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JESSENIUS FACULTY OF MEDICINE IN MARTIN

SELECTED CHAPTERS IN TOXICOLOGY

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University textbook

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The authors are responsible for formal accuracy and language.

The authors devoted themselves to ensuring that the information presented on the drugs corresponded to the level of knowledge at the time of processing the textbook. When administering drugs, the authors recommend that you always follow the information on contraindications and doses listed in the inserted package patient information leaflet. This applies in particular to newly introduced products or products used less frequently.

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Contents

Foreword

The first edition of the university textbook *“Selected Chapters in Toxicology”* aims to serve as a concise, lucid, and compendious study material intended to teach students general and dental medicine.

The use and presence of various chemicals in the living and working environment has been a serious long-term environmental problem that will also be present in the future. Therefore, all junior doctors should be well aware of all the necessary information, not only on acute poisonings they may encounter in emergency medicine, but also on the long-term and chronic effects of chemicals that need to be considered in the differential diagnosis of diseases.

Scientific research constantly provides new information on various negative factors in the environment, which obviously degrade the quality of all its components. It is doctors who, based on their extensive general and professional knowledge, including knowledge in the field of toxicology, should be at the forefront of the fight against inherited and new chemicals in the living and working environment. The extraction of raw materials, exponential growth of new chemicals, their use and landfilling lead to contamination of the air, water, and soil, which directly affects the health of the current population and will endanger the health of future generations.

We believe that this textbook edition will provide all missing information necessary for the study of internal medicine, dentistry, and occupational medicine in a more comprehensive form and at the same time will help all practising physicians in diagnosing and treating selected acute and chronic intoxications.

Doc. MUDr. Oto Osina, Ph.D.

List of abbreviations used

AAS	Atomic absorption spectrophotometry
AChE	Acetylcholinesterase
AV	Atrioventricular
CCBs	Calcium channel blockers
CNS	Central nervous system
CT	Computed tomography
CVS	Cardiovascular system
DMA	Dimethylarsinic acid
DMPS	Sodium dimercaptopropanesulphonate
DMSA	Dimercaptosuccinic acid
DNA	Deoxyribonucleic acid
GC	Gas chromatography
GIT	Gastrointestinal tract
IARC	International agency for research on cancer
ICP-MS	Inductively coupled plasma – mass spectrometry
LC	Lethal concentration
LD	Lethal dose
MDMA	Methylenedioxymethylamphetamine
MMA	Monomethylarzenoic acid
MPEL	Maximum permissible exposure limit
NTIC	National toxicological information centre
PPE	Personal protective equipment
PNS	Peripheral nervous system
TCA	Tricyclic antidepressants
TRV	Toxicity reference value

1 General Toxicology

Toxicology is a multidisciplinary scientific discipline that helps us understand the harmful effects that poisons can have on living organisms, including humans. In terms of approaches to the subject of research, the science of toxicology can be subdivided into the following principal disciplines:

Experimental toxicology – examines the harmful effects of poisons in vitro, in vivo, determines maximum tolerated doses or participates in the development of antidotes.

Analytical toxicology – deals with qualitative and quantitative analysis of various toxins.

Taxonomic toxicology – addresses the classification and division of toxic substances in terms of occurrence in nature and use in various sectors of human activity (agriculture, general or pharmaceutical industry).

Preventive toxicology – deals with risk assessment, legislation and standards to minimize the impact of the use of toxic substances on the environment and humans.

Applied toxicology – has a special position in relation to human and veterinary medicines and its content integrates the following subdivisions:

Clinical toxicology – deals with the monitoring of intoxication symptoms, their dynamics, consequences in organ systems, their elimination and treatment.

Industrial toxicology – examines the effects of various substances used in various industries on employee health. It determines the maximum permissible exposure limits (MPELs), and analyses, identifies and monitors the kinetics of their action.

Military toxicology – deals with the research, production, identification, protection, detoxification or treatment of intoxications with highly toxic substances that can be used as weapons of mass destruction in military conflicts.

Forensic toxicology – from a legal and forensic point of view, identifies and investigates organ changes related to evidence gathering in criminal investigation process.

Veterinary toxicology – deals with the identification, diagnosis and treatment of toxicosis of various animals. It investigates the possible transmission of toxins to humans through food products.

Environmental toxicology – examines the movement of toxic substances in the environment, their penetration into the food chain or their degradation.

1.1 Glossary of Terms Used in Toxicology

Xenobiotics, from a toxicological point of view, are all chemical substances that are foreign to the body and thus may or may not cause harm to the organism.

A poison (toxin) is any substance which, when accidentally or intentionally administered in small quantities, causes damage or death to a biological system.

The effect of the toxin on the organism depends on the one hand on the dose, physicochemical properties, routes of entry, on the other hand on the condition and properties of the biological system.

The toxin can enter the body in several ways, most often through the respiratory system after inhalation, also through the gastrointestinal system after drinking or ingestion, or through intact or damaged skin in direct unprotected contact. In special cases also intravenously, intramuscularly, subcutaneously, through the rectum (*per rectum*), through the vagina (*per vaginam*) or by the upper respiratory tract mucosa.

Poisoning (intoxication) is a disease state caused by the penetration of poison into the body. In terms of time, intoxications can be divided into acute and chronic.

Acute intoxication occurs when the toxin suddenly enters the body, and the resulting effect depends on the physicochemical properties of the toxin and the state of the body.

Chronic intoxication occurs as a result of the long-term exposure of the body to the continuous or repeated low doses of toxins, which accumulate in the body (heavy metals) or cause repeated "minor" damages, which gradually develop the disease state with later clinical manifestations.

Exposure means exposing a biological organism to a toxin. Exposure can be single or repeated. Single exposure occurs when the body is accidentally or intentionally exposed to toxic substances. Repeated exposure occurs when the body is exposed to toxins for a long time.

Toxicity – the property of chemicals to cause poisoning (intoxication) after penetration into the organism.

Toxic dose – the amount of poison that causes clinically manifested intoxication, but does not result in death. The lower the dose required for intoxication, the more toxic the substance.

Lethal dose (LD) – the minimum amount of toxin that causes death.

LD_{50} (Lethal dose, 50%) – the dose required to kill half (50%) the members of the tested laboratory animal population after oral, transdermal or intravenous administration.

Lethal concentration (LC) – the concentration of a chemical in the inhaled air that causes death.

LC_{50} (Lethal concentration, 50%) – the concentration of a chemical in the inhaled air that will kill 50% of the laboratory animal population.

Maximum Permissible Exposure Limit (MPEL) – an upper limit on the acceptable concentration of a chemical hazard in workplace air of the employee's respiratory zone for a specific length of time.

Technical Reference Value (TRV) – set for carcinogenic and mutagenic factors of groups 1 and 2, for which the maximum permissible exposure limit cannot be set. It represents the average value of the concentration of a carcinogenic or mutagenic factor in the air of a employee for a specific length of time.

1.2 Health Effects of Chemicals in General

1.2.1 Toxic Health Effects of Chemicals

The effects of chemicals are the result of the interaction between the organism and the substance itself. The resulting effect is influenced by several factors. From the point of view of the organism, these include: general health, age, nutrition, presence of other diseases, metabolic capacity, or activity performed. From the point of view of the chemicals, these include: physical and chemical properties of the chemical substances, duration of exposure, total dose, etc. In some cases, the current living or working conditions (temperature, humidity, air flow, etc.) may also play an important role.

Toxic effects can cause damage to the whole organism or to individual organ systems, tissues or cells. In terms of the leading effect, chemical substances can be divided into irritant, allergenic, carcinogenic, haematotoxic, neurotoxic, hepatotoxic or nephrotoxic substances. In general, one substance can have multiple toxic effects.

1.2.2 Irritant Health Effects of Chemicals

Irritants are substances that may cause irritation or even more serious injuries to the conjunctiva, mucous membranes or skin. Their effect depends on the route of entry into the organism, their state and concentration. Common irritants include inorganic acids and bases, which cause local corrosive and even necrotic injuries. Local irritation or even more serious injury to the conjunctiva, airways or lungs can be caused by various chemical substances, e.g. phenols, iodine, fluorine, chlorine, sulphur dioxide, ammonia and others.

1.2.3 Allergizing Health Effects of Chemical Substances

The immune system can react to various substances in the living or working environment by increased production of antibodies called Immunoglobulin E (IgE). Sensitization occurs upon the first contact with an allergen. More often, sensitization can develop in patients with atopic dermatitis, who have a hereditary predisposition to allergic reactions. Repeated contact of a sensitized individual with allergens causes an immune reaction, the result of which is the release of mediators of the allergic reaction: histamine, serotonin and others. The result is an increase in the permeability of cell

membranes with local or global manifestations. Proteins, polysaccharides, chromium, nickel, platinum, isocyanates, epoxies and others can be included into this group.

1.2.4 Carcinogenic Health Effects of Chemical Substances

According to current knowledge, oncological diseases can result from DNA damage, which can arise spontaneously or be caused by external influences. Usually, it is a combination of genetic factors, lifestyle, and the activity of the immune system with the environmental factors such as ionizing radiation, chemical substances or microorganisms.

Carcinogens are the cancer-causing substances, organisms or exposures. Examples include chemical substances, microorganisms (oncogenic viruses), radiation (ionizing, non-ionizing) or work processes that are capable of causing or promoting the emergence and development of cancer in humans or animals.

Carcinogens induce somatic DNA mutations and result in the induction of tumorigenesis. Carcinogenesis is a multistep process that includes initiation, promotion, and progression. In the initiation phase, irreversible DNA damage occurs, however, the initiation itself does not lead to the development of cancer. In the promotion phase, the formation of specific factors (proteins) that prevent the transcription of damaged DNA is inhibited, which allows the growth of damaged (tumour) cells and ultimately leads to the progression of cancer.

Exposure to carcinogens does not always lead to developing the oncological disease. Depending on the properties of the substance, several years of exposure or a high concentration of the substance exceeding the technical reference values are necessary for the development of cancer.

Tumour diseases can manifest themselves clinically with a delay of several years (latency period) from exposure. For most tumours, the latency period ranges from 12 to 25 years. Ionizing radiation-induced cancer has a latency of 3 – 5 years. However, the median latency period from asbestos exposure to the development of mesothelioma is 40 years.

The International Agency for Research on Cancer (IARC) is the specialized cancer agency of the World Health Organization (WHO), and its role is to conduct and coordinate research into the causes of cancer. At the same time, IARC has devised a system of categories to evaluate the carcinogenicity of an agent to humans. Within this

classification, the chemical substances and physical factors are divided into 5 groups according to their carcinogenic potential.

Individual groups and their nomenclature are listed in Table 1. Selected carcinogens of group 1 and their target organs are listed in Table 2.

Table 1. Classification of carcinogenic substances according to IARC

Group	Description
1	Evidence of carcinogenicity in humans
2A	Probably carcinogenic to humans with limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals
2B	Possibly carcinogenic to humans with inadequate evidence of carcinogenicity in humans but sufficient evidence of carcinogenicity in experimental animals
3	Not classifiable as to its carcinogenicity to humans
4	Probably not carcinogenic to humans

Table 2. Cancer localization and selected carcinogens of the 1st group according to IARC

Cancer localization	A chemical carcinogen
Urinary bladder	4-Aminobiphenyl, benzidine, coal-tar and coal-tar pitch, α-naphthylamine, β-naphthylamine, soot, etc.
Kidneys	Polycyclic aromatic hydrocarbons, α-naphthylamine, β-naphthylamine, benzidine, etc.
Lungs	Arsenic (As) and its compounds, asbestos, Cadmium (Cd), Cr6+, nickel (Ni), radon (Rn), bis(chloromethyl) ether, soot and tars, etc.
Paranasal sinuses	Nickel (Ni), chromium (Cr)
Skin, scrotum	Coal-tar and coal-tar pitch, mineral oils, bituminous shale (oil shale), soot, tars, oils, etc.
Liver	Arsenic (As) and its compounds, vinyl chloride, etc.
Bone marrow and blood components	Radium (Ra), benzene, ethylene oxide, etc.

1.2.5 Hepatotoxic Health Effects of Chemical Substances

The liver, as the main biotransformation organ, can be exposed to damage either directly, after oral intoxication when toxic substances enter the portal system, or indirectly after the penetration of xenobiotics into the bloodstream, e.g. via respiratory system. According to the effect on the liver, the chemical substances can be divided into primary hepatotoxic and facultative hepatotoxic. Primary hepatotoxic chemical substances can damage the hepatocyte directly or through their metabolites. The extent of damage is directly proportional to the dose and results in steatosis, cirrhosis or necrosis of hepatocytes. Primary hepatotoxic chemical substances include most of the substances used in various industries. Facultative hepatotoxic chemical substances can cause hepatocyte damage only in susceptible individuals and the extent of damage is not directly proportional to the dose. Among the facultative hepatotoxic drugs, the following can be included: isoniazid (Nidrazid tbl.), diclofenac, amoxicillin and others.

The liver also plays an important role in the excretion of chemical substances. Several chemical substances are secreted directly into the bile, by which they are subsequently transported to the intestine and excreted in the stool. However, their reabsorption and re-transportation to the liver can occur in the small intestine (enterohepatic circulation). As a result of metabolic processes, toxic metabolites may form in the liver, and their negative effects on the hepatocyte are far more serious than the effects of the original chemical substance. After long-term exposure, liver cirrhosis may develop, which may further progress to hepatic failure. Common chemical substances that can cause hepatotoxicity include ethyl alcohol, tetrachloromethane, copper. The well-established hepatotoxic drugs include isoniazid, phenylbutazone, cytostatics and others. Tumour diseases of the liver, e.g. angiosarcoma or hepatocellular carcinoma may develop after exposure to vinyl chloride, some auramine-based dyes, etc.

1.2.6 Haematotoxic Health Effects of Chemical Substances

The sensitivity of blood elements and bone marrow cells to chemical substances depends not only on the properties of the chemical substance, but also on the age of the intoxicated person. Children are more sensitive to chemical substances due to the higher activity of the bone marrow and of the entire haematopoietic system.

In older adults, on the other hand, the activity of metabolic processes and the immune system decreases, which also increases the risk of damage by chemical substances and drugs. Haematologic diseases can be divided into primary and secondary.
Primary haematologic diseases arise as a result of direct damage to all or individual components of the haematopoietic system. This type of damage can be caused by benzene (medullary depression), arsenic (haemolysis), lead (hypochromic anaemia) and others.
Secondary haematologic diseases of the hematopoietic system are diseases where a damage to the other target organ system occurs primarily and haematologic damage is associated. As an example, secondary haematotoxic effect has been observed in trinitrotoluene (primarily being hepatotoxic, secondarily causing anaemia).

1.2.7 Nephrotoxic Health Effects of Chemical Substances

One of the primary functions of the kidneys, in addition to maintaining the stability of the internal environment, is to cleanse the blood of waste products, toxins and their metabolites. After exposure to a toxic dose, the clinical picture and the course of acute intoxication are similar for most chemical substances with nephrotoxic effects. Nephrotic syndrome may develop when damage occurs to the glomeruli, e.g. after intoxication with cadmium or metallic mercury. The toxic effects of most substances affect the tubules, where tubular necrosis occurs due to an increase in the concentration of toxins or their metabolites. At the tubular level, the effects of organic solvents, heavy metals, lithium, analgaesics, non-steroidal anti-rheumatic drugs and other drugs are noticeable. As a result of tubular necrosis, which occurs hours to days after exposure, urine production decreases to the level of oliguria or anuria, blood creatinine and urea increase, and uremic syndrome may develop. At the same time, there is a disruption of the internal environment with electrolyte imbalance and metabolic acidosis.
Haemodialysis or haemoperfusion may not always lead to the acceleration of the elimination of the toxic substance from the body. In general, the extracorporeal removal of chemical substances from the body is more effective for substances that are well soluble in water, which have a low volume of distribution, low molecular weight, low affinity for plasma proteins and low tissue binding ability.

1.2.8 Neurotoxic Health Effects of Chemical Substances

The effects of chemical substances on the nervous system are influenced by the anatomical structure of its central and peripheral parts. The nervous system is partially protected from the penetration of toxic and pathogenic substances by specific barriers that, in addition to the protective functions, also have other functions, e.g. transport or regulatory. From an anatomical-functional point of view, it is possible to distinguish the blood-brain barrier, the blood-liquid barrier, the blood-spinal barrier and the haematoneural barrier. Low-molecular, non-polar and lipophilic substances can pass through the mentioned barriers. Some chemicals can damage the nervous system in several places at once. In the case of several poisonings, central symptoms dominate due to the direct action of the toxin on the CNS. However, the damage to the CNS can also occur as a result of hypoxia caused by dissociation of O_2 from haemoglobin or reduction of its saturation in the lungs.

Toxic peripheral neuropathies are usually symmetric – the same in both limbs. They can have the character of sensitive or sensitive-motor polyneuropathy. The toes and feet of both lower limbs are usually affected first, then both hands. The first to appear are sensory disturbances (tingling, prickling, burning), described as a sensation of wearing an invisible "sock" or "glove".

1.3 Diagnostics, General Principles of First Aid and Intoxication Treatment

The basis of the diagnosis of all intoxications is the anamnestic data from a patient. If the patient is unconscious, the data can be obtained from relatives, friends or colleagues. The possible sources of poisoning (medicines, alcohol, chemicals, leakage of toxic substances in the working environment) need to be sought at the place of intoxication. In the case of unconscious patient without an obvious cause of intoxication, it is important to find out what medications he/she is taking, or to contact a general practitioner. Intoxication can also be caused by plants, animals or improperly used preparations of traditional Chinese medicine. A thorough physical examination may reveal puncture wounds or other signs of self-harm. Unknown substances, food or drink residues must be labelled and sent for toxicological analysis. The symptoms that may indicate a possible intoxication are listed in Table 3.

Table 3. Sets of symptoms and possible causes of intoxication

Sets of symptoms	Possible cause of intoxication
Coma, mydriasis, divergent strabismus, tachycardia, increased muscle tone, plantar hyperreflexia	Tricyclic antidepressants, anticholinergics (Atropa belladonna)
Coma, hypotension, respiratory depression, decreased muscle tone	Barbiturates, benzodiazepines, possible combination with alcohol
Coma, sharp miosis, hypoventilation	Opiates, organophosphates
Tinnitus, hyperventilation, sweating, tachycardia, nausea, hearing impairment	Salicylates
Agitation, tremor, mydriasis, tachycardia	Sympathomimetics, amphetamines, cocaine, ecstasy, selective serotonin inhibitors
Profuse sweating, salivation, lacrimation, history of mushroom consumption	Muscarine, parasympathomimetics

In patients suspected of intoxication, it is necessary:

- To do a complete and quick physical examination.
- To assess and record consciousness regularly using the Glasgow Coma Scale (GCS).
- To monitor respiration and O_2 saturation using a pulse oximeter.
- to record and monitor the ECG for the possible occurrence of tachycardia, bradycardia or arrhythmias in unconscious patients.
- To provide venous access,
- To measure and record blood pressure and body temperature.
- To check blood glucose in comatose or confused patients.
- To interrupt exposure or reduce absorption of toxin.

In case of intoxication by some known poisonous substances, specific antidotes are available, which need to be administered in a targeted manner as soon as providing first aid or immediately after the patient is admitted to the hospital.
Selected toxic substances and their specific antidotes are given in Table 4.

In case of suspected or obvious acute intoxications, it is possible to contact helpline consultation service 24 hours a day provided by the National Toxicological Information Centre (NTIC). The NTIC concentrates, analyses and provides information on industrial preparations, plant and animal toxins, as well as antidotes and drugs used in the treatment of intoxications.

NTIC contacts:

Tel.: 24-hour service: +421 2 5477 4166

Further information: +421 2 5465 2307

GSM: +421 911 166 066

E-mail: ntic@ntic.sk

Table 4. Selected toxic substances and their antidotes

Toxic substance	Antidote
Acetaminophen (metabolite of paracetamol) Acrylonitrile	Acetylcysteine (ACC Inject amp.)
Amanita phalloides	Silibinin inj. (Legalon Sil amp.)
Arsenic trioxide (white arsenic, As_2O_3), mercury	Dimercaptopropane Na-sulphonate cps. (Dimaval -DMPS cps.)
Atropine, scopolamine, Datura stramonium, Atropa belladonna	Physostigmini salicylas inj. (Anticholium amp.)
Antidepressants	
Antihistamines	
Beta blockers	Glucagon inj.
Benzodiazepines	Flumazenil inj. (Anexate amp.)
Digoxin	Digitalis-Antidot BM inj. in case of unavailability Kalium chloratum 4 - 10 g/d in slow i.v. infusion.
Ethylene glycol	Ethyl alcohol, Fomepizole
Methyl alcohol	
Cyanides (HCN, KCN, NaCN)	4-Dimethylaminophenol, inj. (4 DMAP amp.)
Methemoglobinizing substances (aniline, benzidine, o-toluidine, nitrobenzene)	Tolonium chloride inj. (Toluidine blue amp.) Methylene blue inj. (Methylene blue amp.)
Opioids	Naloxone hydrochloride inj. (Naloxone amp.)
Organophosphates	Atropini sulfas inj. (Atropine Biotika inj.) Obidoximi chloridum inj. (Toxogonin amp.)
Carbon monoxide (CO)	Oxygen (100 % O_2)
Paracetamol	Acetylcysteine (ACC Inject amp.)
Toxic and radioactive metals - lead, chromium, cobalt, vanadium, zinc, cadmium	Calcium disodium Edetate inj. (Calcium Edétate de Sodium SERBIA inj.) (Chelintox)
Tricyclic antidepressants	$NaHCO_3$ (Sodium bicarbonate)

2 Toxicology of Selected Industrial Substances

2.1 Inorganic Compounds

2.1.1 Arsenic

English term	Arsenic
Chemical element	As
Toxicologically significant oxidation states	3^+, 5^+
IARC classification	**1** (confirmed human carcinogen)
Main target organs or systems	**GIT, KVS, CNS, PNS, lungs, skin**

Characteristics and occurrence: Arsenic (As) is a toxic metalloid, tasteless and odourless chemical element, already known in ancient Greece and Egypt. Its trivalent inorganic compounds, especially the highly toxic arsenic trioxide As_2O_3 (white arsenic), have higher toxicity than the pentavalent ones. In nature, arsenic occurs primarily in its sulphide form. Arsenopyrite (FeAsS) is the most common arsenic sulphide mineral and the major source of arsenic. Arsenic is found in various types of metalliferous deposits; it is common in iron, nickel, silver or gold, trace amounts are found in coal deposits.

Environmental and professional exposure: In the environment, arsenic and its compounds are found in the atmosphere, soil and water. Generally, arsenic is released into the atmosphere by high-temperature processes such as volcanic activity, coal-fired power plants, burning vegetation, mining and smelting of non-ferrous metals, or application of pesticides. Water is the main distribution medium of arsenic and its compounds. Through rainfall, it can be transported even over long distances. Arsenic compounds present in sediments can found in rivers, lakes, and also in groundwater. Increased exposure of the population can be detected in the areas with the increased accumulation of arsenic in groundwater intended for human consumption. From water and soil, arsenic enters the human food chain through algae and plants.

Arsenic and its compounds are widely used in the semiconductor and electronics industries – gallium arsenide in the production of semiconductors and microprocessors, in the hardening of lead, in the production of ammunition and battery cells. The arsenic-organic compound "Lewisite" is a chemical warfare agent with blistering and irritating effects. In agriculture, it is used in the production of fungicides, insecticides, and herbicides.

Toxicokinetics: Arsenic-soluble compounds are well absorbed after inhalation and ingestion. Dermal absorption also occurs, but to a lesser extent. Inorganic As^{3+} is methylated in the body into less toxic monomethylarsinic acid (MMA) and dimethylarsinic acid (DMA). Arsenic is eliminated from the blood relatively quickly; the biological elimination half-life is 10 hours. Arsenic enters into all organs, passes through the blood-brain barrier and the placenta. Its accumulation occurs in the liver, kidneys, hair, nails and skin.

The effects of arsenic on the organism are multisystemic. Trivalent inorganic arsenic compounds have an affinity for the SH groups of proteins, which they block. The most sensitive are hydrolases (lipase, α-amylase, enterokinase, urease, pepsins).

The genotoxic and carcinogenic effects of As^{3+} are caused by direct damage to the DNA structure, inhibition of DNA repair processes or disruption of gene expression.

Acute symptoms of intoxication:

Cardiopulmonary symptoms: these occur in 2-24 hours after inhalation exposure to hydrogen arsenic (AsH_3). They are manifested by cough, chest pains. Following absorption, haemolysis develops, accompanied by headache, nausea, high body temperature and chills. Arrhythmias and prolongation of the QT interval appear. Manifestations of multi-organ intoxication occur later.

Gastrointestinal symptoms: after oral intoxication, nausea, vomiting, severe diarrhoea, and abdominal pain appear. Increased capillary permeability in the mesenteric area leads to hypotension, tachycardia and the development of shock.

Central symptoms: these are variable and can be manifested by convulsions, confusion, unconsciousness, failure of breathing and circulation, which lead to death.

Late symptoms: these appear after 1-4 weeks if the patient survives the acute stages of intoxication. Peripheral sensorimotor polyneuropathy, anaemia, leukopenia develops. Cancers may appear later.

Subacute manifestations of intoxication:

They develop after absorption of doses higher than 0.05 mg/kg/d lasting weeks to months. The multisystem effects of arsenic are manifested by fatigue, peripheral neuropathy, gastrointestinal symptoms, an increase in hepatic enzymes, a decrease in haemoglobin, and arrhythmias with prolongation of the QT interval.

Chronic symptoms of intoxication:

These arise after multi-year oral exposures to doses lower than 0.01 mg/kg/d. Epidemiological studies indicate a relationship to the development of diabetes mellitus, hypertension and increased cardiovascular mortality.

Dermal damage: hyperpigmentation, palmar and plantar hyperkeratosis, alopecia, brittle nails with typical transverse lines (Mees' lines) develop.

Polyneuropathies: the sensorimotor ones; the upper and lower extremity disability is symmetrical, or of the "glove" or "sock" type, which is manifested by a loss of sensitivity up to the development of painful paraesthesia.

Peripheral angiopathy: manifests itself with the progressive loss of peripheral circulation, which ultimately leads to necrosis and gangrene. Blackfoot disease occurs as a result of prolonged drinking of arsenic-contaminated water. The highest incidence was recorded in Taiwan.

Carcinomas: arsenic can also cause lung, kidney, bladder, and skin cancer, and also liver angiosarcoma.

Diagnosis and differential diagnosis: It is necessary to exclude other causes of gastrointestinal complaints, hepatopathy, polyneuropathy and simultaneously confirm exposure to arsenic. Work anamnesis and confirmation of exposure are important.

Treatment: After accidental, acute oral intoxication, it is necessary to induce vomiting as soon as possible, or perform gastric lavage, administer activated charcoal, support blood circulation, and prevent shock.

DMPS-Dimaval (sodium salt of 2,3 dimercapto-1-propanolsulfonic acid) is administered as an antidote for acute and chronic intoxication according to the therapeutic protocol.

Preventive measures: The use of arsenic and its compounds in Europe is controlled by a regulation of the European Commission. The biological exposure test determines the presence of arsenic in the hair, and MMA and DMA are determined in the urine. It is important to monitor arsenic in the living and working environment.

2.1.2 Chromium and its Compounds

English term	Chromium
Chemical element	Cr
Toxicologically significant oxidation states	3^+, 5^+, 6^+
IARC classification	**1** Cr^{6+} and its compounds (confirmed human carcinogen) **3** Cr^{3+} (not classified as a human carcinogen)
Main target organs or systems	**Skin, GIT, lungs, immune system**

Characteristics and occurrence: Chromium (Cr) is a hard steel-gray metal element, occurring in nature in Earth's crust, in the form of ores, especially in crocoite ($PbCrO_4$) and chromite ($FeCr_2O_4$). From a toxicological point of view, the effects of chromium are conditioned by its oxidation form, with the most stable form being Cr^{3+}.

Environmental and professional exposure: In the environment, chromium, as a product of human activity, is found in water and air, mainly in industrial agglomerations. Hexavalent chromium is part of cigarette smoke, where its content is approximately 300 µg/kg. Professional exposure occurs in the mining, crushing and smelting of ores, in the production of stainless steel, galvanic chrome plating of other metals, in the tanning industry, in the preservation of wood, in the production of colour pigments, in the production of materials for endoprostheses. Further, it is found in welding smoke, and in small quantities in cement.

Toxicokinetics: Chromium enters the human body orally, by inhalation and to a lesser extent through the skin, e.g. while tattooing. Trivalent chromium is essential for humans, it participates in the metabolism of carbohydrates and lipids. Trivalent Cr^{3+} is also part of the glucose tolerance factor (GTF), which interacts with membrane insulin receptors, thereby supporting the insulin-mediated transfer of glucose from the bloodstream into the intracellular space. After absorption, Cr^{3+} binds to plasma proteins (transferrin).

Toxic and carcinogenic Cr^{6+} is selectively absorbed by erythrocytes in the bloodstream, binds to haemoglobin, easily penetrates cells, where it is converted to Cr^{3+} and forms bonds with proteins and nucleic acids. Accumulation of chromium in the organism generally does not occur. Chromium is excreted by the kidneys.

Acute symptoms of intoxication:

Irritable symptoms: irritation of the eyes, nose, throat and respiratory tract, cough, chest pain, shortness of breath. All these can appear after inhalation of high concentrations of Cr6+.

Allergic symptoms: sneezing, rhinorrhoea, bronchospasm, attacks of irritating cough. These appear with a latency of several hours.

Dermal symptoms: irritant or allergic dermatitis, eczema. Painless ulcerations with impaired healing (chrome holes) may appear on the fingers after only a short exposure.

Gastrointestinal symptoms: after ingestion of high doses of Cr^{6+} compounds, nausea, vomiting, abdominal colic pains appear. Death can occur as a result of uraemia in renal tubular necrosis.

Chronic symptoms of intoxication:

Damage to the respiratory system: after a long-term exposure, atrophic rhinitis develops with ulcerations, epistaxis and even perforation of the nasal septum, anosmia. Laryngitis and chronic bronchitis are more common.

Dermal symptoms: dermatitis, non-healing chronic ulcers.

Carcinomas: lung and paranasal sinus tumour can appear even many years after the exposure.

Diagnosis and differential diagnosis: It is necessary to exclude other diseases of the respiratory tract, bronchial asthma, damage by other chemical substances, skin allergies and dermatitis of other origin. Confirmation of chromium exposure can be done by ICP-MS or AAS from urine, blood, plasma and hair. Work anamnesis is important.

Treatment: Acute inhalation intoxication requires urgent treatment – oxygen therapy, bronchodilators and monitoring of electrolyte balance. It is possible to administer ointment containing $CaNa_2$ – EDTA for skin and nasal ulcerations. Immediate and permanent termination of exposure is important.

Preventive measures: Technical measures to limit dust are of primary importance. Depending on the circumstances it is necessary to use PPE (respirators, masks, protective clothing, rubber gloves). Entrance and preventive medical examinations are important. Follow-up medical examinations are carried out in order to timely diagnose possible malignant diseases of the respiratory system.

2.1.3 Cadmium and its Compounds

English term	Cadmium
Chemical element	Cd
Toxicologically significant oxidation states	2^+
IARC classification	**1** Cd^{2+} and its compounds (confirmed human carcinogen)
Main target organs or systems	**Lungs, kidneys**

Characteristics and occurrence: Cadmium (Cd) is a silver-white, soft metal, found in nature as cadmium sulphide (CdS) in several ores, mainly together with zinc. It burns in air to form brown cadmium oxide (CdO).

Primarily, it is used in the production of rechargeable Ni-Cd batteries, bearings or semiconductors. It is also a part of soft soldering wires. Thanks to its corrosion resistance, it is used in galvanic plating. However, due to its toxicity, it is currently being replaced by other materials.

Environmental and occupational exposure: Cadmium has been widely dispersed into the environment through the air and water man-made routes. More than any other metals, cadmium can be transported over long distances by these carriers. Cadmium accumulates in the soil and, due to its solubility in water, can accumulate in economically important plants, e.g. rice, lettuce, champignons. It is also found in cigarette smoke.

Exposure in the working environment can occur during melting, galvanic plating, soldering, production of Ni-Cd batteries, production of some dyes and plastic substances, etc.

Toxicokinetics: Cadmium enters the body through the respiratory system after inhalation or through the GIT after ingestion, while the lack of calcium, iron and proteins in food increases its absorption. After inhalation, 10–40% of cadmium is absorbed into the bloodstream, depending on the chemical composition and particle size. Absorption through the GIT is approximately 5%. Absorbed cadmium is bound to plasma proteins. In the liver and kidneys, it binds to the cadmium-binding protein metallothionein (MT). Cd-bound to MT reduces toxicity, but at the same time it is responsible for cadmium accumulation in tissues. Smaller amounts of cadmium accumulate in the pancreas and testicles. In the kidneys, it is reabsorbed and accumulated in the proximal tubules

(cadmium-induced proximal tubule injury), the so-called *cadmium kidney* is formed. Urinary cadmium excretion is slow and lasting process.

The mechanism of toxicity involves the inhibition of Ca membrane pathways and Ca^{2+}-ATPase. In addition, it inhibits the DNA repair that has been damaged by other chemical substances, which is associated with the induction of tumour formation.

Acute symptoms of intoxication:

Gastrointestinal symptoms: nausea, vomiting, diarrhoea, colicky abdominal pain, tremors, toxic liver damage and even kidney failure appear after oral intoxication.

Respiratory symptoms: sore throat, headache, myalgia, and nausea appear with a latency of several hours after severe inhalation exposure. Intoxicated patients report a metallic taste in the mouth. Fever, shortness of breath and chest pain signal toxic pneumonitis with the development of pulmonary oedema and possible respiratory failure.

Chronic symptoms of intoxication:

Nephrotoxic symptoms: long-term exposure to low doses of cadmium leads to damage of renal tubular functions. Microalbuminuria and β2-microglobulinuria appear in the urine with the gradual development of Fanconi syndrome (glycosuria, aminoaciduria, hypercalciuria, phosphaturia).

Pneumotoxic symptoms: chronic obstructive lung disease with emphysema develops.

Bones: as a result of long-term exposure, calcium loss and bone demineralization occur, resulting in osteoporosis.

Carcinogenic symptoms: exposure to cadmium can lead to the tumour development in lungs, kidneys and urogenital system, especially in the prostate.

Diagnosis and differential diagnosis: It is based on work anamnesis and cadmium exposure confirmation. It is necessary to exclude other diseases of the respiratory system and kidneys, osteoporosis and other causes of pathological fractures.

Treatment: After acute oral intoxication, it is necessary to perform a gastric lavage, to administer activated charcoal, which reduces further absorption. Treatment of inhalation intoxication and kidney damage is symptomatic. No effective antidote exists.

Preventive measures: Technical measures to limit dust are of primary importance. Depending on the circumstances it is necessary to use PPE. Follow-up medical examinations are carried out with the aim of early diagnosis of possible malignant diseases of the respiratory system, kidneys and urogenital system.

2.1.4 Nickel

English term	Nickel
Chemical element	Ni
Toxicologically significant oxidation states	2^+, 3^+, 4^+
IARC classification	**1** Ni compounds – sulphides, oxides (confirmed human carcinogen) **2B** Ni – metal and alloys (probably human carcinogens with insufficient evidence of carcinogenicity in humans and sufficient evidence in experimental animals)
Main target organs or systems	**Skin, nose, paranasal sinuses, lungs**

Characteristics and occurrence: Nickel (Ni) is a magnetic, hard metal with a silvery-white, shiny appearance. Nickel is non-toxic in its pure elemental form and occurs extensively in nature in the form of sulphides and silicates. Metal nickel and its compounds are widely used in the metallurgical, steel, electrotechnical or chemical industries. Nickel is most often used as an anti-corrosion protection of other metals, as a catalyst, in alloys, in coinage, in Ni-anhydride and Ni-Cd batteries, dyes, etc.

Environmental and occupational exposure: Along with other metals, it is found in ores of pentlandite, nickeline (NiAs), chloantite and others in the form of sulphides and arsenides. Nickel is found in iron meteorites falling to earth from space. Nickel belongs to the most widely used metals. Unprofessional exposure occurs in the vicinity of nickel smelters. Further, a small amount of nickel can enter the body during the burning of fossil fuels, from waste dumps. It is also found in many commonly used products. Professional exposure occurs during its mining, production, smelting, and use, e.g. in powder metallurgy, electroplating, glassmaking, ceramics, electrotechnical industry, minting, etc.

Toxicokinetics: Water-soluble nickel compounds and powder forms can enter the human body mainly through the respiratory system. Nickel is resorbed only very poorly in the GIT and it triggers skin allergic reaction. There is no accumulation in the tissues, it is excreted in the stool and kidneys with a half-life of approximately 1 week. Insoluble powder compounds can accumulate in the lungs, where they have carcinogenic effects. Nickel passes through the placental barrier.

Acute symptoms of intoxication:

Dermal symptoms: Nickel and its salts most often cause allergic contact dermatitis manifested by itching and erythema.

Respiratory symptoms: in the case of very rare massive inhalation exposure to soluble aerosols, rhinitis, sinusitis, cough and the development of diffuse interstitial pneumonitis may occur.

Chronic symptoms of intoxication:

Respiratory symptoms: these appear after long-term exposure to soluble nickel compounds. Rhinitis can also occur with the formation of polyps, atrophy of the mucous membrane of the upper respiratory tract and even perforation of the nasal septum.

Carcinogenic symptoms: these are more common in smokers and are manifested by the development of malignant tumours of the lungs, paranasal sinuses, larynx, prostate and kidneys. Latency of carcinogenic manifestations can be 10-40 years from the first exposure.

Diagnosis and differential diagnosis: It is based on the work anamnesis with a necessity to look specifically for nickel and its compound exposure. The presence of nickel can be determined in blood, urine and in long-term exposure also in hair.

Treatment: Avoiding further contact with nickel, dermal manifestations respond well to topically applied corticosteroids. After inhalation exposure with systemic effects, disulfiram or diethyldithiocarbamate can be administered.

Preventive measures: Reduction of exposure by technical and organizational measures; the use of PPE; during entrance and preventive medical examinations it is necessary to exclude persons with diagnosed allergic diseases.

2.1.5 Lead

Latin term	Plumbum
Chemical element	Pb
Toxicologically significant oxidation states	2^+, 4^+
IARC classification	**2A** Inorganic Pb compounds (probably carcinogenic to humans with limited evidence of carcinogenicity to humans and sufficient evidence to animals) **2B** Elemental Pb (probably human carcinogens with insufficient evidence of carcinogenicity in humans and sufficient evidence in experimental animals)
Main target organs or systems	**Hematopoietic system, CNS, PNS, kidneys, GIT**

Characteristics and occurrence: Lead (Pb) is a soft, heavy, bluish-gray metal that oxidizes in air. It has wide industrial use. Lead is found in all biological systems; it dissolves in gastric hydrochloric acid. It occurs in nature in several ores, the most important of which are galena, analgesite and cerussite. Elemental lead, its oxides and other compounds are toxic.

Environmental and professional exposure: Non-professional exposure can occur: during domestic production of ammunition; from retained shots or projectiles in the body; when using lead paint; from imported Asian toys, jewellery, or cosmetics; when improperly storing food in lead-containing packages; etc. In the past, exposure occurred from drinking water flowing through lead pipes or drinking acidic beverages from lead-glazed containers. Professional exposure can occur: in the mining and smelting of lead ores; in the production of non-ferrous metals; in powder metallurgy; in the production of ammunition, pigments, lead glass, accumulators, protective shields against ionizing radiation and many others.

Toxicokinetics: Lead enters the body by inhalation or oral route. After resorption, lead is distributed by blood to the bone marrow, kidneys, liver, muscles, nervous tissues, gonads and skin. It is stored mainly in the bone tissue (not in the bone marrow), from where it can be washed out under various conditions and diseases (osteoporosis, diseases leading to acidosis, pregnancy) even after several years of exposure with

subsequent manifestations of intoxication. Lead passes through the placental barrier, can bring damage the foetus, and also transfers into breast milk. In blood, 95 – 99% of lead is bound to erythrocytes and 1 – 5% is present in plasma. In cells, lead inhibits porphobilinogen synthase, resulting in the accumulation of haem precursors: 5-aminolevulinic acid (5-ALA) and coproporphyrins. After ingestion, the absorption of lead-soluble compounds is about 15% in adults and about 40 – 50% in children. Lack of Fe and Ca in the diet increases lead absorption. It is excreted mainly through glomerular filtration into the urine, less through the stool, but also through the nails and hair.

Acute symptoms of intoxication:

Gastrointestinal symptoms: these occur after massive inhalation and oral intoxication. Following few hours, vomiting, bloody diarrhoea and colicky abdominal pain (colica saturnina) appear.

Nervous system symptoms: these appear after inhalation, but also after oral intoxication. The initial symptom of intoxication is headache, later ataxia, disturbances of perception and even unconsciousness with tonic-clonic seizures.

Chronic symptoms of intoxication:

Chronic intoxication – saturnism – is manifested by multisystem, dose-dependent symptoms that arise after long-term inhalation or oral exposure.

Anaemia: it is manifested by paleness of mucous membranes and skin, scleral icterus and jaundice, increased fatigue, lethargy, apathy, shortness of breath, arthralgia and myalgia.

Neuropsychological symptoms: insomnia, loss of libido, increased irritability, depression, memory disorders appear. Peripheral neuropathy may develop after severe exposure. In the past, toxic encephalopathy appeared in children living in poor hygienic conditions with the presence of lead, manifested by a decrease in IQ, disorders of concentration, behaviour, and attention, etc.

Gastrointestinal symptoms: patients have a metallic taste in the mouth; during physical examination the lead line may be observed with a characteristic of a blue-purple or gray line on the gingival tissue; anorexia, hypersalivation, recurrent colicky pains around the navel lasting 3 – 4 hours, alternating diarrhoea and constipation may be present.

Urinary tract symptoms: the lead-induced proximal tubule damage; development of Fanconi syndrome (aminoaciduria, glycosuria, hyperphosphaturia); brown-red

coloration of morning urine due to an increased level of porphyrins may also be reported.

Diagnosis and differential diagnosis: They are based on the clinical picture and anamnestic data on Pb exposure. In case of acute or recent intoxication, the amount of Pb in the blood is elevated (plumbaemia is determined using AAS), the value of which corresponds to the severity of intoxication and the clinical picture. The increased values of 5-ALA and coproporphyrin in the urine are detected. The higher concentrations of bilirubin, aminotransferases and creatinine may be recorded. With chronic exposure, there are manifestations of normocytic or microcytic hypochromic anaemia, basophilic dots are present in erythrocytes, the number of reticulocytes increases, and there are increased values of plumbaemia, 5-ALA and coproporphyrins in the urine.

With long-term exposure, an increased amount of lead in hair and nails can be detected using ICP-MS or AAS. Lead deposited in bones can be verified by densitometry.

As part of the differential diagnosis, it is necessary to exclude sudden abdominal events of a different nature (pancreatitis, appendicitis, cholelithiasis, nephrolithiasis), other causes of anaemia, porphyria, etc.

Treatment: After acute oral intoxication, it is necessary to perform a gastric lavage with the administration of activated charcoal and ensure sufficient hydration. It is necessary to check the plumbaemia value in the blood. In adults, after chronic intoxications with clinical manifestations or plumbaemia values above 2 μmol. l-1, chelating substances – CaNa2 EDTA (Chelintox 1 amp = 500mg in 500 ml F1/1) are administered for 2 – 5 days while simultaneously monitoring the lead concentration in blood and urine.

Preventive measures: Technical and hygienic measures aimed at reducing exposure are of primary importance. As part of preventive medical examinations, it is necessary to monitor plumbaemia, and if the maximum exposure limit of 700 μg.l-1 is exceeded, the worker must be removed from the risk environment.

2.1.6 Mercury and its Compounds

English term	Mercury
Chemical element	Hg
Toxicologically significant oxidation states	1^+, 2^+
IARC classification	**3** Hg and inorganic compounds (not classified as a human carcinogen) **2B** Organic compounds of Hg (probably human carcinogens with insufficient evidence of carcinogenicity in humans and sufficient evidence in animals)
Main target organs or systems	**CNS, kidneys**

Characteristics and occurrence: Mercury (Hg) is a toxic, heavy, silver-gray, liquid metal that evaporates at room temperature. It occurs in several ores, especially in cinnabarite (vermilion – HgS). Mercury forms alloys – amalgams most easily with metals like gold, silver, cadmium, and copper. The action of methanogenic bacteria in an anaerobic environment results in the methylation of elemental Hg and the formation of toxic methylmercury, which is highly soluble in water and fats and can enter the food chain.

Environmental and professional exposure: Mercury vapours are released into the atmosphere from natural sources, e.g. during volcanic activity, burning of fossil fuels, during its improper disposal (it is released during the burning of mercury-containing landfills) or from industrial emissions. It can be transferred over long distances from the source through rainfall. Professional exposure occurs during extraction, processing, and use of its properties, e.g. as a catalyst; after its release from damaged measuring devices (thermometers, pressure gauges); it is used for the production of amalgams, batteries, electrical equipment, etc. Due to its toxicity, the European Union is trying to reduce its consumption and use.

Toxicokinetics: Elemental Hg and its soluble salts enter the body through the respiratory system and their absorption occurs in the lungs. After ingestion, elemental Hg and its soluble salts are not absorbed from the GIT.

Organic compounds of Hg are absorbed in the lungs, GIT and, in case of direct contact, also through the skin.

After absorption, Hg and all its compounds reach the whole organism, with the kidneys and CNS being the primary organs.
Excretion is slow, in urine and stool. Mercury accumulation with possible dysfunction occurs in the brain, thyroid gland, breast, myocardium, lungs, muscles, kidneys and adrenal glands, liver, pancreas, skin, sweat glands, testes and prostate.
Mercury also has an affinity for SH binding sites on the surface of T-cells, affecting their function.

2.1.6.1 Mercury – Elemental

Acute symptoms of intoxication: these appear after inhalation of high concentrations of Hg or its salts.
Respiratory symptoms: cough, shortness of breath – tracheobronchitis, pneumonia up to respiratory insufficiency.
Systemic symptoms: salivation, metallic taste, vomiting, abdominal pain, diarrhoea, kidney damage.
Chronic symptoms of intoxication:
Early CNS symptoms: personality changes, anxiety, emotional lability, memory disorders. Mild tremor of fingers, later eyelashes and head, chanted speech, metallic taste in the mouth, hypersalivation.
Latter CNS symptoms: psychological (increased irritability, outbursts of anger, depression, hallucinations, dementia), neurological (bulbar paralysis, polyneuropathy, amyotrophic sclerosis, vertigo, hearing impairment).
Respiratory symptoms: frequent inflammation of the upper respiratory tract, epistaxis.
Urinary tract symptoms: swelling due to proteinuria with subsequent hypoproteinaemia (nephrotic syndrome), general alteration of health status.
Endocrine system symptoms: struma, impotence, oligospermia, menstrual disorders.

2.1.6.2 Mercury – Salts – Mercuric chloride $HgCl_2$ (sublimate), Mercuric cyanide $Hg(CN)_2$

Acute symptoms of intoxication:
Gastrointestinal symptoms: stomatitis, esophagitis, gastroenteritis, ulcerative-haemorrhagic colitis.
Urinary tract symptoms: proteinuria, oliguria to anuria, development of uraemia.

Chronic symptoms of intoxication:

After recovery from acute intoxication, the symptoms similar to chronic elemental mercury intoxication persist in patients.

2.1.6.3 Mercury – Organic Compounds – Methylmercury, Ethylmercury, etc.

It can enter the human body after inhalation, ingestion or through the skin.

Acute symptoms of intoxication:

CNS symptoms: an early symptom is numbness of the limbs and lips, later ataxia, dysarthria, fine motor disorder, tremor, drowsiness, narrowing of the visual field, central hearing disorder – these can occur even after latency. Disturbances of behaviour and intellect may be detected.

Chronic symptoms of intoxication:

CNS symptoms: disorders of the intellect, memory, fine motor disorders, tremor, narrowing of the visual field, hearing disorders, disorders of the autonomic nervous system.

Pregnancy: brain anomalies of the foetus – microcephaly, spasmophilic conditions, mental retardation.

Diagnosis and differential diagnosis: These are based on clinical medical, neurological, nephrological, psychological examinations as well as on confirmation of Hg exposure by examining mercury level in blood and urine. It is necessary to exclude diseases of the CNS, kidneys and GIT of other aetiology.

Treatment: After inhalation intoxication, oxygen is administered; after oral intoxication, milk or egg white can be given and gastric lavage performed as a part of first aid. The chelating agent DMPS (sodium dimercaptopropane sulfonate = unithiol, Dimaval inj., cps.) is administered as an antidote after acute and chronic intoxication. The recent chelate NBMI (N, N'-bis(2-mercaptoethylisophthalamide)) is in the stage of clinical trials, which more effectively removes Hg from the CNS.

Preventive measures: Technical and hygienic measures must be taken in the living and working environment with a focus on limiting exposure. As part of preventive medical examinations, it is necessary to monitor the mercury concentration in urine.

2.1.7 Carbon Monoxide

English term	Carbon monoxide
Chemical formula	CO
IARC classification	It is not on the list of carcinogens
Main target organs or systems	**Generalized effects** based on blockade of oxygen transport with a priority effect on **the CNS and myocardium.**

Characteristics and occurrence: Carbon monoxide (CO) is a colourless, odourless gas, lighter than air. It arises as a product of incomplete combustion of organic substances containing carbon. It is the most common cause of non-professional accidental or suicidal poisonings.

Environmental and professional exposure: Non-professional exposure occurs when smoking cigarettes; using damaged stoves or other solid fuel heating devices with non-functioning flues; by car exhaust gases; during fires or volcanic activity; etc.

Professional exposure occurs during the dry distillation of wood and coal.

Carbon monoxide is part of blasting gases in quarries and mines. Increased exposure occurs in professions like fireman, rescuer, welder, car mechanic, smoker, etc.

Toxicokinetics: CO enters the body through the lungs. After resorption, depending on the increasing concentration, CO shows an increasing binding affinity to haemoglobin, with which it forms carboxyhaemoglobin (COHb). Compared to oxygen, the affinity of CO to haemoglobin is 200 times higher.

Carbon monoxide shifts the oxyhaemoglobin dissociation curve to the left, reducing the release of O_2 into the tissues. In cells, CO binds to mitochondrial cytochrome oxidase, cytochrome P-450 and later also to myoglobin. In these ways, total and cellular hypoxia and, due to the accumulation of CO_2, also tissue acidosis arise. The binding of CO to haemoglobin is reversible, which is used in treatment. The half-time of spontaneous release of CO from haemoglobin is 5 – 6 hours.

Acute symptoms of intoxication:

Their severity increases with increasing COHb concentration.

COHb concentration and symptoms of intoxication are shown in Table 5.

Table 5. COHb concentration and symptoms of intoxication

COHb Concentration in %	Symptoms of intoxication
10 – 29	Headache, fatigue, tinnitus, vertigo
30 – 49	Headache, weakness, nausea, vomiting, tachycardia, tachypnoea, impaired coordination of movements and judgment, collapse
50 – 59	Coma, convulsions, Cheyne-Stokes respiration, mydriasis
60 – 79	Coma, convulsions, bradycardia, bradypnea, exitus
70 – 89	Bradypnea to exitus within 1 hour.
90 and more	Exitus within 1 min.

Chronic symptoms of intoxication:

They are not generally recognized, after long-term exposure the incidence of arrhythmias and atherosclerosis increases. In the CNS, after severe intoxication with unconsciousness, toxic encephalopathy with various manifestations of pseudoneurasthenic syndrome may develop.

Diagnosis and differential diagnosis: Anamnesis focused on possible CO exposure is important. In the initial stages of mild intoxication, the clinical picture may be non-specific. The laboratory tests of COHb in the blood will determine the severity of the intoxication and allow monitoring its progress. Laboratory tests reveal hyperglycaemia and glycosuria, and metabolic acidosis develops. Due to possible transient myocardial ischemia, it is necessary to continuously monitor the ECG.

O_2 saturation testing using pulse oximetry and blood gas testing (Astrup) show falsely normal values.

Treatment: As soon as possible, it is necessary to remove the victim from the contaminated area and start oxygen therapy with 100% oxygen. Depending on the state of consciousness and respiration, oxygen can be inhaled with a face mask, in the case of unconsciousness it is necessary to ensure the application of O_2 through an endotracheal tube. If the patient is not breathing, it is necessary to start artificial pulmonary ventilation immediately. After severe intoxications, hyperbaric oxygen therapy is indicated.

Preventive measures: Technical measures (e.g. sealing of flues, not using sources producing CO in closed spaces) should prevent CO leakage. Sufficient ventilation must be ensured in case of fires or accidents with CO leakage. During rescue work, it is necessary to use self-contained breathing apparatus or masks with a special CO filter.

2.2 Organic substances

2.2.1 Alcohols

2.2.1.1 Methyl alcohol

English term	Methanol, Methyl alcohol
Chemical formula	CH_3-OH
IARC Classification	It is not on the list of carcinogens
Main target organs or systems	**CNS, n. opticus, liver, kidneys**

Characteristics and occurrence: Methyl alcohol (Methanol) is a highly toxic, flammable, volatile, clear, colourless liquid with the same odour as alcohol. Low methanol concentrations are linked to enzymatic activities in the fruits and during the alcoholic fermentation process. It resembles ethyl alcohol (ethanol) and in case these two are confused, it brings very dangerous outcomes.

Environmental and professional exposure: Methyl alcohol is produced in the environment as a product of the anaerobic metabolism of many types of microorganisms. It is also found in very small concentrations in the atmosphere, where it is oxidized by sunlight into carbon dioxide and water within a few days. Methyl alcohol was first produced as a by-product of the dry distillation of beech wood (formerly called wood alcohol). Currently, methyl alcohol is primarily made from natural gas. Methyl alcohol was also detected in tobacco smoke (80 – 180 μg per cigarette). It is used as an organic solvent, degreaser, for the denaturation of ethyl alcohol, the production of formaldehyde, etc.

Toxicokinetics: The main source of intoxication is food and drinks. In case of non-professional intoxication, methyl alcohol can enter the body by inhalation or through the GIT after eating food or drinking liquids containing methyl alcohol. From the working environment, it enters the body through the respiratory system or when handling methyl alcohol-containing substances even through intact skin. After absorption, 90% of the absorbed amount is metabolized in the liver by alcohol dehydrogenase to formaldehyde, which is further metabolized to formic acid. Both metabolites cause metabolic acidosis and optic neuropathy. The remaining amount of absorbed methyl alcohol is excreted unchanged in exhaled air and urine.

The lethal dose for a person weighing 70 kg is 56-100 g or 70-130 ml of 100% methyl alcohol.

Acute symptoms of intoxication:

Methyl alcohol has milder CNS narcotic effects than ethyl alcohol. The first symptoms of intoxication include vertigo, ataxia and confusion. Depending on the dose, nausea, vomiting, headache, abdominal pain, diarrhoea, tremors, convulsions and even coma may appear with an interval of 6 – 30 hours. Tachycardia and non-specific T wave changes are evident on the ECG.

Damage to the optic nerve appears with a latency of 12 – 24 hours and is manifested by blurred vision, colour vision disorders, narrowing of the vision field and even permanent blindness.

Severe poisoning leads to disorders of consciousness, metabolic breakdown and even multi-organ failure, especially of the liver and kidneys, with subsequent death.

Chronic symptoms of intoxication:

They occur after exposure in the working environment, when concentrations of methyl alcohol vapours are higher than 260 mg/m^3. The most common symptoms are headache and eye irritation, non-specific central or GIT symptoms may occur. Direct skin contacts cause skin irritation with redness, and subsequently triggers eczema development.

Diagnosis and differential diagnosis: It is necessary to verify the exposure by anamnesis. Methyl alcohol and formic acid in the blood are laboratory determined using the distillation method or with the help of gas chromatography (GC-HSS).

Treatment: After accidental ingestion of methyl alcohol, it is necessary to induce vomiting or perform gastric lavage within one hour. Administration of activated charcoal is ineffective. As an antidote, fomepizole in a dose of 15 mg/kg is given repeatedly by infusion or ethyl alcohol orally in a dose of 100-200 ml of 40% alcoholic beverages (vodka, whiskey, gin). Ethyl alcohol in glucose in a concentration of 5 – 10% is given by infusion in the unconscious. During the treatment, it is necessary to maintain a 1 – 1.5 ‰ level of ethyl alcohol in the blood. In severe or complicated intoxication, haemodialysis is indicated.

Preventive measures: Absolute prevention is not to drink alcoholic beverages, especially distillates of unknown origin. Correct and clear labelling of solutions containing methyl alcohol and training of employees is essential in the working environment.

2.2.1.2 Ethyl alcohol

English term	Ethanol, Ethyl alcohol
Chemical formula	CH_3-CH_2-OH
IARC Classification	It is not on the list of carcinogens
Main target organs or systems	**CNS, liver**

Characteristics and occurrence: Ethyl alcohol (ethanol) is a colourless, flammable liquid, well soluble in water and fats. It is produced by alcoholic fermentation from simple sugars.

Environmental and professional exposure: It belongs to the most widespread substances used in the pharmaceutical, cosmetic or chemical industry. Exposure occurs during its production, use, transport, distribution, but above all during consumption. Ethyl alcohol is used in the production of disinfectants, perfumes, aftershaves, mouthwashes, plastics, and is widely used as an organic solvent. From a toxicological point of view, the production of alcoholic beverages is of great importance. Ethyl alcohol can enter the body after ingestion, it is well absorbed after inhalation, and it does not penetrate intact skin. Poisoning occurs during suicide attempts in combination with medication.

Toxicokinetics: After ingestion, ethyl alcohol penetrates the body by simple diffusion. About 20% of the volume is absorbed through the gastric mucosa, about 80% through the small intestine mucosa. Depending on the concentration, approximately 62% of the inhaled volume is absorbed by the respiratory system. The speed of absorption through the GIT on an empty stomach is approximately 30 – 60 min, when 80 – 90% of ethyl alcohol is absorbed. The composition of the food and its amount can prolong absorption up to 4 – 5 hours.

Acute symptoms of intoxication:

These may appear after excessive consumption of ethyl alcohol: the initial euphoria passes into depression, accompanying symptoms are confusion, ataxia and vertigo. Later, nausea, vomiting, headache, abdominal pain, tremors, convulsions and even coma, dysrhythmias and hypotension may appear.

Life-threatening can be metabolic acidosis and aspiration of vomit in the case of impaired consciousness and coordination disorders.

Laboratory findings report an increase in aminotransferases, hypoglycaemia, and acid-base imbalance.

Intoxication takes place in 4 stages:

1. Excitation stage: (0.5 – 1 ‰ ethyl alcohol in the blood) – excitement, breaking down social inhibitions, prolongation of reaction time, deterioration of motor coordination, deterioration of vision, foetor alcoholicus

2. Hypnotic stage: (1 – 2.5 ‰ ethyl alcohol in the blood) – ataxia (coordination disorders), mild dysarthria (speech disorder), sometimes manifestations of aggression, visual disturbances

3. Narcotic stage: (2.5 – 3.5‰ ethyl alcohol in the blood) – severe dysarthria, significant coordination disorders, vomiting with risk of aspiration, disorders of consciousness up to coma

4. Asphyctic stage: (over 3.5 ‰ ethyl alcohol in the blood) – bradycardia, bradypnoea, convulsions, hypothermia, stupor to coma, death.

In people who drink alcohol excessively for a long period of time, the symptoms of poisoning may only appear with higher concentrations of ethyl alcohol in the blood.

Chronic symptoms of intoxication:

After long-term and excessive drinking of ethyl alcohol, addiction develops – alcoholism. Gastritis, pancreatitis, cirrhosis of the liver, cardiomyopathy, damage to the central and peripheral nervous system, and psychiatric diseases are common.

Diagnostics and differential diagnosis: The concentration of ethyl alcohol in breath and blood can be determined with commonly available alcohol testers. For forensic purposes alcohol is determined in blood by gas chromatography.

Treatment: It is usually symptomatic with an importance to maintain an open airway. According to the state of consciousness it is necessary to take measures to prevent aspiration, including intubation. It is possible to administer glucose by infusion, to ensure adequate hydration and to deal with possible hypothermia.

In severe comatose states, it is possible to administer Naloxone or flumazenil as a non-specific antidote. Haemodialysis is effective – it is used in severe cases and in case of simultaneous drug intoxication.

Gastric lavage is effective for a maximum of 30 minutes after ingestion. Administration of activated charcoal is ineffective.

Preventive measures: Education of employees and the population. Reducing the availability of alcoholic beverages for children and adolescents.

2.2.1.3 Ethylene glycol

English term	Ethylene glycol
Chemical formula	$HO–CH_2 – CH_2–OH$
IARC Classification	It is not on the list of carcinogens
Main target organs or systems	**Cardiopulmonary system, kidneys**

Characteristics and occurrence: Ethylene glycol belongs to the group of glycols (diols) – alcohols with two hydroxyl groups. Ethylene glycol is a colourless, odourless, oily liquid, sweet in taste, completely soluble in water. It has minimal irritating effects on the skin, conjunctivae and upper respiratory tract. It is not classified as a human carcinogen.

Environmental and professional exposure: Ethylene glycol is a key component in automotive antifreeze and coolant, to help keep a car's engine from overheating or from freezing in the winter. It is a major component of de-icing solutions used in cars, boats and aircraft. It is also a component of brake fluid, wood stains, pesticides, etc. Intoxication occurs with accidental ingestion or suicide attempts. In nature, it degrades relatively quickly with a half-life of 2 – 12 days.

Toxicokinetics: Ethylene glycol itself is relatively less toxic, however, its metabolites are toxic. After ingestion, rapid resorption occurs in the GIT. In the liver, ethylene glycol is metabolized by alcohol dehydrogenase into glycolaldehyde, aldehyde dehydrogenase into glycolic acid and glyoxal acid. A small amount is excreted by the kidneys in unchanged form. The minimum lethal dose is 200 ml.

Acute symptoms of intoxication:

Per-oral intoxication and damage to organ systems takes place in 3 phases:

1st phase (4 – 12 hours): Neurological symptoms and metabolic acidosis – signs of drunkenness – dysarthria, ataxia, nausea, vomiting, followed by convulsions, disturbances of consciousness up to coma.

2nd phase (12 – 24 hours): Cardiopulmonary symptoms and acidosis – hyperventilation, pulmonary oedema, tachycardia, arrhythmias and even cardiac failure.

3rd phase (24 – 72 hours): Renal symptoms and acidosis – proteinuria, haematuria, oliguria to anuria, tubular necrosis to renal failure. The laboratory picture shows

significant hypocalcaemia and leucocytosis, oxalate crystals are present in the urine, causing the urine to turn whitish.

Chronic symptoms of intoxication:

In direct contact with the skin, dermatitis may develop after repeated exposure. Per oral or inhalation chronic intoxication does not occur.

Diagnosis and differential diagnosis: These are based on anamnestic data and a typical clinical picture – signs of intoxication without alcoholic foetor ex ore, metabolic acidosis, impaired consciousness, oxaluria (white urine), hypocalcaemia. As part of the differential diagnosis, it is necessary to exclude, above all, methyl alcohol poisoning.

Treatment: Gastric lavage is performed within one hour after ingestion. The antidote is Fomepizole or ethyl alcohol, which preferentially bind to alcohol dehydrogenase and competitively displace ethylene glycol, which is subsequently excreted unchanged in the urine. Ethyl alcohol is administered in an initial dose of 100 – 200 ml of 40% alcoholic beverages (vodka, whiskey, gin); in unconscious patients, ethyl alcohol is administered in an infusion of 5% glucose. During the treatment, it is necessary to continuously maintain a 1 – 1.5 ‰ level of ethyl alcohol in the blood. In severe cases, haemodialysis is indicated. Administration of activated charcoal is ineffective.

Preventive measures: In the working environment, it is necessary to observe the principles of safety and health protection at work, storage of antifreeze mixtures containing ethylene glycol in correctly labelled containers and training of employees.

2.2.2 Formaldehyde

English term	Formaldehyde
Chemical formula	H_2CO
IARC Classification	1 (confirmed human carcinogen)
Main target organs or systems	**Respiratory system, skin**

Characteristics and occurrence: Formaldehyde is a colourless flammable gas with a pungent to irritating smell. A 37 – 50% solution of formaldehyde is referred to as formalin.

Environmental and professional exposure: In the environment – especially in the troposphere, there is a relatively large amount of formaldehyde, which is produced by

the oxidation of hydrocarbons, e.g. methane. It is readily photo-oxidized in sunlight to CO_2. Formaldehyde is widely used in the chemical, textile, wood or food industries. It is mainly used in the production of industrial resins, which is further used for particle board and coating production (plywood), foam insulation and other chemical substances production. It has bactericidal effects. In human and veterinary medicine, it is used as a preservative or disinfectant. It is found in small amounts in car exhaust and cigarette smoke.

Toxicokinetics: It enters the body through the respiratory system or through the GIT. It is absorbed to a small extent by intact skin. After inhalation, it is rapidly absorbed and metabolized to CO_2 and formic acid.

Acute symptoms of intoxication:

Respiratory symptoms: cough, shortness of breath and even whistling sound phenomena appear after inhalation exposure. Exposure to higher concentrations may cause chemical pneumonitis and pulmonary oedema, leading to death.

Visual symptoms: burning eyes to irritating conjunctivitis.

Dermal symptoms: allergic contact dermatitis may develop.

Chronic symptoms of intoxication:

Respiratory symptoms: chronic bronchitis or bronchial asthma may develop after long-term exposure.

Carcinogenic symptoms: possible development of cancers of the nasopharynx, hypopharynx and paranasal sinuses.

Diagnosis and differential diagnosis: Anamnestic data on exposure, clinical picture of respiratory tract or skin irritation are important. To confirm the aetiology of allergic dermatitis, epicutaneous testing is performed during the period without clinical manifestations.

Treatment: After direct contact with the eyes and skin, immediate decontamination with running drinking water is required for 15 min. After inhalation exposure, oxygen is administered; exposure to higher concentrations requires hospitalization in an intensive care unit and symptomatic treatment.

Preventive measures: When working, it is necessary to wear protective glasses, a protective mask with a filter, protective neoprene clothing and shoes.

2.2.3 Organic Solvents

More than 30,000 chemical substances can currently be classified as organic solvents. **Characteristics:** Organic solvents are simple carbon-based organic compounds capable of dissolving or dispersing one or more other substances. Organic solvents are in liquid form at room temperature and standard atmospheric pressure; they dissolve other substances (oils, fats, rubber, plastics and others); they have a low molecular weight; they are very volatile and lipophilic (soluble in fats – direct link to some health effects). The concentration of organic solvents in the air depends on their volatility – the higher the volatility of the solvent, the higher its concentration in the air. They enter the body after inhalation through the respiratory system. Percutaneous absorption of aromatic hydrocarbons is also well known. Highly volatile solvents are absorbed very little through intact skin.

According to their chemical composition, they can be divided into:

a) Aliphatic – open-chain compounds: methane, ethane, n-hexane, etc.

b) Aromatic – with a benzene core: benzene, toluene, xylene, styrene, etc.

Both groups can contain a bound halogen element – halogen hydrocarbons, or an OH group: alcohols, ketones, glycols, esters, ethers, aldehydes and others. Toxicologically significant organic solvents are listed in Table 6.

Table 6. Toxicologically significant organic solvents.

Compound class	Substance	General effects
Aromatic hydrocarbons	Benzene	Irritant, carcinogenic, anaesthetic
	Toluene, Xylene	Renal acidosis, persistent cerebellar ataxia
Alcohols	Methyl alcohol	Irritant, anaesthetic, hepatotoxic
	Ethyl alcohol	
Glycols	Ethylene glycol	Metabolic acidosis, arrhythmias, renal failure
Ketones	Acetone	Irritant, anaesthetic
Halogenated hydrocarbons	Trichlorethylene	Carcinogenic, hepatotoxic, nephrotoxic, cardiotoxic, anaesthetic
	Tetrachloroethylene	
	Chloroform	

Environmental and professional exposure: Organic solvents are used in the production of pesticides, cleaning agents, polymers, as antifreezes, as thinners for glues, paints and coatings, in the chemical industry as intermediates in the production of chemical substances. Their toxicity is very different.

The most widely used industrial solvents are aromatic hydrocarbons – toluene and xylene (mainly in the production of paints, varnishes, asphalt, tar, oils, etc.). About one-third of toluene is used in the production of benzene, and one-sixth is used as a solvent. Toluene is also used to make saccharin, chloramine and trinitrotoluene. Toluene is often abused as a drug because of the initial euphoric symptoms of intoxication.

Toxicokinetics: During professional exposure, organic solvents in the form of vapours or aerosols enter the body through the respiratory system. They reach the circulation through the alveolocapillary membrane very well. Their absorption increases with physical exertion. Oral intoxication can occur after accidental ingestion. They reach the entire body through the bloodstream, but they have an affinity for lipid-rich tissues – the nervous system, adipose tissue, where they accumulate.

The solubility of organic solvents in fats increases with the length of the carbon chain, the substitution of halogen elements or alcohols and the number of free carbon bonds. Organic solvents are slowly released from adipose tissue even after the end of the exposure. Most solvents pass into breast milk and through the placental barrier.

Depending on the properties of a specific substance, after absorption, biotransformation takes place mainly in the liver, via cytochrome P450. Water-soluble conjugated forms emerge, while some metabolites have more serious toxic effects than the substance itself. Excretion occurs through the respiratory system in unchanged form or through the kidneys in the form of metabolites. The biological elimination half-life ranges from several minutes to several days, depending on the compound and its properties.

Common and specific effects by body organ system:

CNS: effects on the CNS are similar for all organic solvents. In the acute stage of poisoning, excitement, euphoria, visual or auditory hallucinations, but also headaches, vertigo, nausea, and vomiting appear first. At higher doses, disorientation, disturbances of consciousness (somnolence to coma), and a general anaesthetic effect with respiratory depression are present. After long-term exposure, chronic effects appear – headaches, fatigue, sleep disorders, deterioration of concentration,

memory, nervousness, mood changes. Brain atrophy can be detected during CT or MRI examinations.

Liver: organic solvents damage the liver to varying degrees and extents. Most often, it is a diffuse damage occurring under the image of steatosis, necrosis and fibrosis. Toxic hepatitis can have an acute, subacute or chronic form and is caused by: a) primarily halogenated hydrocarbons – tetrachloromethane, chloroform, (trichloromethane), tetrachloroethane; b) or some non-halogenated hydrocarbons – n-hexane, toluene, xylene, styrene, etc. Acute hepatic necrosis can lead to hepatic failure and death of an intoxicated person. Symptoms of acute intoxication are non-specific – nausea, vomiting, jaundice, elevation of hepatic markers (ALT, AST, ALP. GMT, bilirubin, etc.). A malfunction of the liver's synthetic functions can lead to bleeding manifestations, ascites can develop, etc. Symptoms of chronic intoxication are similar, but develop later depending on the progression of damage to the hepatic parenchyma.

Kidneys: after exposure to ethylene glycol or tetrachloromethane, acute renal failure with manifestations of oliguria to anuria, proteinuria, glycosuria, electrolyte disturbances (hypokalaemia, hypophosphatemia) may occur due to tubular necrosis.

Respiratory system: irritant effects are manifested in the upper and lower respiratory tract, and their severity depends on the nature of the solvent. Exposure to high concentrations may lead to pulmonary oedema, after repeated exposure to lower concentrations may lead to the development of chronic bronchitis or irritant bronchial asthma. Typical irritating symptoms include burning and itching in the nose and pharynx, cough, chest pain, shortness of breath, cyanosis, conjunctival irritation, lacrimation, etc.

Cardiovascular system: long-term exposure to high doses of aromatic hydrocarbons (toluene abuse) increases the risk of coronary artery damage, arrhythmias and even death may occur. Symptoms of myocardial damage can include palpitations, increased permanent fatigue, various profound disturbances of consciousness from somnolence to comatose states.

Diagnosis and differential diagnosis: Anamnestic exposure data and clinical picture are important. As part of the differential diagnosis in the case of CNS damage, it is necessary to exclude organic brain dysfunction, abuse of prohibited drugs, alcohol, Alzheimer's or Creutzfeldt-Jacobs disease. Acute infectious diseases of the upper respiratory tract, chronic bronchitis, interstitial pneumonia, aspiration pneumonitis and others must be excluded as part of the irritating effects on the respiratory system. As

part of the differential diagnosis of arrhythmias, it is first necessary to exclude ischemic heart disease, myocardial infarction or other cardiomyopathies.

Treatment: Apart from methyl alcohol intoxication, where ethyl alcohol is administered as an antidote, there are no antidotes for poisoning with organic solvents. Treatment is primarily symptomatic. Milk accelerates the absorption of solvents, which means that its administration is contraindicated. Organic solvents sensitize the myocardium to the effects of adrenaline and noradrenaline. Their administration is contraindicated due to the increased risk of severe arrhythmias. After oral intoxication, it is possible to use a laxative containing polyethylene glycol (PEG) to accelerate the elimination of the solvent from the GIT. Forced diuresis is ineffective.

2.2.3.1 Benzene

English term	Benzene
Chemical formula	C_6H_6
IARC Classification	1 (confirmed human carcinogen)
Main target organs or systems	**CNS, Respiratory system, hematopoietic system, skin**

Characteristics and occurrence: Benzene is an organic solvent chemically belonging to the group of aromatic hydrocarbons. Under normal conditions, benzene is a clear, colourless liquid with a sweet smell, only very slightly soluble in water.

Environmental and professional exposure: Due to toxicity and carcinogenicity, its use is limited by legal regulations. It is used as a basic raw material in the production of other substances in the chemical and pharmaceutical industry. About half of the total production is used in the production of ethylbenzene and styrene (polystyrene monomer). It is added to gasoline (less than 1%) to improve the octane number, and in minimal concentrations it can be a part of other organic solvents as a contaminant.

Toxicokinetics: It enters the body through the respiratory system after inhalation, but can be also absorbed through intact skin. After entering the circulation, it is first oxidized in the liver to reactive benzene epoxide and in the second stage to phenol and phenyl mercapturic acid. Both metabolites are excreted in the urine, about 10% of the absorbed amount is excreted unchanged through the respiratory system.

Acute symptoms of intoxication:

CNS symptoms: vertigo, headache, nausea, vomiting, fatigue, feeling drunk, impaired consciousness, slurred speech, disorientation.

Respiratory symptoms: the irritating effect is manifested by coughing and sore throat.

Chronic symptoms of intoxication:

Dermal symptoms: dermatitis - dry reddened and cracked skin.

CNS symptoms: headache, fatigue, short-term memory disorders, mood changes, behavioural disorders.

Bone marrow: reversible pancytopenia first occurs, later aplastic anaemia, which can be fatal, or can progress to various types of leukaemia.

Carcinogenic symptoms: primarily the development of acute non-lymphocytic and chronic myeloid leukaemia.

Diagnosis, differential diagnosis and treatment: They are listed in chapter 2.2.3.

Preventive measures: In the working environment, it is necessary to observe the principles of safety and health protection at work. Exposure can be monitored by biological exposure tests (BET) performed before and after the work shift. It is possible to detect benzene in the blood and a metabolite – S-phenyl mercapturic acid – in the urine.

2.2.3.2 Toluene

English term	Toluene (methylbenzene)
Chemical formula	$C_6H_5CH_3$
IARC Classification	3 (not classified as a human carcinogen)
Main target organs or systems	**CNS, Respiratory system, skin**

Characteristics and occurrence: Toluene is a clear, volatile, highly flammable, water-insoluble liquid. Toluene vapours together with air form an explosive mixture heavier than air.

Environmental and professional exposure: Toluene is typically used in the production of paints, rubber, lacquers, glues (e.g. in model making) and adhesives to help dry, dissolve and thin other substances. In a mixture with benzene and xylene, it is added to gasoline to increase the octane number. It is also used in the synthesis of

other chemical compounds, e.g. trinitrotoluene (TNT). Due to its euphoric effect on the CNS at lower concentrations, toluene is abused as a drug. Toluene induces a strong psychological dependence that leads to the need for daily inhalation.

Toxicokinetics: It enters the body after inhalation through the respiratory system or through intact skin. After absorption, toluene is distributed to all tissues, including the CNS, passing through the placental barrier. It is metabolized in the liver to benzoic acid and is excreted in the urine as hippuric acid – its determination serves as a evidence of exposure. Hippuric acid determination after a work shift is used as a biological exposure test. About 15 – 20% of toluene is excreted unchanged by the lungs.

Acute symptoms of intoxication:

CNS symptoms: intoxication takes place under the guise of a rapidly developing euphoria; disturbances of perception accompanied by vivid, colourful hallucinations occur; later depression, sleep, and various profound disorders of consciousness occur.

Chronic symptoms of intoxication:

CNS symptoms: in workers exposed for a longer period of time, but especially in drug addicts, there is a reduction in intellectual abilities to the point of personality degradation, numbness, a decrease in performance; cerebellar ataxia develops; emotional and behavioural disorders, and aggressiveness occur.

Hepatic symptoms: toxic liver damage gradually develops.

Urinary tract symptoms: sometimes real tubular acidosis can develop.

Corrosion of the upper respiratory tract and aspiration pneumonia can occur in drug addicts.

Diagnosis and differential diagnosis: They are based on anamnestic data on exposure and on the clinical picture. In case of acute intoxication, a characteristic odour is evident from clothing or the environment. Evidence of exposure is the presence of an increased amount of hippuric acid in the urine. As part of the differential diagnosis in unconscious patients, it is necessary to exclude the cause of injury or damage to the CNS from other causes.

2.2.3.3 Acetone

English term	Acetone (dimethyl ketone)
Chemical formula	CH_3COCH_3
IARC Classification	Not classified.
Main target organs or systems	**CNS, Respiratory system**

Characteristics and occurrence: Acetone is a colourless, highly flammable liquid, with a characteristic odour, easily miscible with water, belonging to the group of ketones. Acetone can rarely be abused as a drug.

Environmental and occupational exposure:

It is used as a solvent for surface coatings, in the production of inks, adhesives, paints, and is part of solvents and paint removers used in households. It is used as a basic raw material in the production of plexiglass.

Toxicokinetics: Ketones are well absorbed in the lungs after inhalation of vapours; less through the skin when in contact with liquid. About 45% of acetone is retained in the body and metabolized into intermediate products (alcohols) and CO. The rest is excreted unchanged through the urine and respiratory system.

Acute symptoms of intoxication:

Mild and moderate per oral intoxication – CNS depression, nausea, vomiting, mild metabolic acidosis, hyperglycaemia.

Mild and moderately severe inhalation intoxication – feelings of excitement, drunkenness, later fatigue, disorientation and even impaired consciousness, irritation of the conjunctivae, upper respiratory tract with cough, nausea, vomiting, headaches appear.

Severe intoxication – takes place under the guise of severe depression of the CNS up to coma, convulsions, tachycardia, hypotension appear. Bleeding from the GIT and depression of the respiratory centre are rare.

Chronic symptoms of intoxication:

May lead to chronic dermatitis (dry, cracked, erythematous skin). Headaches and nausea are more often from the smell than from the effect on the CNS.

Diagnosis and differential diagnosis: They are based on exposure anamnestic data and on the clinical picture. In case of acute intoxication, a characteristic odour is evident from clothing or the environment. As part of the differential diagnosis in

unconscious patients, it is necessary to exclude the cause of injury, diabetic ketoacidosis, intoxication with ethanol or isopropyl alcohol, or other damage to the CNS.

Treatment: In the case of acute inhalation intoxication in an unconscious patient, it is necessary to maintain vital functions, ensure free airways, decontaminate the victim (remove contaminated clothing), take the victim out of the contaminated area; administration of oxygen is indicated.

Further treatment is symptomatic. Haemodialysis is indicated in case of severe metabolic acidosis or hemodynamic instability.

2.2.4 Organophosphorus and Carbamate Insecticides

From a toxicological and pathological-physiological point of view, organophosphorus and carbamate insecticides together with nerve agents belong to the same group of toxic substances. Examples of active substances are listed in Table 7.

Table 7. The most important organophosphorus and carbamate insecticides

Class	Active substance	General effects
Organophosphorus insecticides	Malathion, Pirimiphos-methyl [1)] Chlorpyrifos, Chlorpyrifos-methyl, Dimethoate, Etoprophos, Fosmet	Inhibition of acetylcholinesterase activity – muscarinic, nicotinic, central cholinergic effects
Carbamate insecticides	Pirimicarb (Pirimicarb) [1)] Fenoxycarb, Formetanate hydrochloride, Methiocarb	
Nerve paralytic substances	Cyclosarin, Sarin, Soman, Tabun, VX, Novichok group	

[1)] Substances approved for use in the Slovak Republic in 2020

Characteristics: From a chemical point of view, organophosphates are esters of phosphoric acid. Their general chemical structure is $O=P(OR)_3$, which enables them to create a number of organic compounds that, depending on the chemical structure of the chain (R) bound through O to phosphorus, can have different properties. From a toxicological point of view, the most important are insecticides and nerve agents.

Carbamates are esters and compounds of carbamic acid (NH_2COOH). insecticides, polyurethane plastics, and medicines are obtained by replacing one or more H atoms. The toxicity of insecticides of this group depends largely on the form of application. Solutions, sprays and emulsions are more risky when used than solid substances or granules.

Environmental and occupational exposure:

In the environment, organophosphorus and carbamate insecticides are degraded relatively quickly depending on the microbial composition of the soil, sunlight, temperature and humidity. Due to their solubility in water, they are often found in surface and underground waters, where their slow hydrolytic splitting occurs. They can be detected in soil and water for a relatively long time after their use, and from there they can enter the food chain.

Professional exposure can occur in the chemical industry during production and packaging, during distribution and transport, but above all in agriculture during the application of insecticides, disposal of their residues, or packaging. Intoxication is usually associated with a gross violation of safety regulations and measures. In case of improper handling and storage, accidental intoxications occur even in the home environment.

The development, production, stockpiling, transfer, use and disposal of nerve agents as chemical weapons is prohibited by the international convention on the prohibition of chemical weapons. Despite this fact, probable cases of their use against specific persons have been recorded in recent months.

Toxicokinetics: Organophosphorus and carbamate insecticides can penetrate the body through intact skin, mucous membranes, respiratory and gastrointestinal systems. Their absorption into the circulation is fastest after inhalation through the respiratory system, followed by the gastrointestinal tract after oral ingestion. Professional intoxication most often occurs via the transdermal route.

After resorption, organophosphorus and carbamate insecticides are distributed throughout the body, primarily in the CNS, depending on their fat solubility.

Their biotransformation takes place in the liver and metabolites are excreted in the urine.

The toxic effects of organophosphorus insecticides imply the irreversible blockade of acetylcholinesterase (AChE) at nerve endings. Plasma cholinesterase (butyrylcholinesterase) reacts more sensitively and faster to the presence of

organophosphates, while erythrocyte cholinesterase, which is identical to AChE of nerve endings, correlates better with the clinical picture. As a result of AChE blockade, accumulation of acetylcholine occurs at nerve endings and, depending on the receptors, muscarinic, nicotinic or central manifestations emerge. Symptoms of intoxication are listed in Table 8.

Carbamates also cause acetylcholinesterase blockade, but due to their rapid biotransformation and degradation, AChE inhibition is reversible.

Spontaneous reactivation of AChE is slow and takes place in the liver and in erythrocytes.

Table 8. Effects and symptoms of intoxication with organophosphorus and carbamate insecticides

Effects	Organ	Effect	Symptoms
Muscarinic	Eyes	Contraction of ciliary muscles and pupil muscles	Myosis, blurred vision
	Respiratory system	Bronchoconstriction, bronchial hypersecretion	Shortness of breath, wheezing, croaking
	Heart	Stimulation of the vagus	Arrhythmias, bradycardia, cardiac arrest
	GIT	Smooth muscle contractions, intestinal hypersecretion	Vomiting, diarrhoea, colic pain
	Exocrine glands (lacrimal, salivary, bronchial, etc.)	Hypersecretion	Lacrimation, salivation, bronchorrhoea, pulmonary oedema, nausea, vomiting
	Urinary bladder	Contraction	Spontaneous micturition
Nicotine	Musculoskeletal	Excitation	Weakness, fasciculations, convulsions, paralysis
Central	Brain	Early stage excitation	Headache, vertigo, malaise, fear, confusion, hallucinations, behavioural disorders
		Late stage depression	Depression, unconsciousness, central respiratory failure

Acute symptoms of intoxication:

Mild intoxication – usually manifested only by muscarinic symptoms: headaches, vertigo, blurred vision, hypersecretion of exocrine glands, vomiting, colic abdominal pain.

Moderate intoxication – all muscarinic, nicotinic and central symptoms develop: laboured breathing, stridor, profuse sweating, profuse and uncontrollable vomiting, severe abdominal colic and pain, uncontrollable defecation and urination, muscle weakness, seizures, convulsions and paralysis, fear and depression may develop due to bronchoconstriction and bronchial hypersecretion.

Severe to lethal intoxication with organophosphorus insecticides occurs quickly under the guise of respiratory failure – there is massive bronchorrhoea to pulmonary oedema, bronchoconstriction and paralysis of the respiratory muscles. Musculoskeletal symptoms – fasciculations and convulsions – do not occur with severe intoxication.

Severe to fatal intoxication with carbamate insecticides is not known.

Chronic symptoms of intoxication:

Due to rapid biotransformation, chronic intoxications with organophosphorus and carbamate insecticides do not occur.

With repeated exposure or long-term exposure to small doses of organophosphates, prolonged and cumulative inhibition of AChE can occur. After reaching a critical level of AChE blockade, symptoms of acute intoxication appear.

Diagnostics and differential diagnosis:

The basis of diagnosis is anamnestic data on exposure to organophosphates or carbamates within the last 24 hours. Muscarinic and nicotinic symptoms are typical in the clinical picture. The activity of total AChE is laboratory determined. Typical clinical symptoms can be expected when the normal value of AChE drops to the level of 50% and below. Determination of erythrocyte AChE more accurately reflects the state of inhibition on neuromuscular plates and thus the severity of intoxication. In common practice, however, the determination of total AChE is more commonly used.

Determination of AChE activity is also used as a biological exposure test.

Nerve conduction disorders on the neuromuscular plate can be verified by electromyographic examination.

As part of the differential diagnosis, it is necessary to exclude acute respiratory disease and peripheral neuropathies of other aetiology.

Treatment: Remove contaminated clothing as soon as possible, wash contaminated skin with soap and water for at least 15 minutes. In case of eye contact, rinsing with running water is necessary. In the case of inhalation exposure, it is essential to remove the victim from the contaminated area. In oral intoxication, inducing vomiting is contraindicated due to the risk of aspiration with sudden coma and respiratory failure. It is possible to administer a one-time bolus of powdered activated carbon at a dose of 1g/kg of body weight.

Paramedics and medical personnel must use protective clothing and gloves when providing first aid or handling a contaminated patient.

In case of intoxication with organophosphorus insecticides, administration of the antidote Atropine and the AChE reactivator is indicated as soon as possible. Atropine is given to suppress muscarinic symptoms. In case of mild intoxication, 1 – 2 mg is administered; in case of severe intoxication, 2 mg intravenously. If the effect is insufficient, the dose can be repeated after 5 minutes until the symptoms of hyperatropinization emerge – mydriasis, tachycardia over 110/min., subsidence of wet bronchitis phenomena. As AChE reactivators, medicines from the oxime group are given – obidoxime, pralidoxime, HI-6 (azoxime chloride), TMB-4 (trimedoxime bromide). In the SR, obidoxime (Toxogonin) is used – it is administered intravenously in a bolus dose of 250 mg. The duration of combined antidote treatment depends on the clinical condition of the patient. The success of the treatment is indicated by a decrease in erythrocyte AChE activity by 20%. In case of convulsions, it is necessary to administer diazepam to suppress the effects of nicotine.

In carbamate intoxication, atropine and diazepam are administered in the same way as in organophosphate intoxication. Oximes are indicated only in case of combined organophosphate and carbamate intoxication.

3 Drug intoxication

Drug poisoning is one of the most common intoxications in the Slovak Republic. Drug poisoning can occur either: a) accidentally – in drug overdose; or b) intentionally – in suicide attempts, in these cases often in combination with alcohol. Approximately 50% of all acute drug poisonings occur in childhood, especially between the ages of 0 – 5 years. Within this age group, the intoxications are primarily accidental in the home environment, due to the inattention of adults or easy availability of the drugs stored. These poisonings are usually with one type of medicine, from the spectrum used by parents or grandparents. Depending on the child´s weight, age, the content of the active ingredient in one tablet and its chemical properties, serious intoxications can appear after taking 1 – 3 tablets. In the group of adults, acute oral drug poisoning most often occurs in mentally unstable persons, less often with repeated use or overdose due to cumulative effects. In terms of consequences, the most serious intoxications occur after ingestion of various combinations of paracetamol, salicylates, analgaesics, sedatives and hypnotics.

3.1 Analgaesics

Analgaesics are drugs used to relieve pain. They can act on a central or peripheral level. In addition to analgaesic effect, several of them have also antipyretic or antiphlogistic effects. Their consumption and thus the risk of intoxication is increasing. According to their effect, they are divided into non-opioid and opioid.

3.1.1 Non-opioid Analgaesics

3.1.1.1 Paracetamol

Active ingredient	Paracetamol
Drug / application form / content of active substance in mg	PARALEN / tbl. / 125 or 500 PARALEN / supp./ 100 or 500
Toxic dose	60 – 200 mg/kg
Lethal dose (without treatment)	8 – 15 g

Characteristics: Paracetamol is an analgaesic – antipyretic without antiphlogistic activity, with good gastrointestinal tolerance. It does not affect glycaemia, blood

coagulation and is used in cases of contraindication to salicylates. In combination with other drugs, it is part of several over-the-counter medicines.

Toxicokinetics: Paracetamol is quickly resorbed from the gastrointestinal tract, after oral administration it reaches the maximum plasma level in 30 – 60 minutes. Biotransformation occurs in the liver, during conjugation and oxidation reactions. In the cytochrome P450 system, where only about 5% of the ingested dose is metabolized, hepatotoxic and nephrotoxic metabolites are formed, which can damage the liver and cause acute tubular necrosis of the kidneys. Toxic metabolites are excreted in the urine, about 5% of paracetamol is excreted in the unchanged form. The biological half-life of excretion is between 1 – 3 hours; it is significantly prolonged in case of severe hepatic or renal insufficiency.

Acute symptoms of intoxication:

Depending on the dose, sweating, nausea, vomiting, anorexia, abdominal pain may appear within 24 hours. After 24 hours, liver enzymes (bilirubin, ALT, AST) increase due to hepatic cytolysis; prothrombin time increases; hypoglycaemia, acid-base balance disorders, and hypotension – eventually leading to hepatic and renal failure, encephalopathy, coma and even death – may develop.

Chronic symptoms of intoxication:

With long-term use of high doses of paracetamol, which oscillate around the maximum dose, symptoms may develop as in acute intoxication with subsequent hepato-renal failure. Encephalopathy has also been reported. Long-term alcohol consumption increases the risk of paracetamol intoxication even at lower doses.

Diagnosis and differential diagnosis: These are based on anamnestic data and clinical picture. The plasma level of paracetamol in the serum should be determined no earlier than 4 hours after ingestion. As part of the differential diagnosis, it is necessary to exclude other acute diseases of the liver, pancreas or intoxication with other hepatotoxic substances.

Treatment: Inducing vomiting is effective as soon as possible after ingestion, no more than 30 minutes after ingestion, administration of activated charcoal is suitable no later than 1 hour after ingestion. Severe liver damage can develop even with mild symptoms of intoxication. N-acetylcysteine is administered as an antidote, in an initial dose of 150 mg/kg, followed by doses of 50 mg/kg. The maximum protective effect of N-acetylcysteine is given within 8 hours after paracetamol ingestion. Haemodialysis is ineffective, but it is performed in case of renal failure.

3.1.1.2 Acetylsalicylic acid

Active ingredient	Acetylsalicylic acid (ASA)	
Drug / application form / content of active substance in mg	ACYLPYRIN / tbl. / 500	
Toxic dose	Mild intoxication: 150 – 300 mg/kg Severe intoxication: 500 mg/kg	
Lethal dose (without treatment)	Adults: 25,000 – 30,000 mg Children: 4,000 mg	
Recalculation of the toxic dose for severe (lethal) intoxication to patient weight, in mg / number of tablets	50 kg	25 000 / 50
	60 kg	30 000 / 60
	70 kg	35 000 / 70
	80 kg	40 000 / 80

Characteristics: Acetylsalicylic acid (an acetylated salicylate) is classified among the non-steroidal anti-inflammatory drugs (NSAIDs). These agents reduce the signs and symptoms of inflammation and exhibit a broad range of pharmacologic activities: including analgaesic and antipyretic properties. In addition to analgaesic effects, it also has good antipyretic effects. Acetylsalicylic acid belongs to the most used analgaesics – antipyretics. More serious poisoning occurs during suicide attempts (in combination with other drugs and alcohol) or after an overdose.

Toxicokinetics: Acetylsalicylic acid is partially absorbed from the stomach, but mainly from the proximal sections of the small intestine. The presence of food prolongs resorption. It reaches the highest concentration in the fasting plasma after 14 minutes. Resorption is also prolonged by some medicinal forms. After resorption, it is evenly distributed in most tissues. It passes through the placental barrier and is excreted in breast milk. Biotransformation occurs mainly in the endoplasmic reticulum of the liver. Excretion is primarily by the kidneys and depends on the size of the dose and the pH of the urine.

Acute symptoms of intoxication:

Nausea, vomiting, tinnitus, headache, vertigo, sweating, hyperpnoea, tachycardia, acid-base imbalance, petechiae, delirium, convulsions and coma may develop. Hypokalaemia may be present. Children may develop hyperpyrexia and hypoglycaemia; metabolic acidosis may dominate the clinical picture. Rarely, pulmonary oedema and renal failure may develop. With long-term use, tinnitus, headache, vertigo and confusion appear.

Diagnosis and differential diagnosis: These are based on the clinical picture and anamnestic data on the ingestion of drugs containing acetylsalicylic acid. Its plasma concentration is laboratory determined.

Treatment: After ingestion of a toxic dose of 500 mg or more mg/kg, gastric lavage and administration of activated charcoal are indicated within 1 hour. Haemodialysis is highly effective. During hospitalization, it is necessary to repeatedly monitor and adjust the acid-base balance, glycaemia, creatinine, urine, and body temperature. In the development of pulmonary oedema, artificial pulmonary ventilation is required.

3.1.2 Opioid analgaesics

They act on specific CNS receptors and are used when non-opioid analgaesics are ineffective; in severe acute pain conditions (e.g. myocardial infarction, postoperative pain); or in chronic pain accompanying malignant tumour diseases. After repeated administration, pharmacological or psychological dependence occurs. Pharmacological dependence represents the body's adaptation to increased intake of exogenous opioids. Psychological (drug) addiction is characterized by an uncontrollable need to obtain an opioid. After the end of long-term administration of opioids, an abstinence syndrome occurs. Addiction is rare in patients given opioids for severe pain. Symptoms and treatment of intoxication with substances of this group are given in chapter 4.4.

3.2 Hypnotics and sedatives

They form a large group of substances that are used for calming – sedating the patient or inducing sleep. Most substances have both hypnotic and sedative effects, depending on the dose. According to their chemical composition, they are divided into barbiturates (derived from barbituric acid) and non-barbiturates – benzodiazepines.

3.2.1 Barbiturates

Active ingredient	Phenobarbital
Drug / application form / content of active substance in mg	PHENAEMAL / tbl. / 100
Toxic dose	8 mg/kg
Lethal dose (without treatment)	4 – 6 g
Target organ	**CNS, heart**

Characteristics: Barbiturates are derivatives of barbituric acid with a strong depressant effect on the CNS and cardiovascular system. In the last century, they were used as sleeping pills. Due to their serious side effects, consumption has been declining in recent years and they are being replaced by benzodiazepines. A strong physical and psychological dependence on barbiturates develops relatively quickly, which can eventually lead to overdose and death. Intoxications most often occur during suicides. According to the duration of action, barbiturates can be divided into short-term, medium-term and long-term. Long-acting barbiturates, especially phenobarbital, accumulate in the body and can cause overdose or even intoxication. In combination with alcohol, which increases the effect of barbiturates, intoxication may occur even with normal dosage.

Toxicokinetics: After oral administration, phenobarbital is absorbed in the small intestine after 1 – 2 hours. It is distributed to almost all tissues as free or bound to proteins, where 45 – 55% of the absorbed dose is bound. In the CNS, it binds to GABA receptors, resulting in sedative, hypnotic and anticonvulsant effects. The elimination half-life is about 60 – 120 hours, after repeated doses there is a cumulative effect. A part of the absorbed amount is metabolized in the liver into inactive products. It is excreted by the kidneys in unchanged form or after biotransformation in the form of metabolites.

Acute symptoms of intoxication:

Depending on the dose, barbiturate poisoning can be divided into light, moderate and severe.

Mild intoxication – speech slowing, sleepiness, reduced attention, uncoordinated movements, ataxia and nystagmus may appear.

Moderate intoxication – hyporeflexia and weak/shallow breathing are added to the previous symptoms.

Severe intoxication – loss of consciousness, weak/shallow breathing, drop in blood pressure, hypothermia, bradycardia with a risk of cardiac arrest may develop. Respiratory depression increases the risk of aspiration.

Chronic symptoms of intoxication:

With long-term use of high doses of phenobarbital, symptoms of polyneuritis, ataxia, impaired attention, slurred speech, and confusion may occur. Abrupt withdrawal can trigger an epileptic seizure in severe cases. Abrupt discontinuation of the maximum

daily dose, which is 800 mg, leads to signs of weakness, fear, body tremors, convulsions and even delirium. Phenobarbital metabolites can have cytotoxic, mutagenic, teratogenic and carcinogenic effects after long-term use.

Diagnosis and differential diagnosis: These are based on the clinical picture and anamnestic data on the ingestion of drugs containing phenobarbital. As part of the differential diagnosis, it is necessary to exclude other neurological, psychiatric, cardiovascular and respiratory diseases.

Treatment: It is symptomatic and must correspond to the severity of the intoxication. Gastric lavage and administration of activated charcoal are effective within 2 hours of oral intoxication in order to reduce the absorbed amount of barbiturate. Haemodialysis is effective only with long-acting barbiturates – phenobarbital. Severe intoxications with disorders of cardiorespiratory functions require connecting the patient to artificial pulmonary ventilation. During treatment, it is necessary to continuously monitor the ECG, heart rate, blood pressure, O_2 saturation, ventilation, body temperature, presence of reflexes and urine volume. In the spectrum of laboratory parameters, it is necessary to monitor daily liver transaminases, minerals, urea, blood count and, if necessary, other parameters.

3.2.2 Benzodiazepines

Active ingredients	Alprazolam, Bromazepam, Diazepam, Oxazepam, etc.
Drug / application form / content of active substance in mg	XANAX / tbl. / 0,25; 0,5; 1; 2 NEUROL / tbl. / 0,25; 0,5; 1 LEXAURIN / tbl. / 1,5; 3 DIAZEPAM / tbl., inj. / 2; 5; 10 OXAZEPAM / tbl. / 10 and others
Toxic dose	Alprazolam toxic dose – 0.33 mg/kg Bromazepam – more than 60 mg/day
Lethal dose (without treatment)	Not determined

Characteristics: Benzodiazepines are the most commonly used psychotropic substances with anxiolytic, sedative, hypnotic, anticonvulsant and muscle relaxant effects. Their long-term use leads to the risk of addiction. They have negative effects on memory and cognitive functions, and reduce the ability to drive motor vehicles. In combination with alcohol or other pharmaceuticals, they are the most common cause

of poisoning, which can end fatally. Depending on the toxic dose, poisoning takes place under the guise of intensified pharmacological effects.

Toxicokinetics: Absorption from the GIT is fast, the maximum concentrations in the plasma are in 0.5 – 2 hours. As lipophilic substances, they penetrate the CNS relatively quickly, where they bind to specific receptors. Biotransformation occurs in the liver, where active metabolites are formed. Benzodiazepines are excreted in the form of metabolites mainly in the urine, only about 10% is excreted in the faeces.

Acute symptoms of intoxication:

Mild intoxication – confusion, drowsiness, poor speech intelligibility, and lethargy may appear.

Moderate intoxication – ataxia, hypotension, respiratory depression, rarely even coma are associated with it.

Severe intoxication – occurs rarely, usually in combination with alcohol and other drugs.

Diagnosis and differential diagnosis: These are based on the clinical picture and anamnestic data on the ingestion of drugs containing benzodiazepines.

Treatment: After per os intoxication, induction of vomiting is required within 1 hour if the patient is conscious. In the unconscious, it is necessary to perform a gastric lavage and administer activated charcoal after securing the airways. The patient needs to be hospitalized, respiratory and cardiovascular functions need to be monitored.

Flumazenil (Anaxate) is administered as an antidote; haemodialysis and haemoperfusion are not effective enough, due to the strong binding of benzodiazepines to proteins. Improvement of the condition after severe poisoning can be expected within 24 – 48 hours.

3.3 Beta-blockers

Active ingredients	Non-selectively without ISA	**metipranol, propranolol ...**
	Non-selectively with ISA	**bopindolol, pindolol ...**
	Selectively without ISA	**atenolol, betaxolol, metoprolol, bisoprolol ...**
	Selectively with ISA	**acebutol ...**
Drug / application form / content of active substance in mg	Non-selectively without ISA	*Trimepranol / tbl. / 10, 40 *Obsidan / tbl. / 25
	Non-selectively with ISA	*Sandonorm / tbl. / 1 *Visken / tbl. / 5
	Selectively without ISA	****Atenobene / tbl. / 50, 100** ****Lokren / tbl. / 20** ****Betaloc ZOK / tbl. / 25, 50, 100** ****Concor /tbl. / 5, 10**
	Selective with ISA	Sectral
An overdose occurs when the maximum daily dose is exceeded.		

*Currently not registered in the SR ** **Currently registered in the SR**

Characteristics: Beta-blockers inhibit the sympathetic effect on beta-adrenergic receptors. The results of their action are: a) a decrease in the heart rate; b) a decrease in the conductivity of the cardiac electrical conduction system; and c) a decrease in the excitability and force of myocardial contraction. They cause bronchoconstriction. They are used in cardiology in the treatment of hypertension, angina pectoris, myocardial infarction, arrhythmias, but also in thyrotoxicosis, migraine, glaucoma, etc.

Overdose or poisoning with beta-blockers is common, due to their availability.

According to the predominant effect on beta-receptors, beta-blockers are divided into:

Cardio-selective – act mainly on β1-receptors of cardio-myocytes, including the cells of the transmission system.

Non-selective – with an effect on β2-receptors mainly in the wall of blood vessels and bronchi.

The extent of selectivity is not absolute. In case of overdose, a strong non-selective blockade of all types of β receptors is present.

An important feature of beta-blockers is the absence or presence of the so-called internal sympathomimetic activity – ISA (Intrinsic Sympathomimetic Activity). Beta-blockers with ISA have a partial stimulatory effect on beta-adrenergic receptors. For

this reason, they do not have such a pronounced bradycardic and bronchoconstrictive effect as the substances without ISA.

Toxicokinetics: After beta-blockers overdose, which occurs when someone takes orally more than the normal or recommended amount of this medicine, the effects depend on the solubility of the active substance in fats (lipophilic substances – propranolol), in water (hydrophilic substances) or in both fats and water. Fat-soluble substances pass through the blood-brain barrier (feeling of fatigue, sleep disorders), are metabolized in the liver, and active metabolites are formed. Ingestion of high doses of lipophilic beta-blockers leads to: a) saturation of enzyme systems; b) prolongation of elimination half-life; and c) an increase in plasma concentration and thus toxicity.

Water- and fat-soluble substances cross the blood-brain barrier more passively. Overdose leads to a decrease in cardiac output with a subsequent decrease in blood flow through the kidneys and a decrease in elimination.

Acute symptoms of intoxication: They depend on the dose, and according to the severity of the symptoms, it is possible to differentiate 2 stages of poisoning:

1st stage – mild poisoning: Drop in blood pressure (systolic pressure is lower than 80 mmHg), bradycardia (heart rate less than 60 beats per minute)

2nd stage – severe poisoning: Cardiac and extra-cardiac manifestations are present. The following symptoms can be identified in the clinical picture of intoxication:

Cardiovascular symptoms – hypotension, bradycardia, AV block I. – III. degree to asystole. Paradoxical tachycardia and hypertension may occur in substances with ISA, with a typical prolongation of the PR interval on the ECG recording. Pulmonary oedema can result from heart failure.

Neurological symptoms – confusion, disturbances of consciousness up to coma, convulsions, slowed breathing. Coma and convulsions result from cellular hypoxia, hypoglycaemia, blockade of sodium channels in the CNS, or the administration of substances with high lipophilicity.

Other manifestations – nausea, vomiting, hypoglycaemia, bronchospasm is rare. The risk of bronchoconstriction increases in patients with bronchial asthma and in patients with increased airway reactivity. Rare but very serious is hyperkalaemia (arising from metabolic disorders).

Diagnosis and differential diagnosis: Theseare based on the clinical picture and anamnestic data on the ingestion of drugs containing beta-blockers. Early diagnosis is

of fundamental importance in treatment. As part of the differential diagnosis, it is necessary to exclude other cardiovascular or neurological diseases.

Treatment: Within 1 hour of using the drug, gastric lavage is indicated. Activated carbon (even repeatedly) is administered in a dose of 1 g/kg of the patient's weight. Activated charcoal can also be administered with a laxative. Haemodialysis is an effective form of elimination of hydrophilic substances with low protein binding, which are excreted unchanged in the urine (nadolol, sotalol, atenolol). Substances with higher lipophilicity, metabolized in the liver, are eliminated worse by haemodialysis (propranolol, metoprolol, timolol). The basic measure in first aid is the provision of IV access, oxygen supplementation and heart rate monitoring.

Correction of hypotension is carried out by IV administration of full physiological solution; if it is not enough, dopamine or noradrenaline is IV administered.

In case of bradycardia or AV blockade, atropine (0.001 – 0.003 mg/kg) or isoprenaline is applied. Contraindications to their administration are thyrotoxicosis and glaucoma.

Glucagon (Glucagon inj.) is the first-choice drug in case of beta-blocker overdose. It increases heart rate and myocardial contractility by binding to its own receptors (bypasses β-receptors). It is given in a dose of 0.05 – 0.15 mg/kg IV as a bolus, then continuously 1 – 5 mg/hour. If the bradycardia is unmanageable, temporary cardiac pacing is required.

For bronchospasm, it is possible to administer β2-mimetics, for example salbutamol (Ventolin) or aminophylline (Syntophylline).

In case of convulsions, anticonvulsant treatment is required: benzodiazepines are given (lorazepam in a dose of 0.05 – 0.1 mg/kg, diazepam 0.1 mg/kg).

In case of beta-blocker poisoning, the patient's condition improves with the administration of insulin with dextrose infusion. Qualitative or quantitative determination of the plasma concentration of beta-blockers is difficult. Their effect is monitored only indirectly – by monitoring the ECG, examining the level of electrolytes and glucose in the blood, and also by examining the function of the liver and kidneys.

3.4 Tricyclic Antidepressants

Active ingredients	**amitriptyline, imipramine, dosulepin...**
Drug / application form / content of active substance in mg	Amitriptyline / tbl. / 25 Melipramine / tbl. / 25 Prothiaden / tbl. / 25, 75
Toxic dose	Amitriptyline more than 300 mg/d Melipramine more than 300 mg/d Prothiaden more than 400 mg/d
Lethal dose (without treatment)	20 mg/kg

Characteristics: Depending on the active substance, they can have antidepressant, sedative, anti-anxiety, but also central anticholinergic and antihistamine effects to varying degrees. All tricyclic antidepressants (TCAs) are lipophilic; they are absorbed in fatty tissues, from where they are slowly released. They impair attention and coordination of movements, reduce the ability to control machines, or drive motor vehicles; work at heights is unsuitable. There is a relatively high mortality rate in suicide attempts.

Toxicokinetics: After oral administration under fasting conditions, TCAs are well absorbed from the GIT. They reach the maximum concentration in the plasma in approximately 4 – 8 hours. Biotransformation takes place in the liver, where active metabolites are formed. They are mainly excreted from the body by the kidneys in the form of metabolites. Depending on the substance, the elimination half-time from the body varies between 9 – 28 hours. They pass through the placental barrier and are excreted in breast milk.

Acute symptoms of intoxication:

Manifestation of intoxication can appear as early as 1 hour after ingestion and the symptoms can be divided into:

CNS symptoms – ataxia, restlessness, hyperreflexia, significant mydriasis with reaction to light, sweating, in more severe cases drowsiness or coma, muscle stiffness, convulsions, fever.

Cardiovascular symptoms – hypotension, tachycardia, arrhythmias, cardiogenic shock, heart failure.

Respiratory symptoms – depression of breathing, cyanosis.

GIT symptoms – vomiting.

Urinary tract symptoms – oliguria to anuria.

In children, intoxication with tricyclic antidepressants should be considered a life-threatening condition, regardless of the dose.

Diagnosis and differential diagnosis: These are based on the clinical picture and anamnestic data on the ingestion of drugs containing tricyclic antidepressants.

Treatment: There is no specific antidote. Up to 1 hour after ingestion of a toxic dose, it is necessary to induce vomiting or perform gastric lavage, and administer activated carbon (1 g/kg). Further treatment is symptomatic and must take place in a hospital in an intensive care unit, while it is necessary to monitor and correct changes in the ECG, acid-base balance, hypotension, blood gases for 72 hours. Haemodialysis, peritoneal dialysis and forced diuresis are ineffective.

3.5 Calcium Channel Blockers

Calcium channel blockers (CCBs) form a large and diverse group of drugs that are used in the treatment of cardiovascular diseases (ischemic heart disease, arrhythmias, hypertension). Due to the fact that they negatively affect the entry of calcium ions into the cells of the muscles of the myocardium, blood vessels and nerve fibres, they may cause:

a) peripheral vasodilatation;

b) decrease in the conduction of the impulse by the heart muscle, reduced contractility, and decrease in the heart action, decrease in the sinoatrial and atrioventricular (AV) transmission of the impulse, up to AV block or cardiac arrest;

c) suppression of insulin release from the pancreas with subsequent hyperglycaemia.

CCBs are a chemically, pharmacologically and therapeutically heterogeneous group of substances. They work mainly on the so-called calcium L channels (voltage-activated) found in the cardiovascular system. In addition to this group of channels, T channels (controlling the pacemaker functions of excitable cells) as well as N and P channels (in neurons) are also known.

Division of CCBs:

1. Chemical – according to their chemical structure:
    a) dihydropyridines (nifedipine; isradipine, felodipine, nitrendipine, nisoldipine; amlodipine, lacidipine, barnidipine)
    b) non-dihydropyridines – benzothiazepines (diltiazem)
    c) non-dihydropyridines – phenylalkylamines (verapamil)

The first 2 types of CCBs have binding sites for L channels – located

extracellularly, the 3rd type has binding sites intracellular.

2. Generational – according to their historical development:
    a) 1st generation (nifedipine, diltiazem, verapamil)
    b) 2nd generation (isradipine, felodipine, nitrendipine, nisoldipine)
    c) 3rd generation (amlodipine, lacidipine, barnidipine)

CCBs reduce blood pressure by systemic vasodilation, and are used to treat hypertension. Dihydropyridine CCBs (most of them) have a higher vasoselectivity index, without affecting cardiac activity. Non-dihydropyridine CCBs (diltiazem, verapamil), in addition to vasodilation, also affect the heart activity, the result of which is usually a slight decrease in heart rate.

They do not cause orthostatic hypotension; do not promote sodium and water retention; do not negatively affect the metabolism of lipids and carbohydrates; do not lead to bronchoconstriction. They positively influence the regression of left ventricular hypertrophy; blood flow through the kidneys and peripheral blood vessels. Oedema of the lower limbs is a manifestation of increased capillary permeability and not a consequence of an increase in the total extracellular volume. An overview of the most frequently used CCBs is shown in Table 9.

Table 9. The most commonly used CCBs

Medications	**Daily dose**
Amlodipine	1 x 5 – 10 mg
Barnidipine	1 x 10 – 20 mg
Diltiazem retard, SR	2 x 90 – 180 mg, 1 x 240 mg
Felodipine	1 x 5 – 10 mg
Isradipin SRO	1x 5 – 10 mg
Lacidipine	1 x 2 – 6 mg
Lercainidipine	1 x 10 – 20 mg
Nifedipine GITS	1 x 30 – 60 mg
Nifedipine XL	1 x 40 – 80 mg
Nisoldipine	2 x 5 – 20mg
Nitrendipine	1 x 10 – 40 mg
Nivaldipine	1 x 8 – 16 mg
Verapamil SR	1 x 120 – 480 mg

Due to the adverse long-term effect of short-acting dihydropyridines on cardiovascular mortality, they are not used in the treatment of hypertension. They are not administered even in acute conditions (nifedipine was administered in the past). Good effects have been proven with long-acting dihydropyridines (Nifedipine GITS). It should be noted that verapamil, less so diltiazem, are not suitable for the treatment of hypertension accompanied by heart failure or disturbances in AV conduction due to their negative inotropic effect.

Poisoning by calcium channel blockers

It is known that CCBs poisoning leads to transmission disorders, to a decrease in cardiac output, and gradually to the slowing down and cessation of cardiac activity. The primary signs of CCBs intoxication on the ECG recording are first-degree AV block (PQ interval > 0.2s as the 1st sign of intoxication) and sinus bradycardia (45/min), as shown in fig.1. The secondary signs on the ECG recording are second- and third-degree AV block, junctional rhythm and ventricular rhythm.

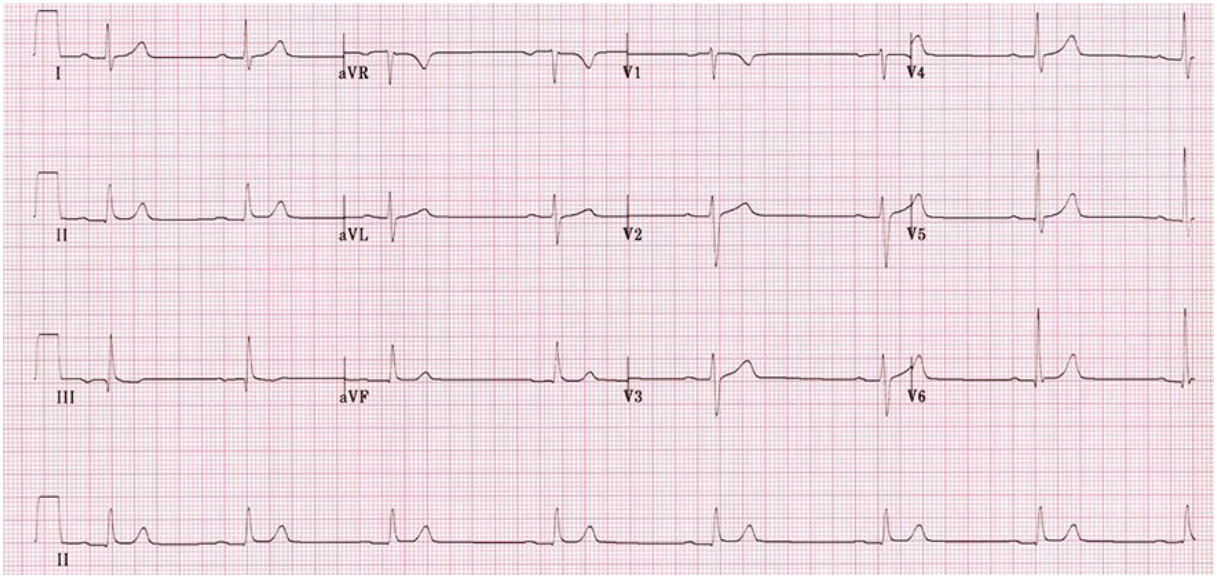

Fig. 1 Primary signs of verapamil intoxication on the ECG recording. First-degree AV block (PQ interval > 0.2s as the 1st symptom of intoxication), sinus bradycardia (45/min)

Possible peripheral vasodilatation in turn leads to critically low blood pressure values. The effect of CCBs on the CNS cells often provokes convulsions. Poisoning with retarded forms of drugs is more severe because the toxic effect manifests itself later (reported up to 48 hours). It is interesting to note that after using several tablets at once, these tablets can stick together in the digestive tract and subsequently cause unpredictable situations in terms of the speed and quantity of the released substance. This corresponds to alternately more severe and milder conditions of the patient with CCB-related intoxication. Sudden deterioration, cardiac arrest and death are no exception.

It should be noted that currently CCBs poisoning is considered one of the most insidious and problematic to treat drug poisonings. Statistically, up to 30% of all drug poisonings are CCB-related intoxications. In case of unclear states of hypotension, or heart rhythm disorders, intoxications with these drugs are to be primarily considered. Children, infants and toddlers are at risk of poisoning after just 1 – 2 tablets.

Treatment: There is no specific antidote; the treatment is only supportive, symptomatic.

1. If the condition of the intoxicated person allows, after the physical examination, we immediately monitor the patient and start the treatment, which is both eliminative and therapeutic.
2. We establish a diagnosis and try to remove the drug from the patient's digestive tract as quickly as possible. Gastric lavage and administration of activated charcoal should be done within 2 hours. If we assume that the drugs have already been eliminated from the stomach, it is advisable to do an intestinal lavage.
3. The next step is to paralyze the circulatory effects of CCBs, namely:
    a) By vigorous and sufficient substitution of the circulating blood volume, i.e. we replenish the circulating volume IV in the vascular bed (physiological, Hartmann's solution, etc.). If necessary, we also administer catecholamines. Speed and quantity is individual. The success of the treatment is indicated by a rise in blood pressure.
    b) We use catecholamines to adjust the effect on blood vessels (dopamine, noradrenaline). We dose them according to the recommended schemes.
    c) Catecholamines also speed up heart activity (dopamine, dobutamine, adrenaline). Atropine is usually without effect.

d) Blockade of calcium transfer on cell membranes is compensated by IV $CaCl_2$ or Calcium gluconate application in large doses.
e) Glucagon 0.05 mg/kg administered IV as a bolus, followed by the continuous application of 0.05 mg/kg/hour. Glucagon contributes to improving contractility and heart rate.
f) With glycaemia, insulin administered IV above 10 mmol/l also appropriately affects haemodynamic parameters.

4. It is often necessary to supplement the mentioned procedure with cardiopulmonary resuscitation.

Research data indicate that none of the procedures may have an effect. The result of the treatment is individual.

4 Intoxication with Narcotic Psychotropic Substances

The history of the use of psychoactive substances goes deep into the past – into the Prehistory. It is impossible not to mention the cave paintings that talk about narcotic drug use. Their use was described as early as in ancient Egypt, Mesopotamia, or Crete. However, they were used ritually or medically and therefore we cannot talk about narcotic drug addiction in these cases. The great boom in the narcotic drug use occurred in the 19th century, when the pharmaceutical industry in the USA and Europe became able to isolate a pure drug from natural substances. It should be emphasized that despite the fact that narcotic drugs were very widespread in the 19th century, we cannot yet speak of the narcotic drug addiction. It was more a sort of recreational use of so-called “weak” narcotic drugs. The breakthrough came with the invention of the injection needle in 1853. Substances – the narcotic drugs could already be administered IV, which multiplied their effect. At the turn of the 20th century, the first problems with addiction and other manifestations accompanying narcotic drug addiction were noted.

Narcotic drugs are psychotropic substances and their use can lead to addiction. Dependence on psychoactive substances is a chronic psychological disorder with a tendency to relapse, which affects all aspects of the patient's life. Abuse of psychoactive substances (*abusus*) is socially unacceptable.

According to the nature of the substance used, psychological addiction can be divided into prescription drug addiction and narcotic drug addiction. A drug is any substance capable of affecting one or more functions after entering the body, acting directly or indirectly on the CNS.

According to the WHO, drug addiction or toxicomania is defined as a psychological or even physical state of dependence characterized by behavioural changes and other reactions that always lead to a morbid desire to use a drug repeatedly (regularly or intermittently) in order to avoid unpleasant conditions induced by the absence of the drug in the body. The motive for use can be: a) curiosity – to find out what it's like; b) trying to fit into a certain social group – party; c) stress or life problems that a person is unable to solve other than by escaping into the world of drugs.

Toxicomania (drug addiction) includes **the compulsion** to continue using the drug and obtain it regularly by any means. With some substances, there is also a need to (constantly) **increase the dose** as the tolerance to the substance develops. In the case

of some groups of substances, not only **psychological** but also **physical (somatic) dependence** arises.
After the sudden cessation of drug administration, very unpleasant conditions, so-called **addiction withdrawal symptoms** of varying, sometimes even life-threatening, severity may occur.

According to the International Classification of Diseases (ICD – 10th revision), the diagnosis of drug addiction is assessed according to 6 criteria, while drug addiction should be considered if three of the listed criteria are found in an individual:

- Desire or urge to consume (craving)
- Limited ability to control consumption
- Abstinence syndrome
- Proof of tolerance
- Dominance of drug consumption over other interests
- Ongoing consumption despite negative consequences

According to the nature of psychosomatic addiction, drugs are divided into:
Soft drugs – marijuana, hashish, nicotine, caffeine, coca leaves, etc.
Hard drugs – ecstasy, LSD, morphine, cocaine, meth, heroin, toluene, etc.
In relation to the legal system and applicable laws, psychoactive substances – narcotic drugs are divided into legal and illegal.

Legal psychoactive substances – alcohol, nicotine, caffeine (in some countries also marijuana). They are produced and distributed officially, their consumption is socially tolerated. However, they might have some legal restrictions (e.g. driving a motor vehicle, age limit, etc.)
Alcohol – about 5% of men and 2% of women are addicted. The development of this addiction takes several years, it progresses faster in young people and in people with problems. Dependence on alcohol is permanent.
Nicotine – its source is tobacco. It belongs to the alkaloids with a psychostimulant and slightly euphoric effects. It ranks among the most widespread dependence of mankind. The smoke that enters the smoker's body is a concentrated aerosol that – depending on the type of tobacco, its production and smoking method – contains about 1400

substances (nicotine, CO, ammonia, acetone, formaldehyde, etc.). Harmful substances in cigarette smoke are divided into 3 groups:

- carcinogenic substances;
- substances with an irritating effect mainly on the respiratory system;
- potentially harmful substances.

Nicotine has adverse effects on the respiratory, cardiovascular, urogenital, nervous and locomotor systems.

Caffeine – is a well-known psychostimulant. In addition to coffee, tea and guarana, it is also present in some soft drinks (Coca-Cola, Pepsi-Cola, Red Bull, etc.). Socially, it is the least dangerous drug and it does not have a work restriction.

Illegal psychoactive substances – e.g. amphetamines, cocaine, heroin, cannabis, etc. They are produced and distributed illegally, their consumption is socially unacceptable and prohibited.

According to the pharmacological effect, the narcotic drugs are divided into: a) **stimulants** (stimulants and euphorics), **sedatives** (sedatives, hypnotics and tranquilizers) and **hallucinogenic substances** (psychomimetics and hallucinogens). They enter the body by inhalation (inhalation, smoking), orally or parenterally, or through the skin and mucous membranes.

4.1 Hallucinogenic drugs

Characteristics: Hallucinogenic drugs are substances that distort the perception of objective reality. They induce a state of CNS excitation, manifested by mood changes, mostly euphoria, but also severe depression. Typical are manifestations of consciousness disorders of varying degrees associated with hallucinations, loss of temporal and spatial orientation, and loss of identity.

Natural hallucinogens – occur naturally in many plants in the wild. The most well-known are: the Peyotl cactus (Fig. 2); Psilocybin mushrooms, commonly known as “magic mushrooms” (Fig. 3); some toadstools (muscimol mushrooms of the genus Amanita); plants from the hemp family of Cannabaceae (Fig. 4, 5), belladonna (Solanaceae) plants; nutmeg (Fig. 7); coca; kawa-kawa, and others.

Semi-synthetic and synthetic drugs (piperidine derivatives, tropane alkaloids, indole alkaloid derivatives) – have a pronounced hallucinogenic effect and a delirogenic potential. These drugs are highly addictive and can easily be overdosed. The best-

known example of this type of drugs are: phencyclidine (PCP), amphetamine derivatives, ketamine or atropine, scopolamine, hyoscyamine, LSD (lysergic acid diethylamide) and others. Atropine was originally isolated from the Deadly nightshade (*Atropa belladona* – Fig. 6), and together with other substances it can also be found in the Thorn apple (*Datura stramonium* – Fig. 8) or Black henbane (*Hyoscyamus niger* – Fig. 9).

Fig. 2 Peyote cactus (Lophophora williamsii)

Fig. 3 Bald head (Psilocybe)

Fig. 4 the Hemp family (Cannabaceae)

Fig.5 cultivated Cannabis (Cannabis sativa)

Fig.6 Deadly nightshade
(Atropa belladonna)
(hyoscyamine, atropine, scopolamine)

Fig.7 Nutmeg
(Myristica fragrans)
(myristicin and safrole = ecstasy)
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Fig. 8 Thorn apple (Datura stramonium – scopolamine, hyoscyamine, atropine)

Fig. 9. Black henbane (Hyoscyamus niger – hyoscyamine, atropine)

Toxicokinetics: Hallucinogenic drugs can enter the body in various ways, but primarily orally. Less common routes are sniffing, inhalation and parenteral application. After absorption into the circulation, depending on the specific substance, a part of the absorbed amount is metabolized in the liver by the cytochrome P450 system, and a part reaches the target organs – the CNS – in the unchanged form. Excretion of metabolites and the drug in unchanged form takes place in the kidneys into the urine, where their detection is possible.

Symptoms of abuse and intoxication: After repeated use of hallucinogenic substances, tolerance develops, which leads to the need to increase doses and thereby increases the risk of intoxication. Unexpectedly, the so-called *flash-back* phenomenon (sudden and spontaneous outbreak of a state of acute intoxication, but without prior administration of the drug) can occur. Intoxication – the flash-back phenomenon can last for several months even without taking the drug. Drug addicts who have survived this phenomenon rate it as a very unpleasant condition, because it comes unexpectedly and in various inappropriate situations (e.g. when driving a motor vehicle). In the course of this state, which lasts for several minutes, occupational accidents, traffic accidents and other health-threatening situations are frequent. This phenomenon of repeated intoxication without the introduction of the drug has not yet been clarified.

Intoxication is manifested by heart rhythm disturbances, hypertension and hyperthermia. Psychic symptoms mainly include euphoria, panic, paranoia, visual hallucinations, depersonalization and others. On physical examination, mydriasis, tendon hyperreflexia, amnesia, analgaesia, nystagmus and gait disturbances are very typical.

Diagnosis and differential diagnosis: They are based on the clinical picture and anamnestic data on drug addiction or ingestion of plant or fruit extracts containing hallucinogenic substances. Detection of substances and their metabolites is most often tested from urine.

Treatment: There is no specific antidote. Treatment is symptomatic, priority is a patient monitoring and maintenance of vital functions. An acute panic reaction is dampened by benzodiazepines or haloperidol. Neuroleptics are given for an acute psychological reaction.

4.2 Cannabinoids

Characteristics: Plants from the hemp family of *Cannabaceae* (Fig. 4) are currently considered the most widespread narcotic drug of plant origin. In some countries, their sale is legalized and they are part of the official pharmacopoeia. The basic natural source of cannabis-type drugs, which has been purposefully bred for a high content of narcotic substances, is Cannabis sativa var. indica /Lam/ (Fig. 5). It is an annual plant that is grown exclusively from seeds. The plant reaches different heights – depending on the variety and growing conditions – approximately 3 meters or more.

From the point of view of the presence of hallucinogenic substances, characteristic of cannabis plants, these two forms are important: a) **cannabis resin – hashish** or **hash**, obtained by separating and compressing the resin glands on the leaves; and especially b) **marijuana** or **marihuana** (herbal cannabis), consists of the dried flowers and fruits and subtending leaves and stems of the female cannabis plant. The cannabis resin is a rich mixture of so-called cannabinoid substances that differ in the structure of their molecules. The content of the mentioned substances in the resin is around 40%, while it does not exceed 8 –12% in the leaves and flowers. The amount and concentration of cannabinoids is decisive for what properties the plant will have in terms of psychoactive effects.

Tetrahydrocannabinol (**THC**, delta-9-trans-tetrahydrocannabinol) is considered the most effective psychotropic substance. Other cannabinoids include **cannabidiol (CBD)**, but it does not have psychoactive effects. It has sedative, analgaesic and also antibiotic properties. It counteracts the stimulating effects of THC and delays the onset of action of marijuana. It is a degradation (oxidation) product of THC, so it is not produced by the plant and does not occur naturally in the resin. It causes a feeling of dizziness and internal confusion.

Tetrahydrocannabivarin (THCV) is a propyl derivative of THC. The data on it come from animal testing. THCV has been shown to produce a faster but shorter-lasting effect than THC. **Cannabichromene (CBC)** – its content does not exceed 20% of total cannabinoids. It is not believed to have psychotropic effects on humans, but it is possible that it acts synergistically with THC.

Toxicokinetics: This drug is abused primarily by smoking, but can also be taken orally (chewing leaves, foods and drinks containing plant leaves or plant extracts). The active substances of the drug penetrate into the bloodstream through the alveolocapillary

membrane of the lungs or through the intestinal mucosa. THC is a lipophilic substance and is very quickly distributed throughout the body from the plasma. The effect of smoking begins after 15 minutes and lasts approximately 3 hours; after oral use the effects can be felt for up to 6 hours. Drinks are prepared together with milk or tea. Hemp suspension can also be in perfumed syrup or alcohol, flavoured with anise. The drug can also be consumed randomly in the form of preserves, confections, etc. Metabolites are excreted in the urine within a few days.

Symptoms of abuse and intoxication: Tolerance occurs mainly with long-term use of high doses of THC. Chronic conjunctivitis gradually develops; characteristic is the smell of skin and clothing; varying degrees of euphoria, hallucinations and loss of social inhibitions. Withdrawal syndrome with typical symptomatology does not develop after stopping the use of the drug. Nausea, sweating, irritability, confusion, tachycardia, anxiety, insomnia, tremors, loss of appetite may be present. In general, marijuana is not labelled as addictive.

In addition to psychological symptomatology, heart rhythm disorders, especially tachycardia, are typical for intoxication. Blood pressure values may be normal or reduced, body temperature may also be reduced. Affected persons report feelings of dryness in the mouth and throat, they may have hyperaemic conjunctivae. Non-smokers may have cough and bronchospasm. Neurological symptoms are subjectively manifested by dizziness; at higher doses even balance disorders and hand tremors are typical. After the unpleasant somatic manifestations subside, a feeling of euphoria occurs.

Diagnosis and differential diagnosis: It is based on the clinical picture, typical odour and anamnestic data on drug addiction. THC can be detected by liquid chromatography in plasma or urine. Concentrations of THC in urine do not correspond to the severity of intoxication.

Treatment: There is no specific antidote. The treatment is symptomatic. In case of severe intoxication, it is necessary to monitor ECG, BP, body temperature, hydration status. In case of oral intoxication, gastric lavage and activated charcoal can be administered. In case of convulsions or significant restlessness, diazepam can be administered.

4.3 Stimulants

Characteristics: Various substances with a stimulating effect on the CNS can be included in the group of stimulants. Stimulants, often referred to as “uppers”, are used to reverse the effects of fatigue on both mental and physical tasks. Their use leads to euphoria, increased self-confidence, fatigue retreat, feelings of increased energy, strength, decreased need for sleep or decreased appetite. However, with an overdose, chaotic thought processes and agitation may occur. After variously long periods of abuse, a paranoid hallucinatory syndrome appears, which can progress to the so-called toxic psychosis, which quickly subsides after treatment and usually does not leave permanent consequences. According to the origin, stimulant drugs can be divided into **natural** and **synthetic**.

Natural stimulants include: coca (Erythroxylon coca, fig. 10 – production of cocaine), khat (Catha edulis, Fig. 11 – alkaloid kathinone), coffee (Coffea arabica – Fig. 12), tea or tobacco.

Synthetic psychostimulant drugs include: amphetamines (amphetamine, methamphetamine, dextroamphetamine), methylenedioxy-methamphetamine (MDMA, commonly known as ecstasy), Phenmetrazine, Benzedrine and others.

According to the nature of the addiction, within the group of psychostimulants it is possible to differentiate cocaine type, amphetamine type, cath type, methylxanthine and betel types of addiction.

Fig. 10 Coca (Erythroxylon coca)

Fig. 11 Khat / Qat
(Catha edulis)

Fig. 12 Arabic coffee tree
(Coffea arabica)
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4.3.1 Cocaine

(Synonyms – blow, bump, C or Big C, coke, crack, dust, flake, line, etc.)

Characteristics: The source of cocaine is the cultivated Cocaine plant (Erythroxylon coca Lam. – Fig. 10). It comes from South America, growing in the Andean and Amazonian parts of Bolivia and Peru. It is also grown in Argentina, Brazil, Colombia or Indonesia. It is a richly branched, always green shrub 2 – 3 m high. The leaves contain the alkaloid cocaine. Cocaine, chemically extracted from plant leaves, is a white crystalline powder with a bitter taste and no peculiar smell. It is very soluble in water. It is often diluted with sugars (lactose, mannitol), and with local anaesthetics (lidocaine).

The most common form of application is inhalation of the crystalline form – powder (cocaine hydrochloride) into the nostrils (sniffing). The next most common form is intravenous application. It is rarely applied intramuscularly or subcutaneously. Another form of application is smoking crack in small pipes; sometimes it can be mixed with tobacco or marijuana. It is sold in glass mini-bottles, folded paper or foil.

Toxicokinetics: The speed of onset of effects depends on the form of application. The fastest, practically immediate effects are manifested after inhalation, smoking or IV application. Cocaine is a lipophilic substance, it quickly passes through the blood-brain barrier, increases the level of Dopamine on receptors in the mesencephalon, limbic system, hypothalamus and prefrontal cortex of the brain. It is metabolized relatively

quickly; its inactive metabolites can be detected in urine 3 – 4 days after application. Elimination from the body is fast, takes place mainly in the kidneys. The elimination half-life is 1 – 2 hours.

Symptoms of abuse and intoxication:

Cocaine has a stimulating and euphoric effect, which is manifested by increased self-confidence, uncritical judgements, logorrhoea, increased mental and motor activity.

Intoxication is manifested by anxiety, disorders of consciousness, hallucinations, paranoid delusions, delirium, agitation, etc. In case of acute intoxication, such complications often occur that may be likely to cause death. During the physical examination, arterial hypertension, mydriasis, arrhythmias and even fibrillation are observed. When using cocaine and crack, a feeling of dryness in the mouth, loss of appetite, burning sensations in the nose, sweating, dose dependence, tremors, convulsions and even unconsciousness may occur. A heart or brain attack may also occur. Long-term use of cocaine leads to weight loss, perforation of the nasal septum, permanent nervousness, sleep disorders, recurrent abdominal pain, diarrhoea, depression or paranoid perception of reality. Severe psychological and physical changes can result in suicidal behaviour.

Diagnosis and differential diagnosis: These are based on anamnestic data and an objective history of drug addiction with a typical clinical picture is important. Cocaine metabolites, especially benzoylecgonine, can be detected in plasma within 5 – 7 days after application, and in urine for 3 – 4 days. Cocaine can be detected in saliva 5 – 10 after minutes after consumption and the test may be positive for 2 – 4 days.

Cocaine metabolites can be detected in hair 80 – 90 days after the last use. Single or multi-parameter strip or cassette tests are available for screening or for rapid differential diagnosis.

Treatment: There is no antidote. Treatment of intoxication is symptomatic. The most important thing is to monitor and maintain vital signs. Haemodialysis or haemoperfusion is indicated for severe poisoning with impaired kidney function.

4.3.2 Methamphetamine

(Synonyms – meth, speed, crank, ice, bennie, chalk, chicken feed, glass, shabu, trash, etc.

Characteristics: Methamphetamine is an amphetamine derivative with a non-physiological stimulant effect on the CNS. It increases the number of neurotransmitters (noradrenaline, dopamine and serotonin) in the synaptic cleft. Meth is made from ephedrine or pseudoephedrine, which are found in commonly available drugs, such as Modafen 24, Nurofen, Panadol, Stopgrip, Plusgrip and others. The methods of application depend on the available form – tablets as the most common method of application are administered orally, the powder can be sniffed or administered intravenously in an aqueous solution. The crystalline form is smoked. With long-term use, tolerance develops, which forces the addict to increase doses and creates psychological dependence.

Toxicokinetics: After oral administration, methamphetamine is well absorbed in the GIT, its effects are felt 15 – 20 minutes after application; it reaches its maximum concentration in the plasma after approximately 2 – 3 hours. After IV application or smoking, the effects appear immediately, when sniffing after 3 – 5 minutes. After a single administration, the effects can last for 3 – 12 hours. It is metabolized in the liver by the cytochrome P450 system, producing active and inactive metabolites. Excretion takes place in the kidneys into the urine, where metabolites can be detected for several days.

Symptoms of abuse and intoxication: Clinical symptoms reflect sympathetic activation. After application, feelings of euphoria – cheerfulness, talkativeness, hyperactivity to agitation, loss of inhibitions, psychomotor restlessness, the need for sleep and appetite decrease appear. Hallucinations may also occur. During the somatic examination, it is common to detect hyperventilation, tachycardia, hypertension, sweating, hyperthermia, tremors, convulsions, mydriasis. As a result of hypertension, intracranial bleeding, ventricular fibrillation, acute coronary syndrome, and acute renal failure may occur. In severe cases, there is complete exhaustion of the body, dehydration, disruption of the internal environment (metabolic acidosis, hypoglycaemia). Sometimes death occurs as a result of the collapse of the respiratory centre. Overdose is manifested by hyperthermia and convulsions, chest pains,

unconsciousness may appear. After the euphoric effects wear off, fear, depression and paranoia appear.

Diagnosis and differential diagnosis: Anamnestic data and an objective history of drug addiction are important. The clinical picture is typical. During the somatic examination, it is possible to detect IV punctures, phlebitis or inflammatory skin lesions. Metabolites can be tentatively detected in urine by single or multi-parameter strip or cassette tests. Their exact quantitative and qualitative determination for forensic purposes is carried out from urine by gas chromatography.

Treatment: In case of accidental oral overdose, gastric lavage within 60 minutes is suitable, followed by administration of activated charcoal. For restlessness and convulsions, diazepam is administered IV in a dose of 0.1 – 0.2 mg/kg. The dose can be repeated after 5 – 10 minutes, while the maximum dose of 30 mg must not be exceeded. If it is not possible to provide IV approach, midazolam (Dormicum inj.) is administered intramuscularly at a dose of 0.1 – 0.2 mg/kg. For psychotic symptoms, haloperidol (Haloperidol inj.) 10 mg is administered either IM or very slowly IV. Hyperthermia above 40°C is a bad prognostic symptom, intensive external and/or internal cooling (cooled infusions) and rehydration is necessary. In case of insufficient response to cooling, it is possible to administer IV Dantrolene in a dose of 1 mg/kg.

4.3.3 MDMA – Methylenedioxy-methylamphetamine

(synonyms – ecstasy, molly, Adam, beans, biscuit, clarity, disco biscuit, E, Eve, go, hug drug, lover's speed, peace, STP, X, XTC, etc.)

Characteristics: MDMA was originally synthesized as an antidepressant and weight-loss drug (anorexic). It belongs to the group of hallucinogenic amphetamines and has a psychostimulant and hallucinogenic effect. It is a typical "party drug". It is most often used orally in tablet or capsule form, dissolved in drinks; crushed tablets can be snorted or smoked. Long-term use causes psychological dependence. MDMA has mild teratogenic effects.

Toxicokinetics: After ingestion, the effects start in 20 – 60 minutes and may persist for several hours. Like methamphetamine, MDMA is also metabolized in the liver by the cytochrome P450 system – more precisely by the CYP2D6, which gets inhibited in the long-term use, resulting in the drug tolerance emergence. Metabolites are excreted by the kidneys into the urine.

Symptoms of abuse and intoxication: The effects often depend on the mood the user had before using the drug – thus, they can be positive or negative. After application, there is a slight euphoria, later a feeling of calmness or restlessness and confusion. Some users gradually experience an optimistic mood, loss of inhibitions, hallucinations and increased psychomotor speed. The euphoric feelings associated with the "party" atmosphere can lead to a state of dancing "ecstasy" until complete exhaustion, with the risk of hyperthermia, dehydration, hyponatremia – disruption of mineral metabolism, metabolic acidosis and even death. In addition to psychological manifestations, the clinical picture of overdose or intoxication includes distinct mydriasis, ataxia, headache, hypertension, tachycardia, sweating, hyperthermia, tremors, convulsions. Severe intoxications may be accompanied by cardiac arrhythmias and may lead to hepatic and/or renal failure, CNS haemorrhage, and the development of disseminated intravascular coagulopathy (DIC). The combination with alcohol increases the effects of MDMA, but also increases the risk of serious or fatal consequences.

After the effects wear off when the MDMA level drops, feelings of fatigue, depression, and paranoia appear, which persist for up to 3 days, and later feelings of reduced physical and mental condition persist for a longer time.

Diagnosis and differential diagnosis: The basis is anamnestic data and a typical clinical picture. Metabolites can be tentatively detected in urine by single or multi-parameter strip or cassette tests. Accurate quantitative and qualitative determination for forensic purposes can be performed from plasma, more often from urine by gas chromatography.

Treatment: In case of overdose, administration of activated charcoal is indicated within 60 minutes. It is important to monitor vital functions for at least 4 hours. Further treatment is symptomatic; agitation and restlessness can be reduced by administering diazepam. As far as possible, β-blockers, which can reduce coronary flow, should be avoided when influencing hypertension.

Rehydration and correction of metabolic acidosis are important. In case of hyperthermia above 40°C, it is necessary to ensure external cooling. If the effect is insufficient, it is possible to administer IV Dantrolene in a dose of 1 mg/kg.

4.4 Opioids

Characteristics: Opioids are a group of substances that have analgaesic-sedative effects caused by binding to opioid (endorphin) receptors in the CNS. According to the source from which they are obtained, they are divided into:

- natural (opium alkaloids – morphine, codeine), their source is poppy seeds;
- semi-synthetic (heroin, oxycodone...);
- synthetic (methadone, fentanyl, tramadolium chloride, pethidine ...).

The name “opiates” is being used for substances produced from a natural source – poppy. The sticky juice from unripe poppies is referred to as opium. In medicine, in addition to their analgaesic effects, opiates were also used as antitussives (codeine) or to reduce intestinal motility. Physical and psychological dependence occurs with regular use. The most addictive is heroin (heroinism), the use of which is considered the most serious type of drug addiction. Opioids are most often injected (morphine, heroin), smoked (opium), less often inhaled. This type of drug addiction is often associated with a higher incidence of HIV infection.

Toxicokinetics: Opioids are lipophilic substances that pass well through cell membranes. They are metabolized primarily in the liver by the P450 enzyme system, through which lipophilic substances become hydrophilic metabolites, which are excreted by the kidneys into the urine.

Symptoms of abuse and intoxication: Clinical manifestations of **acute intoxication** are euphoria, indifference, psychological well-being, apathy, numbness, feeling of warmth, especially on the face, pronounced miosis, urticaria, itchy skin. An intoxicated person scratches his/her whole body even when being unconscious. In **severe intoxication**, the respiratory centre becomes depressed – breathing is shallow, bradycardia, hypotension, hypothermia, impaired consciousness up to coma may emerge. A serious complication is the development of non-cardiac pulmonary oedema. Sometimes acute nephrotic syndrome (on the basis of tubular necrosis) occurs as one of the first symptoms of intoxication. Withdrawal symptoms appear after about 5 – 15 hours. They are manifested by tearing, watery discharge from the nose, cold sweat, tachycardia, fear, disorientation, general exhaustion. In this state, bouts of uncontrolled aggression directed against the environment, but also against oneself, often occur.

Diagnosis and differential diagnosis: They are based on anamnestic data on drug addiction. The clinical picture is typical.

During a somatic examination, it is possible to detect traces of injections, phlebitis or skin lesions. Metabolites can be tentatively detected in urine with single or multi-parameter strip or cassette tests. Accurate quantitative and qualitative determination for forensic purposes is carried out from urine by gas chromatography. In severe states of unconsciousness, it is necessary to exclude pulmonary oedema and nephrotic syndrome of other aetiology.

Treatment: For the opioid type of intoxication, the antidote Naloxone (Naloxone inj.) is available – it acts as a specific opioid antagonist. It is applied slowly IV in a dose of 0.4 mg (1 amp.); the dose can be repeated after 2 – 3 minutes, up to a total maximum dose of 10 mg, or until the patient acquires a sufficient level of consciousness and the correction of spontaneous ventilation is present. If there is no improvement in the clinical condition after reaching the maximum dose, the diagnosis of opiate intoxication is questionable. Administering Naloxone can lead to the sudden development of withdrawal syndrome in an opioid intoxicated person.

Further treatment is symptomatic. In severe depression of the respiratory centre and breathing disorders, intubation, artificial pulmonary ventilation, and oxygen therapy are required. After the acute phase of intoxication has passed, withdrawal symptoms appear, which can be alleviated with diazepam, tiapride, or haloperidol.

4.5 Organic solvents

Organic solvents such as acetone, toluene, trichloroethylene and others are readily available drugs that are particularly used by youths from weaker socio-economic groups. Properties of selected organic solvents, symptoms of intoxication, its consequences and treatment are presented in chapter 2.2.3.

5 Mushroom Intoxication

Mushroom foraging for the purpose of consumption is a relatively widespread tradition with rich history in Slovakia. Variety of dishes are prepared from mushrooms, or they can be used as food additives or spices. More than 5,000 types of mushrooms grow in Slovakia, out of which 300 – 400 are edible. The rest can be characterized as inedible or poisonous mushrooms. There are only 7 – 8 species (i.e. around 100 mushrooms) of deadly poisonous mushrooms. Mushroom poisoning is typical for the summer to autumn months, especially from August to October. There is no generally applicable rule for distinguishing between edible and poisonous mushrooms. Most mushroom poisonings are caused by occasional mushroom pickers, or those mushroom pickers who collect mushrooms in foreign, unknown locations.

The only effective way to prevent these types of poisoning is to pick only safely known types of mushrooms. In addition to this fact, it is important to realize that under certain circumstances (mushrooms contaminated with other toxins, steamed mushrooms), even edible mushroom can turn inedible or poisonous.

Mushroom poisoning can be divided into *one-type-mushroom poisonings* and *several-type-mushroom poisonings* (also called *combined poisonings*).

The typical clinical picture usually develops after poisoning by mushrooms that contain thermostable toxins (these are not destroyed by heat).

After consumption of some types of mushrooms containing thermolabile toxins (these are destroyed by long enough boiling), clinical signs of poisoning may not develop.

Depending on the clinical picture and the course of intoxication, it is possible to distinguish the following syndromes caused by thermostable toxins:

1. Phalloidin syndrome (cyclopeptide, hepatorenal, cytotoxic)
2. Gastroenteric syndrome (gastro-entero-dyspeptic, gastrointestinal)
3. Antabuse syndrome (vasotoxic, coprinic)
4. Atropine syndrome (pantherine, psychotroponeurotoxic, anticholinergic)
5. Gyromitra syndrome (hepatotoxic)
6. Muscarinic syndrome (parasympathomimetic)
7. Orelanus syndrome (nephrotoxic)
8. Psilocybin syndrome (psychotropic-neurotoxic)

5.1 Phalloid syndrome (cyclopeptide, hepatorenal, cytotoxic)

Characteristics: Cyclopeptide syndrome is the most serious type of mushroom intoxication. It occurs after consumption of mushrooms containing hepatotoxic, cyclic alkaloids – amanitins and phalloidin. Mushrooms containing these alkaloids are among the most toxic in the world. In the temperate climate zone of Europe and Asia, ***Amanita phalloides*** (commonly known as the Death cap – Fig. 13a) is relatively widespread. Amanitin and phalloidin are also found in: *Amanita phalloides var. alba* (the White death cap – Fig. 13b), *Amanita virosa* (the Destroying angel – Fig. 13c), *Amanita verna* (the Fool's Mushroom – Fig. 13d), *Lepiota helveola* (Fig. 13e), *Lepiota pseudohelveola* (Fig. 13f), and others.

Fig. 13a Death cap
(Amanita phalloides)
Growing period: July – October

Fig. 13b White death cap
(Amanita phalloides var. alba)
Growing period: July – October

Fig. 13c Destroying angel
(Amanita virosa)
Growing period: August – September

Fig. 13d Fool's mushroom
(Amanita verna)
Growing period: May – August

Fig. 13e Lepiota helveola
Growing period: July – October

Fig. 13f Lepiota pseudohelveola
Growing period: July – October

Amanita Phalloides, commonly referred to as the death cap mushroom, is one of the most poisonous mushrooms in the world. From a morphological point of view, toxic toadstools have 3 basic features different from other mushrooms: membranous, sac-like loose to sheathing volva, skirt-like membrane (called a ring) and pure white gills (Fig. 13a, 13b).

The largest mass poisoning with *Amanita Phalloides* was recorded in 1918 in a holiday camp in Poland, where 31 boys died after eating food prepared from this mushroom. The lethal dose of amanitin for an adult individual is less than 0.1 mg/kg of body weight. The most toxic part of the fruitbodies of *Amanita Phalloides* are the gills. Spores of gills contain up to 50% of the total amount of amanitin. Young fruitbodies contain less amanitin than older ones. Eight amatoxins were isolated from *Amanita Phalloides*, the

most important of which are alpha, beta and gamma amanitins. Chemically, they are: a) bicyclic octapeptides soluble in polar solvents (water, ethanol, methanol); b) stable under the action of enzymes; c) not destroyed by boiling, freezing, drying; and d) not subject to degradation by aging. Amanitin has a toxic effect on enterocytes, hepatocytes, cells of the myocardium and the proximal tubule of the kidneys.

Toxicokinetics: Consumption of *Amanita Phalloides* leads to the development of the cyclopeptide-hepatorenal syndrome. Amanitin binds to RNA polymerase in the liver and thus inhibits the synthesis of cellular proteins. Free amanitins are excreted in the bile, reabsorbed from the intestine and repeatedly pass through the enterohepatic cycle. Amanitin is excreted in urine and faeces. Phalloidins are highly toxic after parenteral administration. After oral administration, they are not absorbed from the intestine.

Clinical picture: Characteristic feature for *Amanita Phalloides* poisoning is that the onset of the first symptoms typically occurs rapidly, between 6 and 24 hours. These symptoms include gastroenteritis with nausea, vomiting, recurring diarrhoea, and spasmodic abdominal pain. Gastroenteritis may persist for 2 – 3 days and may lead to severe dehydration and mineral breakdown. In some cases, there is a deceptive, several-hour improvement. About 36 hours after consuming the mushroom, hepatic damage develops with gradual liver and kidney failure. Laboratory findings show a clear increase in bilirubin, serum aminotransferases, prolongation of prothrombin time, clinically evident icterus, and encephalopathy.

The course of intoxication in an untreated patient is given below in Table 10. Depending on the amount of amanitin consumed, mortality in untreated or improperly treated cases is up to 50%, in the development of acute hepatorenal failure up to 90%.

Table 10. Stages and symptoms of intoxication with *Amanita Phalloides*.

Time since consumption	Intoxication phase	Symptoms
0 – 24 hours	Latent phase	Without clinical symptoms
6 – 48 hours	Gastrointestinal phase	Nausea, vomiting, crampy abdominal pain, diarrhoea
36 – 72 hours	Phase of false improvement	Regression of clinical symptomatology, deterioration of hepatic and renal functions in laboratory findings
4 – 9 day	Acute hepatorenal failure	Toxic hepatitis – icterus, hepatomegaly, coagulation disorders, hepatic encephalopathy, coma, renal failure with anuria, multi-organ failure, death.

Diagnosis: It is based on the anamnestic data on the consumption of mushrooms and the clinical picture. It is very important to find out the latency period from the ingestion of mushrooms and the onset of the first symptoms. A longer latency of 6 – 24 hours after consumption is typical for this type of poisoning. In the case of poisoning with other types of mushrooms, gastrointestinal symptoms occur earlier, already after 2 – 4 hours. In unclear cases, a microscopic – mycological examination of the remains of fungi from gastric lavage or vomitus is necessary. Amatoxin can be examined qualitatively and quantitatively in specialized laboratories using various methods, e.g. RIA, ELISA, HPLC, which are highly sensitive if realized in the first 48 hours after ingestion.

Treatment: There is no specific antidote. The rule for this type of poisoning: the earlier the treatment starts, the more successful it is! ! !

At the slightest signs of suspected phalloidin poisoning, the following first aid steps are necessary to perform: a) inducing repeated vomiting (mechanical irritation of the pharynx or administration of salty warm water – 3 tablespoons of salt per 5 litres of water); b) intensification of bowel movements (administration of laxatives); and c) a large supply of mineral water or pure water (alcohol and milk are contraindicated !!!). At the same time, it is necessary to ensure rapid transport of the intoxicated person to the hospital.

During hospitalization, gastric lavage is performed, especially in cases when vomiting has not been induced until then. Lavage is most effective in the latent phase (suspected amanitin intoxication, suicide attempt). Following lavage, activated

charcoal is administered in doses of 1 g/kg of body weight, repeatedly every 4 hours. Laxatives are administered at the same time. In the gastrointestinal phase of intoxication, the effect of lavage is problematic. It is necessary to send samples from lavage or vomit for mycological examination.

Silibinin (Lagalon SIL inj.) is not a specific antidote, but it competitively blocks the transport of amanitin into the hepatocyte and regenerates RNA polymerase. This reduces the extent of necrosis in the liver. It is administered intravenously at a dose of 20 mg/kg/day for 3 – 5 days. Silibinin should also be administered if this poisoning is suspected only. In cases when Silibinin is not available, it is possible to administer N-acetylcysteine (ACC INJECT inj.), the initial dose is 150 mg/kg, then 50 mg/kg.

Administration of high doses of G-penicillin was withdrawn.

Complex supportive treatment is essential – intravenous rehydration, correction of internal environment disorders; in case of bleeding conditions we administer vitamin K (Kanavit gtt.) and fresh frozen plasma. At the same time, hepatoprotectors, glucose, and lactulose are administered.

Haemodialysis and haemoperfusion are indicated in patients with liver and kidney failure.

In severe cases, liver transplantation is indicated.

5.2 Gastroenteric syndrome (gastroenterodyspeptic)

Characteristics:

This syndrome is common, but mostly with a good prognosis. It is caused by the consumption of a relatively large group of different types of mushrooms that contain heat-labile toxins. Dyspeptic complaints appear after consuming mushrooms that have been insufficiently heat-treated (canned without prior heat treatment) or in a raw state (tasting, in the form of a salad), but also when improperly stored in airtight plastic containers.

This syndrome occurs after ingestion of ***Boletus satanas***, commonly referred to as the Satan's bolete (Fig. 14), and related mushrooms. The toxins of this and related mushrooms are thermolabile, and are destroyed by boiling for 40 minutes. Gastroenteric syndrome can also be caused by the consumption of ***Russula emetica*** (commonly known as the Vomiting russula – Fig. 15) and other mushrooms of the genus Russula, ***Agaricus xanthodermus*** (commonly known as the Yellow-stainer – Fig. 16) – this is very similar to the edible *Agaricus campestris* mushroom (the Field mushroom), ***Scleroderma citrinum*** (the Common earthball – Fig. 17), ***Lactarius helvus*** (Fig. 18), ***Lactarius torminosus*** (the Woolly milkcap – Fig. 19), ***Hygrophoropsis aurantiaca*** (the False chanterelle – Fig. 20), ***Omphalotus olearius*** (the Jack-o´-lantern mushroom – Fig. 21), or ***Armillaria mellea*** (the Honey fungus – Fig. 22). The mushroom ***Macrolepiota rhacodes var. hortensis*** (Fig. 23) which grows in the gardens and

Fig. 14: Satan's bolete
(Boletus satanas)
Growing period: May – September

Fig. 15 Vomiting russula
(Russula emetica)
Growing period: June - October

in the composts, is also considered slightly poisonous (the parasol type mushrooms growing outside the forest are not recommended to be picked).

Fig. 16 Yellow-stainer
(Agaricus xanthodermus)
Growing period: June – November

Fig. 17 Common earthball
(Scleroderma citrinum)
Growing period: July – November

Fig. 18 Lactarius helvus
Growing period: July – November

Fig. 19 Wooly milkcap
(Lactarius torminosus)
Growing period: July – October

Fig. 20 False chanterelle (Hygrophoropsis aurantiaca) Growing period: September – November

Fig. 21 Jack-o´-lantern mushroom (Omphalotus olearius) Growing period: June – November

Fig. 22 Honey fungus (Armillaria mellea) Growing period: August – October

Fig. 23 Macrolepiota rhacodes var. hortensis Growing period: July – November

Toxicokinetics: After ingestion, insufficiently heat-processed mushrooms cause irritation of the mucous membrane of the stomach and intestine. This syndrome is caused by various chemical substances; it is not known exactly which component of the fungus causes gastroenteritis.

Clinical picture: After consumption, symptoms appear relatively quickly, ranging from 15 minutes to 4 hours. The clinical picture is dominated by nausea, vomiting, colic pain in the abdominal cavity, diarrhoea (mild to severe), severe dehydration and

hypotension, paraesthesia and tetany may also occur. In some patients – cases, the symptoms subside spontaneously within 3 – 4 hours, complete recovery occurs within 2 days. Others need hospital care.

Treatment: At the first appearance of clinical manifestations, it is necessary to induce vomiting or perform a gastric lavage (the contents must be sent for toxicological examination). Subsequently, activated carbon is administered in a 20 – 25% suspension (20 – 25 g of activated carbon per 100 ml of lukewarm water). If the patient does not have diarrhoea, we give a laxative – lactulose or MgSO4 (Na2SO4), i.e. Glauber's salt in a dose of 1 – 2 spoons per 0.5 l of lukewarm water. Activated charcoal together with a laxative is administered repeatedly every 2 – 4 hours until the patient is stabilized. Depending on the patient's condition, the following may be required: parenteral rehydration; monitoring of the electrolyte balance, especially potassium; and depending on the circumstances, administration of the antispasmodics. H_2-receptor blockers and antacids can be given for gastritis.

5.3 Antabuse syndrome (vasotoxic, coprinic)

Characteristics: Alcohol intolerance occurs after consumption of mushrooms containing coprine in combination with alcohol. The syndrome is caused by these mushrooms: ***Coprinus atramentarius*** (the Common ink cap – Fig. 24a), ***Coprinus insignis*** (Fig. 24b), ***Tricholoma aurantium*** (the Golden orange tricholoma – Fig. 24c), ***Boletus torosus*** (the Imperator torosus – Fig. 24d) and others.

Fig. 24a Common ink cap (Coprinopsis atramentarius) Growing period: April – November

Fig. 24b Coprinopsis insignis Growing period: May – November

Fig. 24c Golden orange tricholoma (Tricholoma aurantium) Growing period: August – November

Fig. 24d Imperator torosus (Boletus torosus) Growing period: July – November

Toxicokinetics: Coprine is chemically non-poisonous N5-/1-hydroxycyclopropyl/-L-glutamine. It inhibits aldehyde dehydrogenase in the liver. In combination with alcohol, it stops the breakdown of alcohol in the body and causes antabuse syndrome – poisoning with acetaldehyde, which is an intermediate product of alcohol metabolism. Antabuse effect lasts 3 – 24 hours after eating mushrooms. It mainly damages cells of the liver, kidneys, but also the central nervous system.

Clinical picture: Depending on alcohol consumption, symptoms may appear within 5 – 120 minutes. Redness on the face and neck, nausea, sweating, palpitations, headaches, tachycardia, pain in the abdominal cavity, diarrhoea, hypotension, shortness of breath may appear. Symptoms subside within 48 – 72 hours.

Diagnosis: It is based on anamnestic data on the consumption of mushrooms and the clinical picture. It is important to find out the latency period from the ingestion of mushrooms and, if possible, to ensure mycological examination of mushroom residues during gastric lavage or vomiting.

Treatment: When symptoms of mushroom poisoning occur, it is necessary to induce repeated vomiting as soon as possible or perform a gastric lavage and then administer activated charcoal. Further treatment is symptomatic; the patient's prognosis is good.

5.4 Atropine syndrome (pantherine, anticholinergic)

Characteristics: Atropine syndrome, also sometimes referred to as psychotropic-neurotoxic in the literature, occurs after consumption of ***Amanita panterina*** (the Panther cap – Fig. 25a), ***Amanita muscaria*** (the Fly amanita – Fig. 25b), ***Amanita***

regalis (the Royal fly agaric – Fig. 25c), ***Amanita gemmata*** (the Gemmed amanita – Fig. 25d) and others. The main toxins of these mushrooms are ibotenic acid and muscimol – both toxins are well soluble in water and alcohol. Poisoning occurs rarely, young forms can be confused with the edible toadstool *Amanita caesarea* (the Caesar's mushroom).

Fig. 25a Panther cap
(Amanita panterina)
Growing period: May – November

Fig. 25b Fly amanita
(Amanita muscaria)
Growing period: June – November

Fig. 25c Royal fly agaric
(Amanita regalis)
Growing period: July – October

Fig. 25d Gemmed amanita
(Amanita gemmata)
Growing period: May – October

Toxicokinetics: After ingestion, depending on the amount consumed and the type of mushroom, symptoms appear in the time span between 30 minutes and 2 hours. The maximum effects appear around 5 hours after ingestion and can last up to 12 hours. Psychological effects may persist for several days.

Clinical picture: Typical symptoms of poisoning include mild nausea, vertigo, ataxia, excitement, visual and auditory hallucinations, disorientation, euphoria alternating with depression, muscle twitching, convulsions, motor restlessness, skin is warm and dry, coma is rare. After overcoming the acute phase, a deep sleep follows. After waking up, the patient suffers from amnesia for the course of the poisoning.

Diagnosis: The basis is anamnestic data on the consumption of mushrooms and the clinical picture. It is important to find out the latency period from the ingestion of mushrooms and, if possible, to ensure mycological examination of mushroom residues from gastric lavage or vomitus.

Treatment: As soon as possible after ingestion, it is necessary to induce vomiting or perform a gastric lavage and then repeatedly at intervals of 2 – 4 hours give activated charcoal 1 g/kg. In case of convulsions and restlessness of the patient, diazepam can be administered; to reduce neuromuscular irritability administer calcium gluconicum; in severe cases administer physostigmine 1 – 2 mg SC, or 1 mg/5 min. IV. If the patient does not suffer from other serious diseases of the kidneys, liver or cardiovascular system, the prognosis is good, death is rare.

5.5 Gyromitra syndrome (hepatotoxic)

Characteristics: Gyromitra syndrome develops after the consumption of ***Gyromitra esculenta*** (Fig.26), which grows throughout the temperate zone of the northern hemisphere. The mushroom contains hepatotoxic gyromitrin. Poisoning by this mushroom mainly occurs due to confusion with *Gyromitra gigas*.

Fig. 26 Gyromitra esculenta
Growing period: March – June

Toxicokinetics: Gyromitrin is an unstable, thermolabile substance. It decomposes in the acidic environment of the stomach into methyl-formyl-hydrazine, from which acetaldehyde is released. Its amount and concentration in the fungus depends on climatic conditions, the duration of development and the survival of fruitbodies. The lethal dose is estimated at 10 – 50 mg/kg. The IARC classifies gyromitrin into the Group 3 – not classified as a human carcinogen, but cancer has been found in experimental animal studies. The toxin causes damage up to necrosis of liver and kidney cells, but also affects the CNS.

Clinical picture: Intoxication proceeds similarly to poisoning with Amanita phalloides. After a latency of 5 – 10 hours, nausea, vomiting, diarrhoea and abdominal discomfort may appear after consumption. The condition can result in severe dehydration and mineral breakdown. Similar to the phalloid syndrome, acute gastrointestinal symptoms subside, followed by a transient improvement and then transition to severe hepatorenal syndrome with coagulation disorders and, in the terminal stage, to cardiorespiratory failure.

Diagnosis: The basis is anamnestic data on the consumption of mushrooms and the clinical picture. The latency from the ingestion of mushrooms and the appearance of the first symptoms is important. A mycological examination of the remains of mushrooms or vomit is justified. Toxicological and laboratory examinations.

Treatment: The principles of first aid and treatment are similar to those of phalloid poisoning. In addition, high doses of vitamin B6 (pyridoxine 25 – 70 mg/kg, max. 5 g in one dose) are administered.

5.6 Muscarinic syndrome (parasympathomimetic)

Characteristics: It occurs after consuming mushrooms containing the thermostable alkaloid muscarine (2-methyl-3-hydroxy-trimethylammoniumtetrahydrofuran), consisting of several isomers. The representation of isomers and their content varies according to the type of mushroom. Muscarinic syndrome is caused by the mushrooms of the genus: a) *Inocybe* – ***Inocybe erubescens*** (the Deadly fibrecap – Fig. 27); and b) *Clitocybe* – ***Clitocybe agrestis*** (Fig. 28). Low levels of muscarine can also be found in other mushrooms, e.g. ***Boletus luridus*** (the Lurid bolete – Fig. 29), ***Lactarius rufus*** (the Rufous milkcap – Fig. 30), ***Mycena rosea*** (the Rosy bonnet – Fig. 31) and others. This syndrome occurs less often, but is very serious, rarely even fatal.

Fig. 27 Deadly fibrecap
(Inocybe erubescens)
Growing period: May – September

Fig. 28 Clitocybe agrestis
Growing period: August – November

Fig. 29 Lurid bolete
(Boletus luridus)
Growing period: May – September

Fig. 30 Rufous milkcap
(Lactarius rufus)
Growing period: June – November

Fig. 31 Rosy bonnet
(*Mycena rosea)*
Growing period: July – November

Toxicokinetics: Due to the effect of muscarine – as a result of selective stimulation of cholinergic muscarinic, sometimes also nicotinic receptors – an acute neurotoxic parasympathomimetic (cholinergic) syndrome arises. Some isomers have effects similar to histamine (feeling of heat, facial flushing, hypotension, bronchospasm). The patient's prognosis is usually good, however, after consuming *Deadly fibrecap*, death can occur.

Clinical picture: In the clinical picture, along with the general symptoms such as nausea, vomiting, and diarrhoea (watery), strikingly specific symptoms of poisoning – a feeling of heat, very strong sweating, salivation, lacrimation, colic pains abdomen, myosis, blurred vision, bradycardia, hypotension, chills, bronchospasm, dyspnoea, and increased bronchial secretion – may also appear very quickly (in 30 – 120 minutes).

Diagnosis and differential diagnosis: The anamnesis of mushroom ingestion and the unique clinical picture – parasympathomimetic (cholinergic, autonomic) syndrome are of fundamental importance. As part of the differential diagnosis, it is necessary to consider poisoning by organophosphates, carbamates, but also other mycointoxications. In diagnosis, a set of 3 symptoms is of particular importance – heavy sweating, significant salivation and significant lacrimation, which are not so markedly manifested in any other mushroom poisoning.

Treatment: At the first appearance of clinical manifestations, it is necessary to induce vomiting or perform a gastric lavage (the contents must be sent for toxicological examination). The treatment continues with the administration of activated charcoal in the form of a 20 – 25% suspension (i.e. 20 – 25 g per 100 ml of lukewarm water). If the patient does not have diarrhoea, a laxative – MgSO4 – Glauber's salt (1 – 2 spoons per 0.5 l of lukewarm water) or lactulose are administered. Activated charcoal with a laxative is administered repeatedly every 2 – 4 hours until the patient's condition stabilizes. An effective part of the treatment is the administration of atropine (parasympatholytic) in a dose of 1 mg IV or IM. Atropine is not an antidote, it is given in severe cholinergic symptoms (sweating, salivation, lacrimation) until they subside.

5.7 Nephrotoxic syndrome (orellanine)

Characteristics: This syndrome is caused by the ingestion of a toxic alkaloid – orellanine, which is found in mushrooms from the Cortinarius genus, e.g. ***Cortinarius orellanus*** (commonly known as the Fool's webcap – Fig. 32). It is a very dangerous poisoning – a lethal dose of orellanine is found in a 30-gram fruitbody of this deadly fungus. The content of orellanine in fruitbodies is variable, mostly it is found in the cap.

Fig. 32 Fool's webcap (Cortinarius orellanus) Growing period: June – October

It causes renal lesions with the same latency period in animals and in humans. Mass poisonings also occurred in the past.

Toxicokinetics: Orellanine damages the proximal tubules in the kidneys. The probable mechanism of toxic action consists in the formation of free radicals, inhibition of the macromolecule synthesis, proteins, RNA and DNA. Liver damage has not yet been confirmed experimentally in animals.

Clinical picture: Intoxication takes place in four phases: latent, pre-renal, renal and recovery.

1. *Latent phase* – its length is determined by the severity of intoxication and can last form 36 hours to 21 days after consuming the mushroom. The shorter the latent phase, the more severe the poisoning. A short latent phase is often associated with acute renal failure. According to the length of the latent phase, we divide the severity of orellanine intoxication into 3 groups:
    - o Severe intoxication – the duration of the phase is 2 – 3 days.
    - o More serious intoxication – the duration of the phase is 6 – 7 days.
    - o Mild intoxication – the duration of the phase is 10 – 17 days.
2. *Pre-renal phase* – lasts about 7 days. Non-specific gastrointestinal, neurological and general symptoms dominate: headache, myalgia, nausea, vomiting, abdominal pain, thirst, pain in the lumbar region, somnolence, tinnitus, chills. Serum creatinine is elevated in laboratory parameters.

3. *Renal phase* – develops from the 3rd to the 20th day after consuming the mushroom. It starts with oliguria to anuria, which often ends with acute kidney disease, which is present in about 30 – 46% of cases. Proteinuria, microscopic haematuria and leukocyturia are often present in the urine. Histological examination shows tubulointerstitial nephritis with interstitial inflammatory oedema and necrosis of the tubular epithelium. In about 30 – 50% of patients, acute kidney disease turns into chronic renal insufficiency.
4. *Recovery phase* – lasts several weeks to months, some patients have permanent kidney damage.

Diagnosis and differential diagnosis: Anamnestic data on the consumption of mushrooms and the clinical picture are of fundamental importance. If there is uncertainty in the diagnosis of Cortinarius poisoning, it is necessary to determine the diagnosis based on a group of signs that do not occur in other poisonings. This is a mass occurrence of poisoning, a long latency phase, absence of liver damage, dry mouth, thirst, polyuria, sweating, chills, headaches, pain in the lumbar region, paraesthesia of the limbs.

Treatment: Due to the long latency of the onset of the first symptoms, gastric lavage, the administration of activated charcoal and laxatives are unnecessary in poisonings with mushrooms containing orellanine.

There is no specific antidote for this type of intoxication. Due to possible increase in nephrotoxicity, forced diuresis is not recommended. Haemodialysis is the only causal solution to acute renal insufficiency.

In severe chronic kidney damage, a kidney transplant may be indicated. Administration of corticosteroids is not indicated because they do not favourably affect the development of renal failure.

5.8 Psilocybin syndrome (psychotropic-neurotoxic)

Characteristics: Psilocybin syndrome occurs after oral ingestion of mushrooms from the genus of Psilocybe, which contain the toxic alkaloids of psilocybin and psilocin. This group includes the mushrooms as ***Psilocybe semilanceata*** (the Liberty cap – Fig. 33) or ***Psilocybe bohemica*** (Fig. 34).

Fig. 33 Liberty cap
(Psilocybe semilanceata)
Growing period: August – December

Fig. 34 Psilocybe bohemica
Growing period: September – December

Toxicokinetics: Symptoms appear within 30 – 60 minutes, persist for 4 – 6 hours and subside within 10 hours after consumption. Psilocybin and psilocin are thermostable alkaloids with similar effects to LSD. Psilocybe genus fungi are abused as drugs for their hallucinogenic effects.

Clinical picture: Somatic symptoms of poisoning include: headache, mydriasis, nausea, vomiting, vertigo, tachycardia, hypertension, muscle weakness. At the forefront of psychological symptomatology is euphoria, hallucinations, feeling of happiness, feeling of being able to fly. Less common are excitement, depression, fear, anxiety and suicidal tendencies.

Treatment: If clinical symptoms occur after accidental ingestion, it is necessary to induce vomiting or perform gastric lavage. Subsequently, activated carbon is administered in the form of a 20 – 25% suspension (20 – 25 g of activated carbon per 100 ml of lukewarm water). The patient's restlessness can be reduced by administering diazepam in a dose of 10 – 20 mg IV. For drug addicts, it is necessary to consider the combination with other drugs or alcohol.

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