Organic Solvents

Most of the solvents described in this chapter have no specific therapeutic use. Additional solvents used in pharmacy and described in other chapters include alcohols, chlorinated hydrocarbons such as chloroform and trichloroethylene, fixed oils, glycols, paraffins, and water.

Organic solvents are widely used in industry and toxicity has been associated with acute or chronic exposure. due to inhalation, ingestion, or absorption through the skin. Organic solvents are irritant to the skin and mucous membranes, and often affect the CNS. They may sensitise the myocardium to catecholamines and cardiac arrhythmias may occur. Chronic exposure may lead to central and peripheral neurotoxicity, as well as to renal toxicity and hepatotoxicity.

◊ References.

1. White RF, Proctor SP. Solvents and neurotoxicity. *Lancet* 1997; **349:** 1239–43.

Abuse. Since they are volatile liquids and have CNS effects many organic solvents are implicated in volatile substance abuse. Clinical features of intoxication are similar to those of alcohol intoxication, with initial CNS stimulation followed by CNS depression, which may progress to delirium, convulsions, coma, and death. Sudden death due to cardiac arrhythmias has also been reported.

References.

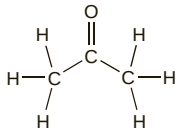
1. Proceedings of a meeting on substance abuse. *Hum Toxicol* 1989; **8:** 253–334.
2. Ashton CH. Solvent abuse. *BMJ* 1990; **300:** 135–6.

Acetone

Aceton; Acetona; Acetonas; Acétone; Acetonum; Asetoni; Dimethyl Ketone; Propanone; 2-Propanone.

Ацетон

C_3H_6O = 58.08.
CAS — 67-64-1.



Pharmacopoeias. In *Eur.* (see p.vii). Also in *USNF.*

Ph. Eur. 6.2 (Acetone). A volatile, clear, colourless liquid; the vapour is flammable. Miscible with water and with alcohol. Protect from light.

USNF 26 (Acetone). A transparent, colourless, mobile, volatile, very flammable liquid, having a characteristic odour. Sp. gr. not more than 0.789. Miscible with water, with alcohol, with chloroform, with ether, and with most volatile oils. A 50% solution in water is neutral to litmus. Store in airtight containers remote from fire.

Adverse Effects and Treatment

Inhalation of acetone vapour causes excitement followed by CNS depression with headache, restlessness, fatigue, and possibly convulsions, leading to coma and respiratory depression in severe cases. Vomiting and haematemesis may occur. There may be a latent period before the onset of symptoms of acetone poisoning. Similar symptoms may be seen after ingestion of acetone although hyperglycaemia has also been reported. The vapour is irritant to mucous membranes in high concentrations.

Acetone is commonly implicated in volatile substance abuse (see above).

Treatment of adverse effects consists of removal from exposure and general supportive and symptomatic measures; activated charcoal may be given if the patient presents within 1 hour of ingestion.

◊ For the possible effect of acetone on the metabolism of acetonitrile, see under Acetonitrile, below.

Pharmacokinetics

Acetone is absorbed through the lungs after inhalation. Some absorption occurs from the gastrointestinal tract. It is mostly excreted unchanged, predominantly through the lungs and also in the urine.

Uses

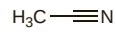
Acetone is widely used as an industrial, pharmaceutical, and domestic solvent; it is also used as an extraction solvent in food processing.

Acetonitrile

Acetonitrilo; Acetonitryl; Ethanenitrile; Methyl Cyanide.

Ацетонитрил

C_2H_3N = 41.05.
CAS — 75-05-8.



Description. Acetonitrile is a colourless liquid with an aromatic odour. Wt per mL about 0.79 g. B.p. about 81°. It emits highly toxic fumes of hydrogen cyanide when heated to decomposition or when reacted with acids or oxidising agents. Store in airtight containers.

Adverse Effects and Treatment

As for cyanides (see Hydrocyanic Acid, p.2045).

◊ Cyanide poisoning, including a fatality, has been reported[1,2] in a number of infants after ingestion of artificial nail removers containing acetonitrile. As acetonitrile is slowly metabolised to cyanide, serious toxic effects may not occur until several hours after ingestion and there is the danger that these products may be confused with acetone-based nail polish removers which are less toxic. In a report[3] of an adult who died after ingestion of acetonitrile, the onset of symptoms was delayed for 24 hours. It was considered that concomitant ingestion of acetone had slowed the metabolism of acetonitrile. In another case[4] vomiting, diarrhoea, convulsions, and reduced consciousness developed in a 35-year-old man 15 hours after occupational exposure to acetonitrile. Despite treatment for cyanide poisoning, acute renal failure and rhabdomyolysis subsequently developed.

1. Caravati EM, Litovitz TL. Pediatric cyanide intoxication and death from an acetonitrile-containing cosmetic. *JAMA* 1988; **260:** 3470–3.
2. Losek JD, *et al.* Cyanide poisoning from a cosmetic nail remover. *Pediatrics* 1991; **88:** 337–40.
3. Boggild MD, *et al.* Acetonitrile ingestion: delayed onset of cyanide poisoning due to concurrent ingestion of acetone. *Postgrad Med J* 1990; **66:** 40–1.
4. Muraki K, *et al.* Massive rhabdomyolysis and acute renal failure after acetonitrile exposure. *Intern Med* 2001; **40:** 936–9.

Pharmacokinetics

Acetonitrile is absorbed by inhalation, ingestion, and through the skin. It undergoes metabolism to cyanide, which is responsible for the toxicity of acetonitrile.

Uses

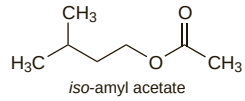
Acetonitrile is used as an industrial solvent. It may also be present in artificial nail removers.

Amyl Acetate

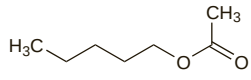
Acetato de amilo.

Амилацетат

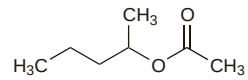
$C_7H_{14}O_2$ = 130.2.
CAS — 123-92-2 (iso-amyl acetate); 53496-15-4 (sec-amyl acetate); 628-63-7 (n-amyl acetate).



iso-amyl acetate



n-amyl acetate



sec-amyl acetate

Description. Amyl acetate is a mixture of isomers, principally *iso-*, *sec-*, and *n*-amyl acetate. *iso*-Amyl acetate is a clear colourless liquid with a sharp, fruity odour. Wt per mL about 0.87 g. B.p. about 140°. Slightly soluble in water; miscible with alcohol and with ether. Store in airtight containers.

Adverse Effects and Treatment

Prolonged exposure to amyl acetate may produce headache, fatigue, and depression of the CNS. Irritation of mucous membranes may also occur.

Treatment of adverse effects consists of removal from exposure and general supportive and symptomatic measures; activated charcoal may be given if the patient presents within 1 hour of ingestion.

Effects on the heart. A 27-year-old man developed headache, nausea, and vomiting after using a paint containing amyl acetate as the solvent in an unventilated room.[1] Some days later chest pain and dyspnoea developed; he was admitted to hospital 2 weeks after exposure with heart failure which slowly responded to treatment.

1. Weissberg PL, Green ID. Methyl-cellulose paint possibly causing heart failure. *BMJ* 1979; **ii:** 1113–14.

Uses

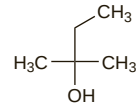
Amyl acetate is used as a pharmaceutical and industrial solvent.

Amylene Hydrate

Aethyldimethylmethanolum; Dimethylethyl Carbinol; Hidrato de amileno; Tertiary Amyl Alcohol. 2-Methylbutan-2-ol.

Амилгидрат

$C_5H_{12}O$ = 88.15.
CAS — 75-85-4.



Pharmacopoeias. In *USNF.*

USNF 26 (Amylene Hydrate). A clear, colourless liquid having a camphoraceous odour. Sp. gr. 0.803 to 0.807. Distilling range 97° to 103°. Freely soluble in water; miscible with alcohol, with chloroform, with ether, and with glycerol. Its solutions are neutral to litmus. Store in airtight containers.

Adverse Effects

Amylene hydrate is irritant and has a depressant effect on the CNS.

Uses

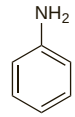
Amylene hydrate is used as a pharmaceutical solvent. It was formerly used as a hypnotic.

Aniline

Anilina; Phenylamine.

Анилин

C_6H_7N = 93.13.
CAS — 62-53-3.



Description. Aniline is a colourless or pale yellow oily liquid with a characteristic odour, readily darkening to brown on exposure to air and light. Wt per mL about 1.02 g. B.p. about 183°. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

Inhalation, ingestion, or cutaneous absorption of aniline results in methaemoglobinaemia, with cyanosis, headache, weakness, stupor, convulsions, and coma. Irritation of the skin or mucous membranes, nausea and vomiting, and cardiac arrhythmias may occur. Haemolysis has been reported and may give rise to renal damage or jaundice. Death is usually a result of cardiovascular collapse.

Treatment may involve oxygen, methylthioninium chloride (p.1451), transfusions, or possibly haemodialysis. Gastric aspiration or activated charcoal may be considered in patients who present within 1 hour of ingestion.

Bladder papillomas have been reported in workers previously exposed to aniline. Commercial aniline may be contaminated with β-naphthylamine, a potential carcinogen.

Handling. Suitable precautions should be taken to avoid skin contact with aniline as it can penetrate skin and produce systemic toxicity.

Uses

Aniline is a solvent with wide industrial applications.

Benzene

Benceno; Benzen; Phenyl Hydride.

Бензол

C_6H_6 = 78.11.

CAS — 71-43-2.

NOTE. Benzene may be known as 'benzina', 'benzol', 'benzole', or 'benzolum'. However, 'benzol' is also used to describe a mixture of hydrocarbons and 'benzin' or 'benzine' is used as a name for a petroleum distillate (see also Petroleum Spirit, p.2026).

Description. Benzene is a clear colourless flammable liquid with a characteristic aromatic odour. Wt per mL about 0.88 g. B.p. about 80°. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

Symptoms of acute poisoning after inhalation or ingestion of benzene include initial excitement or euphoria followed by CNS depression with headache, dizziness, blurred vision, and ataxia, which in severe cases may progress to coma (accompanied by hyperactive reflexes), convulsions, and death from respiratory failure. Other symptoms include nausea and irritation of the mucous membranes; ventricular arrhythmias may occur. Direct skin contact with liquid benzene may result in marked irritation, and dermatitis may develop on prolonged or repeated exposure.

Prolonged industrial exposure to benzene vapour has been associated with adverse effects on the gastrointestinal tract and the CNS but in particular with marked effects on the bone marrow and blood. Decreases in the numbers of red or white blood cells or of platelets may occur, producing symptoms of headache, fatigue, anorexia, pallor, and petechiae. In severe cases pancytopenia or aplastic anaemia may develop. Leukaemia, particularly acute myeloid leukaemia, has also developed, often many years after exposure to benzene has ceased. These effects have been reported in workers exposed to relatively high concentrations of the vapour (around 200 ppm or more) but reduced red blood cell counts and anaemia have also been reported at lower concentrations. Chromosome abnormalities have been observed after prolonged exposure to benzene, particularly at the higher concentrations associated with blood dyscrasias; however, the significance of these abnormalities in the development of leukaemia is unclear.

Treatment of poisoning consists of symptomatic and supportive measures. The UK National Poisons Information Service considers that gut decontamination (gastric lavage) is contra-indicated because it may increase the risk of aspiration. In chronic poisoning, repeated blood transfusions may be necessary. Adrenaline and other sympathomimetics should be avoided because of the risk of precipitating cardiac arrhythmias.

◊ Reviews.

1. Health and Safety Executive. Benzene. *Toxicity Review 4*. London: HMSO, 1982.
2. WHO. Benzene. *Environmental Health Criteria 150*. Geneva: WHO, 1993. Available at: http://www.inchem.org/documents/ehc/ehc/ehc150.htm (accessed 29/06/04)

Malignant neoplasms. Epidemiological data support an association between benzene exposure and acute myeloid leukaemia, but the risk after low levels of exposure (1 to 10 ppm) is less clear.[1] However, a large cohort study[2] suggested that there is an increased risk of acute myeloid leukaemia and of non-Hodgkin's lymphoma with benzene exposure at levels below 10 ppm.

1. Austin H, *et al.* Benzene and leukemia: a review of the literature and a risk assessment. *Am J Epidemiol* 1988; **127:** 419–39.
2. Hayes RB, *et al*. Benzene and the dose-related incidence of hematologic neoplasms in China. *J Natl Cancer Inst* 1997; **89:** 1065–71.

Pregnancy. An evaluation of the USA National Natality and Fetal Mortality Survey noted that maternal or paternal occupational exposure to agents such as benzene was associated with an increased risk of still-birth and that paternal exposure to benzene increased the risk of low-birth-weight infants.[1]

1. Savitz DA, *et al*. Effect of parents' occupational exposures on risk of stillbirth, preterm delivery, and small-for-gestational-age infants. *Am J Epidemiol* 1989; **129:** 1201–18.

Pharmacokinetics

Benzene is absorbed after inhalation and ingestion, but is not significantly absorbed through the skin. Some is excreted unchanged from the lungs. Oxidation to phenol and related quinol compounds occurs, the metabolites being excreted in the urine as conjugates of sulfuric or glucuronic acid.

Uses

Benzene was formerly applied as a pediculicide. Its use as an industrial solvent is decreasing.

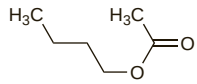
Butyl Acetate

Acetato de butilo; Butylu octan. *n*-Butyl acetate.

Бутилацетат

$C_6H_{12}O_2$ = 116.2.

CAS — 123-86-4.



Description. Butyl acetate is a clear, colourless flammable liquid with a strong fruity odour. Wt per mL about 0.88 g. B.p. 123° to 126°. Slightly soluble in water; miscible with alcohol. Store in airtight containers.

Adverse Effects

Butyl acetate is irritant. High concentrations may cause CNS depression.

Uses

Butyl acetate is used as an industrial solvent and as an extraction solvent in food processing.

Butyl Alcohol

Alcohol butílico; *n*-Butanol; *n*-Butyl Alcohol. Butan-1-ol.

Бутиловый Спирт

$C_4H_{10}O$ = 74.12.

CAS — 71-36-3.

Pharmacopoeias. In *USNF*.

USNF 26 (Butyl Alcohol). A clear, colourless, mobile liquid having a characteristic, penetrating vinous odour. Sp. gr. 0.807 to 0.809. It distils within a range of 1.5°, including 117.7°. Soluble in water; miscible with alcohol, with ether, and with many other organic solvents. Store in airtight containers at a temperature not exceeding 40°.

Adverse Effects and Precautions

Butyl alcohol may be irritant and may cause mild CNS depression with headache, dizziness, and drowsiness.

◊ References to the toxicity of butyl alcohol.

1. WHO. Butanols—four isomers: 1-butanol, 2-butanol, tert-butanol, isobutanol. *Environmental Health Criteria 65*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/ehc/ehc/ehc65.htm (accessed 29/06/04)
2. WHO. 1-Butanol health and safety guide. *IPCS Health and Safety Guide 3*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg003.htm (accessed 29/06/04)

Handling. Suitable precautions should be taken to avoid skin contact with butyl alcohol as it can penetrate skin and produce systemic toxicity.

Uses

Butyl alcohol is used as an industrial and pharmaceutical solvent and as an extraction solvent in food processing.

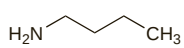
Butylamine

Butilamina; *n*-Butylamine; Butyloamina.

Бутиламин

$C_4H_{11}N$ = 73.14.

CAS — 109-73-9.



Description. Butylamine is a colourless to pale yellow flammable liquid with an ammoniacal odour. Wt per mL about 0.744 g. B.p. about 78°. Miscible with water, with alcohol, and with ether. Store in airtight containers.

Adverse Effects and Precautions

Butylamine is irritant. Symptoms of CNS depression may be observed after exposure to high concentrations of the vapour.

Handling. Suitable precautions should be taken to avoid skin contact with butylamine as it can penetrate skin and produce systemic toxicity.

Uses

Butylamine is used as a solvent.

Carbon Disulfide

Carbon Bisulphide; Carbon Disulphide; Carbonei Sulfidum; Carboneum Bisulfuratum; Carboneum Sulfuratum; Disulfuro de carbono; Schwefelkohlenstoff; Węgla disiarczek.

Сероуглерод

CS_2 = 76.14.

CAS — 75-15-0.

Description. Carbon disulfide is a clear, colourless, volatile, flammable liquid with a chloroform-like odour. Commercial grades have an unpleasant odour described by some as being reminiscent of decaying radishes. Wt per mL about 1.26 g. B.p. about 46°. Store in airtight containers.

Stability. The vapour of carbon disulfide when mixed with air in the proportions of 1 to 50% is highly explosive.

Adverse Effects, Treatment, and Precautions

Carbon disulfide is irritant. Toxic effects may occur as a result of inhalation, ingestion, or absorption through the skin.

Acute poisoning may result in gastrointestinal disturbances and euphoria, followed by CNS depression. Symptoms include headache, dizziness, mood changes, and in severe cases, manic psychoses, delirium, hallucinations, coma, convulsions, and death due to respiratory failure.

Chronic poisoning has been associated with occupational exposure to carbon disulfide vapour for prolonged periods. It is characterised by peripheral neuropathies; CNS effects such as headache, fatigue, insomnia, tremor, emotional lability, extrapyramidal disorders, bipolar disorder, and encephalopathy; gastrointestinal effects including anorexia, dyspepsia, and ulcerative changes; and effects on the eye. Occupational exposure to carbon disulfide has been shown to be associated with an increased incidence of mortality from coronary heart disease. The action of carbon disulfide on endocrine function has resulted in menstrual irregularities, an increased incidence of spontaneous abortions and premature births, loss of libido, sperm abnormalities, and decreased serum-thyroxine concentrations; there is limited evidence of impaired glucose tolerance.

Treatment consists of removal from exposure and general supportive and symptomatic measures. Gastric lavage should be avoided. Adrenaline and other sympathomimetics should also be avoided because of the risk of precipitating cardiac arrhythmias. Peripheral neuropathies may be only slowly reversible.

◊ Reviews of the toxicity of carbon disulfide.

1. WHO. Carbon Disulfide. *Environmental Health Criteria 10*. Geneva: WHO, 1979. Available at: http://www.inchem.org/documents/ehc/ehc/ehc010.htm (accessed 29/06/04)
2. WHO. Recommended health-based limits in occupational exposure to selected organic solvents. *WHO Tech Rep Ser 664* 1981. Available at: http://libdoc.who.int/trs/WHO_TRS_664.pdf (accessed 03/09/08)
3. Health and Safety Executive. Carbon disulphide. *Toxicity Review 3*. London: HMSO, 1981.
4. Beauchamp RO, *et al.* A critical review of the literature on carbon disulfide toxicity. *Crit Rev Toxicol* 1983; **11:** 169–278.

Effects on endocrine function. The effects of exposure to carbon disulfide were studied retrospectively in 265 female workers in the rayon industry exposed for at least 1 year, and 291 non-exposed female workers.[1] Levels of exposure varied over the study period from 0.7 to 30.6 mg/m^3. Women exposed to carbon disulfide had a higher risk of menstrual disturbances than non-exposed women. However, there was no difference between the 2 groups in incidence of toxaemia, emesis gravidarum, spontaneous abortion, premature or overdue delivery, or congenital malformation.

1. Zhou SY, *et al.* Effects of occupational exposure to low-level carbon disulfide (CS) on menstruation and pregnancy. *Ind Health* 1988; **26:** 203–14.

Effects on the heart. An increased incidence of mortality from cardiovascular disease has been found in workers occupationally exposed to carbon disulfide.[1-3] The evidence suggested that the risk decreases after cessation of exposure. However, the association has been critically reviewed.[4]

1. Nurminen M, Hernberg S. Effects of intervention on the cardiovascular mortality of workers exposed to carbon disulphide: a 15 year follow up. *Br J Ind Med* 1985; **42:** 32–5.
2. Sweetnam PM, *et al.* Exposure to carbon disulphide and ischaemic heart disease in a viscose rayon factory. *Br J Ind Med* 1987; **44:** 220–7.
3. MacMahon B, Monson RR. Mortality in the US rayon industry. *J Occup Med* 1988; **30:** 698–705.
4. Sulsky SI, *et al.* Critical review of the epidemiological literature on the potential cardiovascular effects of occupational carbon disulfide exposure. *Int Arch Occup Environ Health* 2002; **75:** 365–80.

Handling. Suitable precautions should be taken to avoid skin contact with carbon disulfide as it can penetrate skin and produce systemic toxicity.

Pharmacokinetics

Carbon disulfide is rapidly absorbed after inhalation and ingestion, and is also absorbed through intact skin. It is excreted unchanged through the lungs and in the urine mainly as metabolites.