome** - occurs as a result of atrophy of the cerebral cortex → irreversible, characterized by disturbances in concentration, memory, drop in IQ, personality changes, loss of interest in the environment, this diagnosis is confirmed by a psychologist, EEG or CT scan of the brain.
- **PNS** - very few organic solvents damage the PNS, examples include sulphur carbon or ethyl alcohol.
- *Skin* - repeated hand washing with organic solvents can lead to dermatitis (ORs dry and degrease the skin).
- *Myocardium'* - organic solvents increase susceptibility to the arrhythmogenic effects of Catecholamines; inhalation of high concentrations of ORs may cause dysrhythmias (common death in toluene inhalers).
- **Respiratory system** - respiratory irritation can be caused by petroleum distillates, more serious is pulmonary edema - can occur after exposure to phosgene.
- *Liver'* - hepatotoxicity is mainly caused by ORs with halogen group - trichloromethane, chloroform, carbon tetrachloride.
- **Haematopoietic system** - haematotoxicity is known mainly from chronic exposure to benzene (development of acute or chronic myeloid leukaemia).
- *Kidney'* - renal failure following ethylene alcohol exposure or carbon tetrachloride intoxication, otherwise there is little information on nephrotoxicity in the OR.
- **Reproductive system** - negative effect on reproductive processes, can pass through the placental barrier and to a small extent to the testes.

Healing

- **Interruption of exposure** (in acute intoxications, symptomatic therapy and maintenance of basic vital

functions).
- **Antidotum** is known for ethylene glycol and methyl alcohol and it is ethyl alcohol or the drug fomepizole, there is no antidote for other ORs → administration of a saline laxative is indicated for rapid removal from the body (e.g. sodium sulfate) or forced diuresis – has an effect on OR excreted in urine (it makes no sense for petrol or ether, they are substances excreted by the lungs).
- '*Contraindicated* is *giving milk* (accelerates absorption due to the fat content), *inducing vomiting* (risk of aspiration) and *gastric lavage* (however, this is indicated after ingestion of a toxic dose together with airway intubation), *administration of adrenaline and noradrenaline* is contraindicated in all ORs (due to the risk of arrhythmias).
- Administration of antibiotics is indicated in case of inhalation or aspiration bronchopneumonia caused most often by petrol or diesel.

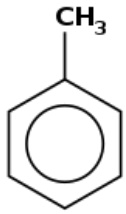
Division by chemical structure

1. Aromatic hydrocarbons

- They contain at least 1 benzene nucleus, have an aromatic smell, are produced from petroleum or tar.
- They are absorbed through the lungs.
- They are substantially biotransformed, the main metabolite is used as a biological exposure test.
- Effects:
  - **main effects** - neurotoxic, benzene hematotoxic;
  - **acute effects** - CNS - excitation, disorientation, nausea, drowsiness to unconsciousness;
  - **chronic effects** - dermatitis, neuropsychiatric disorders and, in the case of benzene, blood formation disorders, pancytopenia;
  - **late effects'** - benzene - acute non-lymphocytic and chronic myeloid leukemia.

Representatives

1. Benzene – Limited use due to high toxicity (e.g. in the pharmaceutical industry or for analytical work in laboratories), the largest source is oil, but it is also released in coke plants during the production of coke as part of coal tar, the lethal dose per person is about 10 – 15 ml, the main metabolite is benzepoxide – reactive, has carcinogenic properties and is able to '*react with DNA*. About 15% of benzene can be excreted unchanged by the lungs, and the rest is mainly excreted in the urine as phenol (it is also there as a product of amino acid metabolism), therefore we use S-phenylmercapturic acid as a suitable metabolite for assessing benzene exposure. After acute intoxication with benzene, neurotoxic manifestations are in the foreground, with long-term intoxication hematotoxic manifestations (leukopenia, thrombocytopenia, anemia, pancytopenia), after 10-20 years a *reversal in leukemia* is observed.



Toluene formula

2. Toluene – A very frequently used solvent, mainly for paints, glues and varnishes, it is one of the most abused solvents due to its easy availability, it has hallucinogenic effects (sound, vision). The lethal dose is 150 – 400 ml. It is first oxidized to benzoic acid in the human body, and after conjugation with glycine, it forms *hippuronic acid*, which can be detected in the urine.
3. Ethylbenzene – Used to produce styrene, its effects are neurotoxic. We use mandelic acid to detect it in urine (it is not present in urine under physiological conditions).
4. Xylenes – Industrial solvents and extraction agents, irritate and dry the skin, are completely metabolized to **methylhippuronic acid** and are excreted in the urine. Kidney damage has been reported after high exposure.

2. Chlorinated hydrocarbons

- Substitution of hydrogen by chlorine reduces flammability, hepatotoxicity and narcotic effect increase with increasing number of chlorine atoms, presence of double bonds reduces hepatotoxicity.
- Professional exposure is mainly in dry cleaners, in the metal industry, as a solvent for resins, varnishes and oils, tetrachloromethane was once widely used as a filler for fire extinguishers due to its non-flammability.
- Chlorinated hydrocarbons are well absorbed through the lungs, and with long exposure also through the skin.
- Effects:
  - **acute effects'**: CNS – excitation, disorientation, dizziness, drunkenness, nausea, unconsciousness (formation of CO in dichloromethane), hepatotoxicity and nephrotoxicity in tetrachloromethane and chloroform, pulmonary edema in the formation of phosgene after contact with flame or hot metal;
  - **chronic effects** - dermatitis, neuropsychiatric disorders, hepatotoxicity and nephrotoxicity (for tetrachloromethane and chloroform).

Representatives

1. Trichlorethylene – It is metabolized in the liver by alcohol dehydrogenase and aldehyde dehydrogenase to trichloroacetic acid and trichloroethanol and these are excreted in the urine. Trichloroethanol has a narcotic effect (with a half-life of 10 – 24 hours → therefore, in severe oral poisoning, it can cause new unconsciousness after temporary improvement). Trichlorethylene is not hepatotoxic or neurotoxic.
2. Perchlorethylene – Excreted unchanged by the lungs. Only a small part is metabolized to **trichloroethanol'** (via trichloroacetic acid).
3. Tetrachloromethane (CCl_4) and chloroform – about ½ are exhaled unchanged, ½ are metabolized in the liver. **Hepatotoxicity** is especially pronounced after oral poisoning, histologically we describe fatty degeneration

and subsequent necrosis. Steatosis indicates damage to endoplasmic reticulum and disruption of lipid transport from hepatocytes. Necrosis is apparently caused by the release of lysosomal enzymes by free radicals. CCl_4 is decomposed by the P-450 microsomal system, Cl^- and trichloromethyl radical are formed, HCl and phosgene $COCl_2$ are gradually formed and this is the main source of final CO_2 (this is the reason for the vulnerability of the liver, especially in alcoholics who have high levels of P-450 isozymes). Chloroform damages the liver only in high concentrations. **Nephrotoxicity** - tetrachloromethane damages the cells of the renal tubules, the glomeruli are more resistant and are not damaged. Kidney damage can also occur independently, especially after inhalation or percutaneous entry.

- For trichlorethylene, we use the determination of trichloroacetic acid and trichloroethanol in urine as an investigative method for determining exposure. For others, we only use the determination of the given solvent in exhaled air, urine or blood.

🔎 *For more information see Chlorinated hydrocarbon and benzene intoxication.*

3. Solvents refined from petroleum

- A mixture of hydrocarbons resulting from the distillation of crude oil.
- Professional exposure: solvents, fuels and propellants, gasoline (technical, varnish, automotive, aviation and others).
- Aliphatic saturated and unsaturated or aromatic hydrocarbons with low viscosity and low surface tension.
- Gasoline begins to evaporate already at room temperature and can therefore cause acute inhalation trauma.
- Effects:
  - **acute effects**: CNS – excitation, disorientation, dizziness, drunkenness, nausea, drowsiness, unconsciousness. Others – convulsions, after inhalation respiratory tract irritation, chemical pneumonia, pulmonary edema, after aspiration aspiration bronchopneumonia;
  - **chronic effects**: CNS – neuropsychiatric disorders, skin – dermatitis.

Representatives

1. Gasoline – At lower temperatures, a pronounced narcotic effect. The lethal dose per os is about 500 ml, as a result of aspiration death can occur even with a smaller dose (see below);
2. Kerosene and diesel – Higher temperatures are needed to irritate the respiratory tract, they are absorbed very well by the lungs, they are also excreted unchanged mainly by the lungs, therefore, apart from the CNS, the lungs are the most affected organ. High concentration in the air leads to '*chemical pneumonia.*

- Because all petroleum derivatives have low viscosity and low surface tension, it is enough for the victim to aspirate even a very small amount and aspiration bronchopneumonia will occur. This disease leads to a local decrease in lung surfactant function, alveolar instability, closure of peripheral airways, hypoxemia and direct damage to pulmonary capillaries. Predilection localization is the right lung basally, the onset is with a latency of 24 hours.
- **Treatment** - *vomiting is contraindicated*. We administer a small amount of activated carbon, monitor the pulmonary findings, and in the case of incipient bronchopneumonia, administer antibiotics. If a toxic dose is ingested, a larger amount of activated charcoal is administered, the patient is intubated and only then is gastric lavage performed.
- To determine the exposure, we use the amount in exhaled air or blood.

4. Carbon disulfide (CS_2)

Carbon disulfide molecule

- Colorless flammable liquid with a sweet smell.
- Evaporates at room temperature.
- The lethal dose per person is 10-15 ml.
- It is absorbed by inhalation, orally and percutaneously.
- The majority is retained in lipophilic tissues (CNS, PNS, liver), about 90% is then metabolized.
- Mainly damages the brain and peripheral nerves, neurotoxicity is caused mainly by the formation of dithiocarbamates (they cause antabuse - alcohol intolerance).
- They are then conjugated with SH-groups and 2-mercaptothiaturenic acid is formed, which is used to prove exposure.
- We can observe degenerative changes in the cerebral cortex, basal ganglia and cerebellum, pyramidal tracts and peripheral nerves (edema and fragmentation of axons).
- Degenerative changes in the musculature, significant changes are also seen in the cardiovascular system - the development of atherosclerosis, especially in the coronary arteries, and hemorrhage in the CNS.
- Professional exposure is in the production of viscose fibers and cellophane.
- Effects:
  - **acute effects** - euphoria, confusion, delirium, manic states, unconsciousness, mild respiratory tract irritation, skin erythema;
  - **chronic effects** - CNS - pseudoneurasthenic syndrome, organic psychosyndrome, manic-depressive states, extrapyramidal symptoms (Parkinsonian type), polyneuropathies (affecting the PNS), ischemic heart disease.
- Clinical picture
  - **acute**: irritation of the respiratory tract, conjunctiva and skin erythema, delirium, manic states, excitation, hallucinations, paranoid states and even unconsciousness;

    - **chronic**: milder intoxication is manifested by a pseudoneurasthenic syndrome, more severe by the development of depression, manic states, hallucinations and suicidal tendencies, typical is the involvement of peripheral nerves - n. peroneus (both sensitive and motor), areflexia;
- Investigation methods - in acute intoxication, an increase in liver enzymes and creatinine or the so-called iodazide test in the urine (mainly in the case of exposure to higher concentrations, i.e. above 50 mg. m^{-3}) - react in it except for free carbon disulfide also thiourea, 2-mercaptothiazolin-5-one and other substances, in case of chronic intoxication conduction disorder in EMG examination and changes in psychological tests, another test in urine is the detection of xanthurenic acid – this test is not specific and is positive in hypovitaminosis B6 and in [[diabetes mellitus]].

5. Alcohols

- Hydrocarbons containing one OH group.
- Liquids with a characteristic smell.
- Mainly simple alcohols are absorbed through the lungs, mainly methyl alcohol through the skin.
- They are metabolized by liver alcohol dehydrogenase into aldehydes and aldehyde dehydrogenase into carboxylic acids and then into carbon dioxide and water.
- Professional exposure: component of cleaning agents, solvents, for extractions, syntheses of plastics, varnishes, detergents, etc.
- Effects:
    - **acute effects'** - on the CNS - excitation, logorrhea, loss of judgment, drunkenness, dizziness, disorientation, drowsiness, vomiting, unconsciousness. Methyl alcohol causes damage to the retina and neuropathy of the optic nerve (impaired vision, glare, photophobia, blindness);
    - **chronic effects'** – *Methyl alcohol* (rare): CNS disorders. *Ethyl alcohol*: chronic alcoholism, organic psychosyndrome, polyneuropathy, liver cirrhosis;
    - **late effects** - consumption of ethyl alcohol has been shown to be associated with cancer of the oral cavity, pharynx, larynx, liver, less stomach cancer, breast and rectum.

Representatives

- **Methyl alcohol** (formerly wood alcohol) – Well absorbed through the lungs and skin, these exposures can also lead to serious consequences. It is mainly taken orally, mistaking it for alcohol, it is exhaled unchanged through the lungs, the rest is oxidized to formaldehyde and then rapidly metabolized to formic acid. Detoxification of this metabolite is provided by folic acid - but its capacity varies from person to person, and moreover, oxidation to end products - water and carbon dioxide is slow, which is why the terrible accumulation of formic acid. Intoxication with methyl alcohol causes severe metabolic acidosis, which is the main contributor to visual impairment. Suspension disorders usually appear with a 24-hour latency, are manifested by blurred vision, flashes of light and feelings of glare or changes in color vision. On the background of the eye, we observe hyperemia and edema in the n. opticus area, formic acid salts damage retinal cells also by reducing cytochrome oxidase activity and thus oxygen supply. Blindness is already described after ingestion of 15 ml, death after 30-40 ml. Metabolism of methyl alcohol is about 6 times slower than that of ethyl alcohol.
    - **Treatment** - the antidote is ethyl alcohol administered orally (40 - 80 ml of ethyl alcohol). We keep the level at 1 - 1.5 per thousand, so that the alcohol dehydrogenase is saturated. We also administer folic acid and correct metabolic acidosis. It is important to take care of vital functions, hemodialysis is indicated at a level of methyl alcohol in the blood of 400 mg/l. The ideal antidote is fomepizole (preparation ``Antizol*) – it inhibits alcohol dehydrogenase. Its availability is limited due to its high price.*
    - **Examination of exposure** - methyl alcohol in the urine, in case of intoxication in the blood, formic acid in the blood and urine is more reliable (the maximum is after 2-3 days after ingestion). However, its determination is not carried out.
- **Ethyl alcohol** - almost completely metabolized. Up to 10% is exhaled through the lungs unchanged or excreted in sweat and urine. The main effects are CNS depression and coma with respiratory depression, an irritating effect on the GIT (vomiting, together this leads to the risk of aspiration, intoxicated persons are often susceptible to cold due to vasodilation). It is absorbed quickly from the digestive tract, spirits the fastest, beer more slowly. The maximum level appears 30-40 minutes after ingestion. The concentration of alcohol in the blood (per mille) can be roughly estimated from the amount of alcohol consumed in grams and divided by (0.7 x body weight). Ethyl alcohol is oxidized to acetaldehyde - acetic acid - carbon dioxide and water. The rate of detoxification is constant, independent of the dose and represents about 0.1 g of ethyl alcohol/kg of weight per hour.

- **Clinical picture'**:
    - *1 per thousand* - euphoric stage, suppression of gluconeogenesis and hypoglycemia.
    - "2 per thousand" – prolongation of reaction times, movement coordination and balance disorders, analgesia, feeling of intoxication.
    - *3 per thousand* - narcotic stage, coma and respiratory depression. In an experienced drinker, however, consciousness can be preserved even at 5 per thousand, when normally there is an asphyxic stage with hypothermia, cyanosis, convulsions and even respiratory arrest.

The cause of death is usually aspiration of vomit, colds, bronchopneumonia, pulmonary edema.

- **Treatment** - placing the victim in a stabilized position (protection against aspiration), treatment of hypothermia, administration of glucose and thiamine. No specific alcohol receptor antagonist is available. In the case of coma, the beneficial effect of the antidotes naloxone and flumazenil is described. Gastric lavage is important no longer than 30 minutes after ingestion, activated charcoal or forced diuresis have no effect.

Hemodialysis has a good effect, but it is performed at levels of 4-5 parts per thousand, most patients wake up after 4-6 hours.
- Examination methods - we examine the level in the blood, indicative qualitative evidence in the exhaled air.

1. Isopropyl alcohol.
2. Cyclohexanol.

6. Glycols (ethylene glycol)

- Hydrocarbons with two OH groups.
- They are syrupy liquids with a sweet taste.
- Toxicity is very different, there is a biotransformation into glycolaldehyde, glycolic, glyoxylic and oxalic acid - acidic metabolites damage renal tubules by forming calcium oxalate - kidney damage and acidosis, osmolality increases significantly, lethal dose is 100 ml of ethylene alcohol.
- Professional exposure: industrial solvent, production of antifreeze mixtures (Fridex, brake fluids).
- Effects:
  - **acute effects** - resorption by the lungs at room temperature due to low vapor tension is not considered. Skin absorption is low, Per os – excitation, later CNS depression, acute renal failure and metabolic acidosis;
  - **chronic effects** - dermatitis.
- Clinical picture:
  - ***neurotoxic stage*** - transient drunkenness, vomiting, drowsiness, development of metabolic acidosis with hyperosmolality within 12 hours, twitches to convulsions, impaired consciousness to coma (secondary brain edema). Exceptionally, death within 12 hours;
  - ***cardiopulmonary stage*** - within 24 hours, dysrhythmia, severe acidosis with hyperventilation, circulatory collapse, hypocalcemia, convulsions, pulmonary edema, cerebral edema, cardiorespiratory arrest;
  - ***renal stage*** - within 74 hours, hematuria, albuminuria, oliguria, acute tabular necrosis to anuria, oliguria may persist for several weeks, kidney function does not return to the physiological norm.
- Treatment – the antidote is ethyl alcohol, administered as quickly as possible per person. Its level is maintained at 1-1.5 parts per thousand (it has a 100x higher affinity to alcohol dehydrogenase). The unconverted ethylene glycol is then excreted in the urine. Vitamins B1 and B6 and folic acid are also administered, hemodialysis is indicated at a level above 300 mg/l. The optimal antidote is fomepizole (inhibition of alcohol dehydrogenase). Because of its high price, it is rarely indicated, especially in children.
- Investigation methods - determination of ethylene glycol in the blood.
  1. Diethylene glycol.
  2. Propylene glycol.

Links

Related Articles

- Intoxication by chlorinated hydrocarbons and benzene
- Safety data sheets

References

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