

General Description

Carbon disulfide (CS₂) in its pure form is a colourless, volatile and in-flammable liquid with a sweet aromatic odour. The technical product is a yellowish liquid with a disagreeable odour.

Sources

Carbon disulfide is used in large quantities as an industrial chemical for the production of viscose rayon fibres. In this technological process, for every kilogram of viscose produced, about 20-30 g of carbon disulfide and 4-6 g of hydrogen sulfide are emitted (1). Additional release of carbon disulfide, carbonyl sulfide and hydrogen sulfide takes place from coal gasification plants; data on the total emission from these plants are not available.

The ventilation discharge from viscose plants can reach several millions of m³ per hour, with a carbon disulfide content varying from 20 to 240 mg/m³, which represents a total emission of 15-40 tonnes of carbon disulfide daily (2).

Exposure to carbon disulfide is mostly confined to those engaged in technological processes in the viscose industry. However, the general population living near viscose plants may also be exposed to carbon disulfide emissions.

Occurrence in air

The primary source of carbon disulfide in the environment is emission from viscose plants, around which environmental pollution is especially great. A scientific review of Soviet literature indicates values ranging from 0.01 to 0.21 mg/m³ around viscose plants (2).

A recent Austrian study reports that concentrations of 0.05 ppm (157 µg/m³) were often exceeded in the vicinity of viscose plants, even at a distance of several kilometres, and concentrations close to the plants could be 5-10 times higher. The highest peak concentrations were between 3 and 6 mg/m³ (3).

During soil treatment with a 50% carbon disulfide emulsion for fumigation, carbon disulfide concentration in the respiration zone was found to be as high as 0.03 mg/m³ on the first day. This concentration decreases quickly, so that carbon disulfide is not detectable the next day (2).

Carbon disulfide present in air could be partially decomposed by light. Oxidation leads to the formation of carbonyl sulfide, sulfur dioxide and carbon monoxide (4). Carbonyl sulfide in particular causes an unpleasant odour.

Workplace concentrations of carbon disulfide have been found to range from less than 9 mg/m³ to peaks exceeding 6200 mg/m³ (1). As a result of various precautions taken over a period of time, average carbon disulfide concentrations have been reduced from about 250 mg/m³ in 1955-1965 to about 20-30 mg/m³ (5).

Conversion factors

$$\begin{aligned} 1 \text{ ppm} &= 3.13 \text{ mg/m}^3 \\ 1 \text{ mg/m}^3 &= 0.32 \text{ ppm} \end{aligned}$$

Routes of Exposure

The main source of environmental pollution (indoor and outdoor) by carbon disulfide is emission into the air from viscose plants. There are no data for pollution on a regional or global scale, nor is information available on dispersion and transformation.

Air

Inhalation is the main route of carbon disulfide absorption in both occupational and environmental exposure.

Drinking-water

Carbon disulfide can reach waterways via the wastewaters of viscose rayon plants. Drinking-water normally does not contain carbon disulfide.

Food

Carbon disulfide can contaminate juice and wine distilled from grapes harvested in vineyards treated with carbon disulfide (2).

Other routes of exposure

Dermal absorption of carbon disulfide can represent an additional route of entry in occupational exposure. In environmental exposure it does not constitute a hazard.

Kinetics and Metabolism

Absorption

The majority of studies showed that in man an equilibrium between the carbon disulfide concentrations in inhaled and exhaled air is achieved during the first 60 minutes of exposure. In the state of equilibrium, retention is about 40-50%, depending on the amount of carbon disulfide in inhaled air and on the coefficient of its partition between blood and tissues. Higher retention was registered in volunteers exposed to carbon disulfide for the first time, in comparison with continuously exposed workers (4).

Distribution

In humans 10-30% of carbon disulfide absorbed by the body is exhaled and a further 70-90% undergoes biotransformation. The metabolites produced, together with less than 1% of unchanged carbon disulfide, are excreted in the urine (4).

After absorption, carbon disulfide is transported by the blood, being distributed between blood erythrocytes and plasma in the ratio 2 : 1. It disappears relatively quickly from the blood and is distributed to various tissues and organs. The solubility of carbon disulfide in lipids and fats and its binding to amino acids and proteins govern its distribution in the body.

Biotransformation

The metabolism of carbon disulfide is basically performed by two main pathways: reaction with amino acids and protein (glutathione) and via the microsomal cytochrome P-450 monooxygenase system (4,5).

Amino acids of blood plasma react with carbon disulfide, forming dithiocarbamic acid and a cyclic compound of the thiazolinone type. The "free" carbon disulfide present in the blood is distributed to various tissues and organs, where it reacts with endogenous amines to form acid-labile metabolites (dithiocarbamates and 2-thio-5-thiazolidinone) excreted in the urine. Dithiocarbamate metabolites are potential chelating agents. A part of the carbon

disulfide is bound to glutathione (GSH), forming thiazolidine-2-thione-4-carboxylic acid and then 2-oxythiazolidine-4-carboxylic acid, which is excreted in the urine.

The other metabolic pathway involves the microsomal cytochrome P-450 monooxygenase system catalyzing the oxidative desulfuration of carbon disulfide to an unstable oxygen intermediate. The intermediate spontaneously degrades to atomic sulfur and carbonyl sulfide or undergoes attack by water, forming atomic sulfur and monothiocarbamate. Carbonyl sulfide is oxidized to atomic sulfur and carbon dioxide (4,5).

The atomic sulfur liberated in these reactions can be covalently bound to the macromolecules or be oxidized to sulfate and excreted in urine. Formed carbonyl sulfide can be catalyzed by carbonic anhydrase to monothiocarbamate, which is spontaneously degraded to carbon dioxide and HS⁻. The HS⁻ is oxidized to sulfate or other still unknown metabolites. Monothiocarbamate can enter the urea cycle, forming thiourea, which is excreted in urine (4,5).

Elimination

The elimination of carbon disulfide via exhaled air takes place in a typical three-phase process: rapidly from the respiratory tract, more slowly from the blood and very slowly from tissues and organs (4).

A small quantity (about 1%) of unchanged carbon disulfide is excreted via the urine, saliva and faeces. The excretion of the “free” carbon disulfide through the skin is about three times greater than that via the urine. The majority of metabolized carbon disulfide is excreted in the form of “ethereal sulfates” and the other part in the form of the metabolites mentioned earlier (4,5).

Health Effects

Effects on experimental animals and *in vitro* test systems

Toxicological effects

An extensive literature is available on the toxic effects of carbon disulfide on experimental animals; these are reviewed in some publications (1-5).

In acute and subacute exposure of experimental animals (dogs, cats, mice and rats) to carbon disulfide, effects on the central nervous system (CNS) are the first signs to be noted. In experimental animals carbon disulfide produces destruction of the myelin sheath and axonal changes in both central and peripheral neurons. Degenerative changes have been observed in the cortex, basal ganglia, thalamus, brain stem and spinal cord (4,5).

Neuropathy and myelopathy were extensively studied in rats and rabbits. In the muscle fibres atrophy of the denervation type occurred secondary to the polyneuropathy. The slowing down of nerve conduction velocity in the sciatic nerves preceded clinical symptoms (5).

Some studies have shown that carbon disulfide causes vascular changes in various organs of animals as well as myocardial lesions (4). Enhancing effects of carbon disulfide on atherosclerosis (elevated serum cholesterol, phospholipids and triglycerides) were observed in experimental animals and confirmed by biochemical studies (5).

Although many studies on the hepatic effects of carbon disulfide in animals pretreated with phenobarbital have been performed, limited information is available on animals exposed to carbon disulfide only. Sub-chronic inhalation studies on rabbits indicated a hepatotoxic effect (5).

Several studies on animals have demonstrated renal effects of carbon disulfide, but have failed to correlate them with the renal morphology: reduced urinary output, increased urinary

protein and amino acids (5).

Damage to the endocrine structures and functional alterations (increased thyroid activity, depressed adrenal functions) were described in animals exposed to carbon disulfide. These changes may play a part in atherogenic and reproductive effects of carbon disulfide (5).

Histological studies on the ophthalmological effects of carbon disulfide in animals have demonstrated the following: changes in retinal ganglia, vascular degeneration, and tyrolysis of the retina and atrophy of the optic nerve (4,5).

The teratogenic and embryotoxic potential of carbon disulfide was examined in inhalation studies of several animal species, but with no positive effects (5). However, some studies indicated impairment of embryo-genesis in female rats (2,4).

Mutagenic and carcinogenic effects

Comprehensive testing of the mutagenic potential of carbon disulfide was performed on several types of bacteria (Ames test) and *Drosophila*, with no positive results (5).

Effects on humans

Toxicological effects

Numerous epidemiological studies on carbon disulfide exposure among workers in viscose rayon plants have been reviewed (1-5).

Acute and subacute poisoning appear due to exposure to carbon disulfide concentrations of 500-3000 mg/m³ and are characterized by predominantly neurological and psychiatric symptoms, "encephalopathia sulfocarbonica" such as irritability, anger, mood changes, manic delirium and hallucinations, paranoic ideas, loss of appetite, gastrointestinal disturbances and sexual disorders (1-7).

More subtle neurological changes at lower carbon disulfide concentrations have been reported; the symptoms are a reduction of nerve conduction velocities and psychological disturbances (8-10). In workers exposed for 10-15 years to carbon disulfide in concentrations of around 10 mg/m³, sensory polyneuritis and increased pain threshold were reported (11). These neurological disturbances were accompanied by psychological and neurobehavioural disorders (1,4,5).

At an exposure of between 100 and 500 mg/m³ carbon disulfide has neurological, vascular and other effects on the eye: focal haemorrhage, exudative changes, optic atrophy, retrobulbar neuritis, microaneurisms and vascular sclerosis. These morphological changes are accompanied by altered functions (colour vision, adaptation to dark, pupillary light reaction, convergence, accommodation and visual acuity), altered motility (eyelids, bulb) and sensitivity (cornea, conjunctiva) (1,4,5,12,13). Some changes in the eye may be influenced by ethnic differences. For example, "microangiopathia sulfocarbonica" is reported in young Japanese and Yugoslav workers (4,13), but not in Finnish workers (4).

In chronic exposure to medium and lower carbon disulfide concentrations (20-300 mg/m³), the effects of carbon disulfide on blood vessels in various organs and tissues, especially cerebral and renal arteries, producing encephalopathy and nephropathy, are well established (1,4,5).

Reports from Finland and the United Kingdom have drawn attention to the association between occupational exposure to carbon disulfide and coronary heart disease (CHD), even at lower exposures (30-120 mg/m³) (1,4,5,14-17). At low carbon disulfide concentrations (under 30 mg/m³) the question of CHD risk remains to be resolved. However, ethnic differences are noted here too. Reports from Japan, the Netherlands and Yugoslavia (4,5) showed that there was no evidence that carbon disulfide exposure affected CHD incidence. These contradictory observations suggest that carbon disulfide has coronary effects when recognized factors

predisposing to the development of CHD are present.

Chronic exposure to carbon disulfide concentrations of 50-150 mg/m³ affected the endocrine system by causing decreased excretion of some hormones in the urine of young exposed workers (17-ketosteroids, 17-hydroxycorticosteroids, androsterone and etiocholanolone) (4,18). Decreased thyroxine levels in the serum of exposed workers imply a possible reduction in thyroid activity, which could influence vascular changes (4,5).

A report on hypospermia, asthenospermia and teratospermia in young workers exposed to 40-80 mg/m³ of carbon disulfide confirmed gonadal injury (19).

Some conflicting reports have been published on disturbances of reproductive functions in women occupationally exposed to carbon disulfide. According to some reports (20,21), exposure of women to carbon disulfide concentrations under 30 mg/m³ is associated with disturbances of the menstrual cycle and a slight increase in miscarriages. These findings were not confirmed by other studies.

Mutagenic and carcinogenic effects

No reports are available to indicate any carcinogenic or mutagenic effects of carbon disulfide.

Sensory effects

Carbon disulfide is an odorant that has a detection threshold of 200 µg/m³ (22-24). Its sweet and aromatic smell appears in its pure form at concentrations 3-4 times above this detection threshold. In its technical grade it has a very unpleasant smell (22). In effluents from the viscose industry, it is accompanied by other odorous substances, such as hydrogen sulfide and carbonyl sulfide (22). The odour quality of the emission changes according to the specific composition of these mixtures. The formation of carbonyl sulfide from carbon disulfide by photooxidation probably leads to variations in the qualities of the viscose odour in ambient air and to the characteristic smell of burnt rubber (22,23).

It seems unlikely that carbon disulfide in emissions from the viscose industry is the major contributor to odour nuisance. Probably, the nuisance caused by viscose odours is mainly due to hydrogen sulfide and carbonyl sulfide; therefore, it occurs at concentrations below the carbon disulfide odour detection threshold of 200 µg/m³.

Evaluation of Human Health Risks

Exposure

Inhalation represents the main route of entry of carbon disulfide into the human organism. Values in the vicinity of viscose rayon plants range from 0.01 mg/m³ to about 1.5 mg/m³, depending mostly on the distance from the source.

Health risk evaluation

A summary of the most relevant concentration-response findings is given in Table 1.

In the light of numerous epidemiological studies, it is very difficult to establish the exact exposure-time relationship. During the approximate period 1955-1965, carbon disulfide concentrations in viscose rayon plants averaged about 250 mg/m³; they were subsequently reduced to 50-150 mg/m³ and more recently to 20-30 mg/m³. Therefore, it is practically impossible to evaluate the long-term (five or more years) exposure level in a retrospective study. Moreover, most exposure data in occupational studies are not reliable, owing to poor measurement methodology. It is necessary to keep this in mind also when studying Table 1.

Table 1.
Some concentration-response relationships in occupational exposure to carbon disulfide

Carbon disulfide concentration (mg/m ³)	Duration of exposure (years)	Symptoms and signs	Reference
500-2500	0.5	Polyneuritis, myopathy, acute psychosis	6
450-1000	< 0.5	Polyneuritis, encephalopathy	7
200-500	1-9	Increased ophthalmic pressure	12
60-175	5	Eye burning, abnormal papillary light reactions	13
31-137	10	Psychomotor and psychological disturbances	8
29-118	15	Polyneuropathy, abnormal EEG, conduction velocity slowed, psychological changes	9,10
29-118	10	Increase in coronary mortality, angina pectoris, slightly higher systolic and diastolic blood pressure	14-17
40-80	2	Asthenospermia, hypospermia, teratospermia	19
22-44	> 10	Arteriosclerotic changes and hypertension	25
30-50	> 10	Decreased immunological reactions	26
30	3	Increase in spontaneous abortions and premature births	20
20-25	< 5	Functional disturbances of the CNS	27, 28
10	10-15	Sensory polyneuritis, increased pain threshold	11
10	10-15	Depressed blood progesterone, increased estriol, irregular menstruation	21

At exposure levels of 30 mg/m³ and above, observable adverse health effects have been well established. The CHD rate increases at levels of 30-120 mg/m³ of carbon disulfide after an exposure of more than 10 years. Effects on the central and peripheral nervous systems and the vascular system have been established in the same range of concentrations after long-term exposure. Functional changes of the central nervous system have even been observed at lower concentrations (20-25 mg/m³).

Some authors claim to have observed adverse health effects in workers exposed to 10 mg/m³ of carbon disulfide for 10-15 years. However, because of the lack of reliable retrospective data on exposure levels, the dose-response relationship governing these findings is difficult to establish.

Guidelines

The lowest concentration of carbon disulfide at which an adverse effect was observed in

occupational exposure was about 10 mg/m^3 , which may be equivalent to a concentration in the general environment of 1 mg/m^3 . In selecting the size of the protection (safety) factor, the expected variability in the susceptibility of the general population was taken into account, and a protection factor of 10 was considered appropriate. This leads to the recommendation of a guideline value of $100 \text{ }\mu\text{g/m}^3$, with an averaging time of 24 hours. It is believed that below this value adverse health effects of environmental exposure to carbon disulfide (outdoor or indoor) are not likely to occur.

If carbon disulfide is used as the index substance for viscose emissions, odour perception is not to be expected when carbon disulfide peak concentration is kept below 1/10 of its odour threshold value, i.e. below $20 \text{ }\mu\text{g/m}^3$. Based on the sensory effects of carbon disulfide, a guideline value of $20 \text{ }\mu\text{g/m}^3$ (average time 30 minutes) is recommended.

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