Toxicology LEC 7.

Household products

This group of potential poisons comprises many substances often found around the household.

(1) Carbon Monoxide

This is highly toxic gas (odourless and tasteless) found in car exhausts and results from the inefficient burning of hydrocarbon fuels in engines as well as in stoves and boilers especially where there is poor ventilation.

Mechanism of toxicity

Carbon monoxide reacts with the **haemoglobin** in red blood cells to form **carboxyhaemoglobin**. It does this by binding to the iron atom of the haem molecule in the same way as oxygen. **Carbon monoxide** binds more avidly than **oxygen**, however, and the resulting haemoglobin cannot carry out its normal function of transporting oxygen. Therefore, there is **competition for binding** to **haemoglobin** between **oxygen and carbon monoxide** and the concentration of the latter is a crucial factor.

Toxic effects

The result of carbon monoxide poisoning is that the tissues are starved of oxygen and suffer ischaemic damage. Energy production is reduced, only anaerobic respiration being possible and, hence, there is an accumulation of lactic acid causing acidosis.

The symptoms of carbon monoxide poisoning (especially in human):

There is often headache, mental confusion, agitation, nausea and vomiting. The skin becomes characteristically pink due to the carboxyhaemoglobin in the blood. lose consciousness, respiratory failure. There may be brain and cardiac damage resulting from the hypoxia, and also cardiac arrythmias and other malfunctions of the heart can occur.

Treatment

Is relatively simple, especially for mild cases and involves 1-removing the victim from the source of carbon monoxide, or causing fresh uncontaminated air to be introduced into the immediate environment

.2- For severe poisoning cases the use of oxygen .

(2) Antifreeze agents :-

(A) Ethylene Glycol:-

Ethylene glycol is a dihydric alcohol and a sweet tasting liquid, which has effects on the state of mind similar to those of ethanol.

Mechanism of toxicity

It is not intrinsically toxic but requires metabolism. There are various intermediate metabolic products terminating in **oxalic acid.** The intermediate acidic metabolites cause **acidosis directly** and also by **increasing the level of NADH** which is then utilized in the production of **lactic acid**. As well as being acidic, **oxalic acid**

damages the brain by **crystallizing** there. **Calcium oxalate crystals** may also form in the **kidney tubules** and **cause damage**.

Treatment

1- Administration of ethanol by mouth or pure ethanol can be infused i.v. (because the first step in the metabolism of ethylene glycol involves the enzyme alcohol dehydrogenase. The preferred substrate for this enzyme is ethanol and so when ethanol is present in vivo it is preferentially metabolized. The metabolism of ethylene glycol is therefore blocked).

2- Haemoperfusion. 3-Haemodialysis.

(B) Methanol:

It may sometimes be present in **antifreeze,** is also found in methylated spirits (industrial spirit). It is also very toxic due to its metabolism to formaldehyde and formic acid.

Toxic effects:

The former may cause blindness if the dose of methanol is not rapidly fatal.

Treatment:

Administration of ethanol and correction of metabolic acidosis, as methanol is metabolized by alcohol dehydrogenase.

(C) Alcohol

It has both pharmacological and toxic effects which vary with the dose and there is some evidence that it may even have beneficial effects at low doses. Ethanol is rapidly absorbed from the gut and distributes into body water and is metabolized to acetaldehyde, acetic acid and then carbon dioxide and water.

Toxic effects:

(A) Acute exposure:

Depression of the central nervous system, increasing visual impairment, muscular incoordination and slowed reaction times and after large toxic doses, unconsciousness and death (A lethal dose in an adult is between 300 and 500 ml, if taken in less than an hour).

Reversible change in the liver known as fatty liver where triglycerides accumulate in the hepatic cells as a result of impaired mitochondrial oxidation of fatty acids, respiratory depression, hypotension, hypothermia and hypoglycaemia will occur largely due to the inhibition of gluconeogenesis by ethanol.

(B) Chronic exposure:

Liver is the main target organ although the brain may also suffer. Cirrhosis of the liver occurs (the architecture of the liver is altered by the replacement of normal tissue by collagen so that it functions less efficiently).

Cancer of the liver and parts of the gastrointestinal tract as it classified as carcinogenic agent.

(D) Glue Sniffing and Solvent Abuse

Solvents are found in many different household products including glues, paints, paint strippers, aerosols, varnishes, cleaning fluids and fire extinguishers.

Toxic effects

A. ACUTE: The acute toxic effects of solvents are mainly narcosis or anaesthesia and the more serious sensitization of the heart.

B. CHRONIC: The chronic effects are in many cases unknown but may include changes in personality and general morbidity. There are, however, known cases of chronic cardiac toxicity due to trichloroethane exposure.

Industrial Chemicals

There are now many thousands of chemical substances used in industry ranging from metals and inorganic compounds to complex organic chemicals.

Means of Exposure

Just as with environmental exposure, exposure in the workplace may occur via any or all of the three major routes:

(1) By oral ingestion.

(2) By inhalation.

(3) By absorption following skin contact.

These routes of exposure apply to gases, vapours, aerosols, volatile solvents and other liquids as well as to dusts and fibers.

(1) Vinyl Chloride:

Vinyl chloride or vinyl chloride monomer (VCM) as it is commonly known is the starting point in the manufacture of the ubiquitous plastic polyvinyl chloride (pvc).

Exposure:

As vinyl chloride is a gas it can be inhaled but is also readily absorbed through the skin.

Toxic effects:

Chronic exposure to vinyl chloride results in 'Vinyl chloride disease' which comprises Raynauds phenomenon, skin changes, changes to the bones due to ischaemic damage following degeneration and occlusion of small blood vessels and capillaries, damage of the liver that may become fibrotic, and in some cases haemangiosarcoma.

Mechanism of toxicity:

It has been suggested that the vinyl chloride syndrome has an:

(A) Immunological basis: as immune complexes are deposited in vascular epithelium and complement activation is a feature.

(B) Metabolic basis: The toxic effects of vinyl chloride may result in part from metabolic activation, as it is metabolized by cytochrome P450 to the reactive intermediates, chloroethylene oxide or chloroacetaldehyde, which alkylate DNA and this may thereby lead to cancer. The reactive intermediate may also react with other macromolecules and cause the tissue damage seen either directly or via an immunological reaction.

(2) Cadmium

Cadmium is a metal which is widely used in industry in alloys, in plating, in batteries and in the pigments used in inks, paints, plastic, rubber and enamel. It is also found naturally and may be present in food.

Exposure:

By inhalation of cadmium metal or cadmium oxide.

Toxic effects:

(a) Acute inhalation exposure: can result in lung irritation and damage, diarrhoea and malaise.

(b) Chronic inhalation exposure: can result in emphysema occurring before kidney damage is observed.

(c) Cadmium can cause disorders of calcium metabolism leads to osteomalacia and brittle bones.

(d) It can also produce tumor at the site of exposure.

Mechanism of toxicity:

(A) The mechanism involves an effect on the vasculature of the organ. Cadmium reduces blood flow and ischaemic necrosis results from the lack of oxygen and nutrients reaching the tissue.

(B) Kidney damage may be due to the accumulation of cadmium in the kidney, as a complex with the protein metallothionein. Metallothionein is a low molecular weight protein involved with the transport of metals within the body. Due to its chemical similarity to zinc, cadmium exposure induces the production of this

protein. The cadmium-metallothionein complex is transported to the kidney, filtered through the glomerulus and is reabsorbed by the proximal tubular cells. Within these cells the complex is degraded by proteases to release cadmium which may damage the cells or recombine with more metallothionein.

(3) Aromatic Amines

Aromatic amines such as methylene-bis-o-chloroaniline (MBOCA), benzidine, o-tolidine, 4-amino-biphenyl, diaminodiphenylmethane (DADPM), and Naphthylamine are widely used in the rubber and dye industry and cause various toxic effects.

Toxic effects:

bladder cancer especially in dogs, jaundice and bile duct damage, liver tumor in rodents. The simplest aromatic amine, causes methaemoglobinaemia and consequently cyanosis after acute exposure. After chronic exposure anaemia with mild cyanosis may occur.

Mechanism of toxicity:

The mechanism of the bladder cancer is believed to involve metabolism. ß-Naphthylamine undergoes hydroxylation at the nitrogen atom followed by conjugation of the resulting hydroxyl group with glucuronic acid When the conjugate is excreted into the urine, however, it breaks down under the acidic urinary conditions

to yield a reactive metabolite which can then react with cellular macromolecules such as DNA.

(4) Asbestos

The term asbestos covers a group of fibrous mineral silicates which have differing chemical compositions. It is widely used in industry because of its ability to withstand heat and to provide insulation. e.g.,Chrysotile (white asbestos) and Crocidolite (blue asbestos).

Exposure:

Via inhalation or ingestion of food and water in some areas where mining takes place.

Toxic effects:

Exposure to asbestos via inhalation can lead to the following conditions:

1. Asbestosis or interstitial fibrosis of the lung.

2. Benign pleural disease.

3. Bronchial carcinoma.

4. Malignant mesothelioma: is a rare form of cancer which affects the chest lining and is associated only with exposure to asbestos, especially but not exclusively.

Asbestosis:

Is a dose-related disease and requires heavy exposure for a prolonged period. Particles of asbestos can be detected in the

fibrotic areas of the lung and sputum and the air spaces become obliterated with collagen. The asbestos fibers become coated with an iron-containing protein. The disease develops over a variable period of time with breathlessness becoming more severe.

Mechanism of toxicity:

Although asbestos is chemically inert, the fibers are cytotoxic and will haemolyze red blood cells. The length of the fiber seems to be an important factor in the toxicity-fibers which are longer than 10–20 μm will cause fibrosis but shorter ones do not. This is due to the inability of macrophages to phagocytose the long fibers fully and so the macrophage cell membrane is damaged and enzymes leak out. These enzymes and other cellular constituents may be involved in the development of fibrosis.

An immunological mechanism is also involved and asbestos fibers cause a change in the cell surface of the macrophage after ingestion. This is a change in the receptors for C3 complement and IgG antibodies. The complement pathway is also activated.

The mechanisms underlying asbestos-induced cancer are currently unknown. Unlike other types of chemical carcinogen, asbestos is not metabolized or activated, but once present in the tissues it remains there permanently although the fibers do migrate from the airways to the pleural cavity. Consequently, even exposure to high levels for short periods of time may be sufficient to eventually cause mesothelioma.