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.

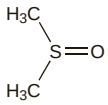
Диметилсульфоксид

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.

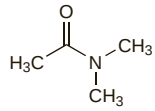
Dimethylacetamide

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.

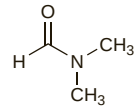
Dimethylformamide

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.