Uses
Carbon disulfide is used as an industrial solvent and has been used, in the vapour form, as an insecticide.

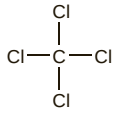
Carbon Tetrachloride

Tetracloruro de carbono; Węgla tetrachlorek. Tetrachloromethane.

Четырёххлористый Углерод

CCl_4 = 153.8.

CAS — 56-23-5.



Description. Carbon tetrachloride is a clear, colourless, mobile, liquid with a chloroform-like odour. Sp. gr. 1.588 to 1.590. B.p. 76° to 78°. Practically insoluble in water; miscible with alcohol, chloroform, ether, petroleum spirit, and fixed and volatile oils. Store in airtight containers at a temperature not exceeding 30°. Protect from light.

Handling. Avoid contact with carbon tetrachloride; the vapour and liquid are poisonous. Care should be taken not to vaporise carbon tetrachloride in the presence of a flame because of the production of harmful gases, mainly phosgene.

Adverse Effects
Individual response to carbon tetrachloride varies widely; inhalation or ingestion of a few mL of carbon tetrachloride has proved fatal and its toxicity appears to be increased by alcohol. Poisoning may follow inhalation, ingestion, or topical application but develops more rapidly after inhalation.

Carbon tetrachloride is irritant; repeated application of carbon tetrachloride to the skin may result in dermatitis. Aspiration may result in pulmonary oedema.

Adverse effects after acute exposure from any route include gastrointestinal disturbances such as nausea, vomiting, and abdominal pain, and CNS disturbances such as headache, dizziness, and drowsiness, with progression to convulsions, coma, and death from respiratory depression or circulatory collapse. Death may also occur as a result of ventricular arrhythmia. Hepatic and renal cellular necrosis can occur and are associated with free radical production; symptoms usually begin a few days or up to 2 weeks after acute exposure to carbon tetrachloride. Renal damage may present as oliguria, progressing to proteinuria, anuria, weight gain, and oedema. Symptoms of hepatic damage include anorexia, jaundice, and hepatomegaly. If hepatorenal necrosis is not fatal recovery is eventually complete.

Symptoms of chronic poisoning are similar to those of acute poisoning; in addition, paraesthesias, visual disturbances, anaemia, and aplastic anaemia have occurred. Carcinogenicity has been demonstrated in *animals.*

◊ References.

1. Melamed E, Lavy S. Parkinsonism associated with chronic inhalation of carbon tetrachloride. *Lancet* 1977; **i:** 1015.
2. Johnson BP, *et al.* Cerebellar dysfunction after acute carbon tetrachloride poisoning. *Lancet* 1983; **ii:** 968.
3. Perez AJ, *et al.* Acute renal failure after topical application of carbon tetrachloride. *Lancet* 1987; **i:** 515–6.
4. Health and Safety Executive. Carbon tetrachloride, chloroform. *Toxicity Review 23*. London: HMSO, 1992.
5. Manno M, Rezzadore M. Critical role of ethanol abuse in carbon tetrachloride poisoning. *Lancet* 1994; **343:** 232.
6. WHO. Carbon tetrachloride health and safety guide. *IPCS Health and Safety Guide 108*. Geneva: WHO, 1998. Available at: http://www.inchem.org/documents/hsg/hsg/hsg108.htm (accessed 29/06/04)

Treatment of Adverse Effects
If carbon tetrachloride vapour has been inhaled the patient should be removed to the fresh air. Clothing contaminated by liquid should be removed and the skin washed. If carbon tetrachloride has been ingested gastric lavage may be performed if the patient presents within 1 hour and activated charcoal may be given.

The usual symptomatic and supportive measures should be instituted. Hepatic and renal function should be monitored closely. Haemodialysis or peritoneal dialysis may be needed if renal function is impaired. Adrenaline or other sympathomimetics should be avoided because of the risk of precipitating cardiac arrhythmias.

Acetylcysteine (p.1550) may be given to patients recently exposed to carbon tetrachloride in an attempt to prevent or modify hepatic and renal damage.

Pharmacokinetics
Carbon tetrachloride is readily absorbed after inhalation and ingestion. It is also absorbed through the skin. Metabolism to reactive free radicals is thought to account for the hepatorenal toxicity of carbon tetrachloride.

Carbon tetrachloride is slowly excreted from the body via the lungs and the urine.

Uses
Carbon tetrachloride is employed in industry as a solvent and degreaser. It was formerly used in certain types of fire extinguisher and as an industrial and domestic dry cleaner but has been largely replaced for this purpose by less toxic substances. Carbon tetrachloride has also been used for the fumigation of cereals.

Carbon tetrachloride was formerly given orally as an anthelmintic but it has been superseded by equally effective and less toxic drugs.

Cyclohexane

Ciclohexano; Cykloheksan; Hexahydrobenzene; Hexamethylene.

Циклогексан

C_6H_{12} = 84.16.

CAS — 110-82-7.

Description. Cyclohexane is a colourless, flammable liquid. Wt per mL about 0.78 g. B.p. about 81°. Store in airtight containers.

Adverse Effects
Cyclohexane is irritant, and may also have effects on the CNS.

◊ Reviews of the toxicity of cyclohexane.

1. Health and Safety Executive. Cyclohexane, cumene, paradichlorobenzene (p-DCB), chlorodifluoromethane (CFC 22). *Toxicity Review 25*. London: HMSO, 1991.

Uses
Cyclohexane is used as an industrial solvent.

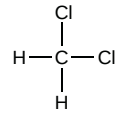
Dichloromethane

Cloruro de metileno; Dichlormethan; Diclorometano; Diklórmetán; Methylene Chloride; Méthylène, chlorure de; Methyleni chloridum; Metileno cloridas; Metyleenikloridi; Metylenklorid; Metylenu chlorek.

Дихлорметан

CH_2Cl_2 = 84.93.

CAS — 75-09-2.



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

Ph. Eur. 6.2 (Methylene Chloride; Dichloromethane BP 2008). A clear, colourless, volatile liquid. Relative density 1.320 to 1.332. It may contain not more than 2% of alcohol and/or not more than 0.03% of 2-methylbut-2-ene as stabiliser. Sparingly soluble in water; miscible with alcohol. Store in airtight containers. Protect from light.

USNF 26 (Methylene Chloride). A clear, colourless, mobile liquid having an odour resembling chloroform. Sp. gr. 1.318 to 1.322. Miscible with alcohol, with ether, and with fixed and volatile oils. Store in airtight containers.

Stability. Phosgene is produced on heating of dichloromethane.

Adverse Effects and Treatment
Acute exposure to dichloromethane vapour may depress the CNS; symptoms progress from headache and dizziness to coma and death in severe cases. Pulmonary oedema has been reported. Significant exposure may result in raised blood concentrations of carboxyhaemoglobin and symptoms of carbon monoxide poisoning. Cardiovascular effects have been attributed to hypoxia secondary to carboxyhaemoglobinaemia. There has been a report of haemolysis after acute ingestion of dichloromethane.

Chronic occupational exposure to dichloromethane vapour has produced gastrointestinal disturbances in addition to symptoms observed after acute poisoning. Dichloromethane is a common constituent of paint strippers and may be implicated in volatile substance abuse (p.2019).

The liquid is irritant and high concentrations of the vapour are irritant to the eyes.

Treatment of acute poisoning consists of removal from exposure and supportive and symptomatic measures. Carboxyhaemoglobinaemia should be managed as for carbon monoxide poisoning (p.1688) by giving 100% oxygen; hyperbaric oxygen may be indicated. After ingestion gastric lavage or activated charcoal are generally contra-indicated, although gastric aspiration may be considered in serious cases if the airway can be protected. Adrenaline and other sympathomimetics should also be avoided because of the risk of precipitating cardiac arrhythmias.

◊ References.

1. WHO. Methylene Chloride. *Environmental Health Criteria 32*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc32.htm (accessed 29/06/04)
2. Health and Safety Executive. Dichloromethane (methylene chloride). *Toxicity Review 12*. London: HMSO, 1985.
3. WHO. Methylene chloride health and safety guide. *IPCS Health and Safety Guide 6*. Geneva: WHO, 1987. Available at: http://www.inchem.org/documents/hsg/hsg/hsg006.htm (accessed 29/06/04)
4. Rioux JP, Myers RAM. Methylene chloride poisoning: a paradigmatic review. *J Emerg Med* 1988; **6:** 227–38.
5. Manno M, *et al.* Double fatal inhalation of dichloromethane. *Hum Exp Toxicol* 1992; **11:** 540–5.
6. Dhillon S, Von Burg R. Methylene chloride. *J Appl Toxicol* 1995; **15:** 329–35.
7. Chang YL, *et al.* Diverse manifestations of oral methylene chloride poisoning: report of 6 cases. *J Toxicol Clin Toxicol* 1999; **37:** 497–504.
8. Jacubovich RM, *et al.* Facial nerve palsy after acute exposure to dichloromethane. *Am J Ind Med* 2005; **48:** 389–92.

Pharmacokinetics
Dichloromethane is rapidly absorbed after inhalation and is also absorbed after ingestion and slowly through intact skin. It appears to be partially metabolised to carbon dioxide and carbon monoxide which are exhaled, although significant blood-carboxyhaemoglobin concentrations may be attained. Some unchanged dichloromethane is exhaled and small amounts are excreted in the urine.

Uses
Dichloromethane is used as a pharmaceutical and industrial solvent. It is also employed as an extraction solvent in food processing.

Dichloromethane is widely used in paint strippers.

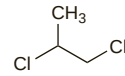
Dichloropropane

Dicloropropano; Propylene Dichloride. 1,2-Dichloropropane.

Дихлорпропан

$C_3H_6Cl_2$ = 113.0.

CAS — 78-87-5.



Description. Dichloropropane is a colourless, mobile, flammable liquid. Wt per mL about 1.16 g. B.p. about 96°. Store in airtight containers.

Adverse Effects
Dichloropropane is irritant; high concentrations may result in CNS depression.

◊ Acute renal failure, haemolytic anaemia, acute liver disease, and disseminated intravascular coagulation has been reported[1] after intentional inhalation of a stain remover containing dichloropropane; the patient recovered after blood transfusions and haemodialysis.

1. Locatelli F, Pozzi C. Relapsing haemolytic-uraemic syndrome after organic solvent sniffing. *Lancet* 1983; **ii:** 220.

Uses
Dichloropropane is used as an industrial solvent, dry cleaning agent, and agricultural defumigant.

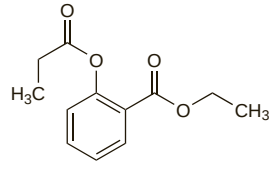
Diethyl Phthalate

Diéthyle, phtalate de; Diethyl-ftalát; Diethylis phthalas; Dietilftalát; Dietilo ftalatas; Dietylftalat; Dietyyliftalaatti; Ethyl Phthalate; Ftalato de dietilo. Benzene-1,2-dicarboxylic acid diethyl ester.

Диэтилфталат

$C_{12}H_{14}O_4$ = 222.2.

CAS — 84-66-2.



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

Ph. Eur. 6.2 (Diethyl Phthalate). A clear, colourless or very slightly yellow, oily liquid. Relative density 1.117 to 1.121. Practically insoluble in water; miscible with alcohol. Store in airtight containers.

USNF 26 (Diethyl Phthalate). A colourless, practically odourless, oily liquid. Sp. gr. 1.118 to 1.122 at 20°. Insoluble in water; miscible with alcohol, with ether, and with other usual organic solvents. Store in airtight containers.

Adverse Effects
Diethyl phthalate is irritant and, in high concentrations, causes CNS depression. There has been concern about potential toxicity resulting from exposure to phthalates used as plasticisers.

◊ References.

1. Health and Safety Executive. Review of the toxicity of the esters of o-phthalic acid (phthalate esters). *Toxicity Review 14*. London: HMSO, 1986.
2. Kamrin MA, Mayor GH. Diethyl phthalate: a perspective. *J Clin Pharmacol* 1991; **31:** 484–9.
3. Shea KM, *et al.* American Academy of Pediatrics Technical Report. Pediatric exposure and potential toxicity of phthalate plasticizers. *Pediatrics* 2003; **111:** 1467–74. [Re-affirmed May 2007]

Uses
Diethyl phthalate is used as a denaturant of alcohol, for example in surgical spirit, and as a solvent and plasticiser.

Dimethyl Sulfoxide *(BAN, USAN, rINN)*

Dimethyl Sulphoxide; Dimethyli Sulfoxidum; Dimethylis sulfoxidum; Dimethylsulfoxid; Diméthylsulfoxyde; Dimetil sulfóxido; Dimetilsulfoksidas; Dimetil-szulfoxid; Dimetylosulfotlenek; Dimetylsulfoxid; Dimetyylisulfoksidi; DMSO; Methyl Sulphoxide; NSC-763; SQ-9453; Sulphinylbismethane.

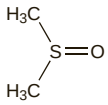
Диметилсульфоксид

C_2H_6OS = 78.13.

CAS — 67-68-5.

ATC — G04BX13; M02AX03.

ATC Vet — QG04BX13; QM02AX03.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Dimethyl Sulfoxide). A colourless hygroscopic liquid or crystals. F.p. not lower than 18.3°. Relative density 1.100 to 1.104. Miscible with water and with alcohol. Store in airtight glass containers. Protect from light.

USP 31 (Dimethyl Sulfoxide). A clear, colourless, odourless, hygroscopic liquid. M.p. about 18.4°. Sp. gr. 1.095 to 1.097. Soluble in water; practically insoluble in alcohol, in acetone, in chloroform, in ether, and in benzene. Store in airtight containers. Protect from light.

Adverse Effects and Treatment
High concentrations of dimethyl sulfoxide applied to the skin may cause burning discomfort, itching, erythema, vesiculation, and urticaria. Continued use may result in scaling.

Systemic effects, including gastrointestinal disturbances, drowsiness, headache, and hypersensitivity reactions, may occur after use by any route. A garlic-like odour on the breath and skin is attributed to the formation of dimethyl sulfide (see Pharmacokinetics, below). Intravascular haemolysis has followed intravenous use. Local discomfort and spasm may occur when given by bladder instillation.

Treatment of adverse effects consists of symptomatic and supportive measures. Gastric lavage may be helpful after acute ingestion, although it should be remembered that absorption is rapid.

◊ Reviews.

1. Brobyn RD. The human toxicology of dimethyl sulfoxide. *Ann N Y Acad Sci* 1975; **243:** 497–506.
2. Willhite CC, Katz PI. Toxicology updates: dimethyl sulfoxide. *J Appl Toxicol* 1984; **4:** 155–60.

◊ Dimethyl sulfoxide given by intravenous infusion for spinal cord injury to 14 patients caused transient haemolysis and haemoglobinuria.[1] Infusion strengths greater than 10% were associated with grossly discoloured urine but there was no evidence of renal damage. In 2 patients, raised liver and muscle enzyme concentrations, mild jaundice, and evidence of haemolysis developed when given dimethyl sulfoxide intravenously for arthritis.[2] One also developed acute renal tubular necrosis, deterioration in level of consciousness, and evidence of cerebral infarction. Acute, reversible neurological deterioration in a patient has been associated with intravenous dimethyl sulfoxide.[3]

Adverse effects have also been reported in patients given haematopoietic stem cells cryopreserved in dimethyl sulfoxide. A patient with pre-existing diabetes insipidus[4] developed serum hyperosmolality when given stem cells after chemotherapy for a malignant germ-cell tumour; symptoms included severe headache, confusion, and abdominal pain. Acute neurotoxicity has also been reported,[5,6] although it appears to be rare;[5] 2 patients also had myocardial damage.[6]

1. Muther RS, Bennett WM. Effects of dimethyl sulfoxide on renal function in man. *JAMA* 1980; **244:** 2081–3.
2. Yellowlees P, *et al.* Dimethylsulphoxide-induced toxicity. *Lancet* 1980; **ii:** 1004–6.
3. Bond GR, *et al.* Dimethylsulphoxide-induced encephalopathy. *Lancet* 1989; **i:** 1134–5.
4. Thomé S, *et al.* Dimethylsulphoxide-induced serum hyperosmolality after cryopreserved stem-cell graft. *Lancet* 1994; **344:** 1431–2.
5. Mueller LP, *et al.* Neurotoxicity upon infusion of dimethylsulfoxide-cryopreserved peripheral blood stem cells in patients with and without pre-existing cerebral disease. *Eur J Haematol* 2007; **78:** 527–31.
6. Chen-Plotkin AS, *et al.* Encephalopathy, stroke, and myocardial infarction with DMSO use in stem cell transplantation. *Neurology* 2007; **68:** 859–61.

Precautions
When used as a penetrating basis for other drugs applied topically, dimethyl sulfoxide may enhance their toxic effects.

Since dimethyl sulfoxide has been associated with lens changes in *animals*, licensed product information recommends assessment of ophthalmic function every 6 months during long-term treatment of cystitis with intravesical instillation of dimethyl sulfoxide. Hepatic and renal function should also be assessed at intervals of 6 months. Bladder instillation may be harmful in patients with urinary-tract malignancy because of vasodilatation.

Interactions
◊ For mention of an interaction between dimethyl sulfoxide and *sulindac*, see p.127.

Pharmacokinetics
Dimethyl sulfoxide is readily absorbed by all routes. It is metabolised by oxidation to dimethyl sulfone (p.2294) and by reduction to dimethyl sulfide. Dimethyl sulfoxide and the sulfone metabolite are excreted in the urine and faeces. Dimethyl sulfide is excreted through the lungs and skin and is responsible for the characteristic odour from patients.

Uses and Administration
Dimethyl sulfoxide is a highly polar substance with exceptional solvent properties for both organic and inorganic chemicals, and is widely used as an industrial solvent.

It has been reported to have a wide spectrum of pharmacological activity including membrane penetration, anti-inflammatory effects, local analgesia, weak bacteriostasis, diuresis, vasodilatation, dissolution of collagen, and free-radical scavenging.

The principal use of dimethyl sulfoxide is as a vehicle for drugs such as idoxuridine (p.881); it aids penetration of the drug into the skin, and so may enhance the drug's effect. It is also used as a 50% aqueous solution for bladder instillation for the symptomatic relief of interstitial cystitis; doses of 50 mL are instilled and allowed to remain for 15 minutes. Treatment is repeated every 2 weeks initially.

Dimethyl sulfoxide has been given orally, intravenously, or topically for a wide range of indications including cutaneous and musculoskeletal disorders, but evidence of beneficial effects is limited.

Dimethyl sulfoxide is used as a cryoprotectant for various human tissues.

Amyloidosis. Oral or local dimethyl sulfoxide has been tried[1-3] as part of the management of some forms of amyloidosis (p.743).

1. Ichida M, *et al.* Successful treatment of multiple myeloma-associated amyloidosis by interferon-alpha, dimethyl sulfoxide, and VAD (vincristine, adriamycin, and dexamethasone). *Int J Hematol* 2000; **72:** 491–3.
2. Malek RS, *et al.* Primary localized amyloidosis of the bladder: experience with dimethyl sulfoxide therapy. *J Urol (Baltimore)* 2002; **168:** 1018–20.
3. Amemori S, *et al.* Oral dimethyl sulfoxide for systemic amyloid A amyloidosis complication in chronic inflammatory disease: a retrospective patient chart review. *J Gastroenterol* 2006; **41:** 444–9.

Cryopreservation. Dimethyl sulfoxide is used as a cryoprotectant in various assisted conception techniques.[1] Adverse effects have been reported in patients receiving haematopoietic stem cells cryopreserved in dimethyl sulfoxide (see under Adverse Effects, above).

1. Trounson AO. Cryopreservation. *Br Med Bull* 1990; **46:** 695–708.

Extravasation of antineoplastics. Several reports have suggested a role for topical dimethyl sulfoxide in the treatment of anthracycline extravasation.[1-4] The problem of antineoplastic extravasation and its management is discussed further on p.640.

1. Lawrence HJ, Goodnight SH. Dimethyl sulfoxide and extravasation of anthracycline agents. *Ann Intern Med* 1983; **98:** 1025.
2. Olver IN, *et al.* A prospective study of topical dimethyl sulfoxide for treating anthracycline extravasation. *J Clin Oncol* 1988; **6:** 1732–5.
3. Rospond RM, Engel LM. Dimethyl sulfoxide for treating anthracycline extravasation. *Clin Pharm* 1993; **12:** 560–1.
4. Bertelli G, *et al.* Dimethylsulphoxide and cooling after extravasation of antitumour agents. *Lancet* 1993; **341:** 1098.

Gallstones. For mention of the use of a mixture containing dimethyl sulfoxide to dissolve gallstones, see Methyl *tert*-Butyl Ether, p.2025.

Interstitial cystitis. Bladder instillation of dimethyl sulfoxide is used[1,2] in the symptomatic management of interstitial cystitis (p.2179). Treatment usually consists of 50 mL of a 50% aqueous solution that is retained in the bladder for 15 minutes. This may be repeated every 1 to 2 weeks for 4 to 8 treatments, and overall response rates of 50 to 90% have been reported. Although relapse rates after a 4 to 8 week course of treatment are high (35 to 40%), about half of these patients will respond to additional dimethyl sulfoxide treatment. Maintenance therapy on either a regular or intermittent basis may be used.[1]

1. Parkin J, *et al.* Intravesical dimethyl sulfoxide (DMSO) for interstitial cystitis—a practical approach. *Urology* 1997; **49** (suppl 5A): 105–7.
2. Rössberger J, *et al.* Critical appraisal of dimethyl sulfoxide treatment for interstitial cystitis: discomfort, side-effects and treatment outcome. *Scand J Urol Nephrol* 2005; **39:** 73–7.

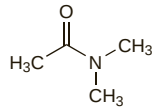
Dimethylacetamide

Acetyldimethylamine; Dimethylacetamid; Diméthylacétamide; Dimethylacetamidum; Dimetilacetamida; Dimetilacetamidas; Dimetylacetamid; Dimetyloacetamid; Dimetyyliasetamidi; DMAC. *NN*-Dimethylacetamide.

Диметилацетамид

C_4H_9NO = 87.12.

CAS — 127-19-5.



Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Dimethylacetamide). A clear, colourless, slightly hygroscopic liquid. Relative density 0.941 to 0.944. B.p. about 165°. Miscible with water, with alcohol, and with most common organic solvents. Store in airtight containers. Protect from light.

Adverse Effects and Precautions
As for Dimethylformamide (below), although a disulfiram-like reaction with alcohol has not been reported.

◊ A review[1] of the toxicology of dimethylacetamide with reference to its use as a vehicle for antineoplastics.

1. Kim S-N. Preclinical toxicology and pharmacology of dimethylacetamide, with clinical notes. *Drug Metab Rev* 1988; **19:** 345–68.

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

Uses
Dimethylacetamide is used as an industrial and pharmaceutical solvent.

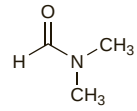
Dimethylformamide

Dimetilformamida; Dimetyloformamid; DMF. *NN*-Dimethylformamide.

Диметилформамид

C_3H_7NO = 73.09.

CAS — 68-12-2.



Description. Dimethylformamide is a colourless liquid. Wt per mL about 0.95 g. B.p. about 153°.

Adverse Effects and Precautions
Dimethylformamide is irritant. Gastrointestinal effects including nausea, vomiting, loss of appetite, and abdominal pain, CNS effects such as headache, dizziness, and weakness, and liver damage have been reported in workers occupationally exposed to the liquid or vapour. Some workers exposed to dimethylformamide have experienced a disulfiram-like effect after consumption of alcohol.

◊ Reviews of the adverse effects of dimethylformamide.

1. WHO. Dimethylformamide. *Environmental Health Criteria 114*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/ehc/ehc/ehc114.htm (accessed 30/06/04)

Effects on the liver. Exposure to dimethylformamide was considered to be the most likely cause of elevated liver enzyme values in 36 of 58 (62%) workers in a fabric coating factory.[1] Symptoms reported were generally mild and included anorexia, abdominal pain, nausea, headache, dizziness, and a disulfiram-type reaction to alcohol.

Hepatotoxicity has occurred after acute poisoning with a veterinary drug formulated in dimethylformamide. There were only minor increases in liver enzyme values in a patient who was treated early with acetylcysteine.[2]

1. Redlich CA, *et al.* Liver disease associated with occupational exposure to the solvent dimethylformamide. *Ann Intern Med* 1988; **108:** 680–6.
2. Buylaert W, *et al.* Hepatotoxicity of N,N-dimethylformamide (DMF) in acute poisoning with the veterinary euthanasia drug T-61. *Hum Exp Toxicol* 1996; **15:** 607–11.