Chloroform

Chloroformium Anesthesicum; Chloroformum; Chloroformum pro Narcosi; Cloroformo. Trichloromethane.

$CHCl_3$ = 119.4.

CAS — 67-66-3.

ATC — N01AB02.

ATC Vet — QN01AB02.

Pharmacopoeias. In *Br.*, *Chin.*, and *Viet.*

BP 2008 (Chloroform). A colourless volatile liquid with a characteristic odour. Not more than 5.0% v/v distils below 60° and the remainder distils at 60° to 62°. It contains 1.0 to 2.0% v/v of ethyl alcohol; amylene 50 micrograms/mL is permitted as an alternative to ethyl alcohol.

Slightly soluble in water; miscible with dehydrated alcohol, with ether, with fixed and volatile oils, and with most other organic solvents. Store in containers with glass stoppers or other suitable closures. Protect from light. The label should state whether it contains ethyl alcohol or amylene.

Stability. The addition of a small percentage of alcohol greatly retards the gradual oxidation that occurs when chloroform is exposed to air and light, and which results in its becoming contaminated with the very poisonous carbonyl chloride (phosgene) and with chlorine; the alcohol also serves to decompose any carbonyl chloride that may have been formed.

From a study[1] of chloroform losses from chloroform water and from 6 typical BPC mixtures under various conditions of storage the following shelf-lives were recommended: chloroform solutions and non-sedimented mixtures could be stored in well-closed well-filled containers for 2 months at ambient temperatures; when stored in partially-filled containers and periodically opened the shelf-life should not exceed 2 weeks; sedimented mixtures could be stored for 2 months in well-closed well-filled containers, but because loss of chloroform could be expected in containers periodically opened such mixtures should be prepared as required or packed in their final containers; for chloroform-containing mixtures in the home a shelf-life of 2 weeks was suggested.

1. Lynch M, *et al*. Chloroform as a preservative in aqueous systems: losses under "in-use" conditions and antimicrobial effectiveness. *Pharm J* 1977; **219:** 507–10.

Storage. It has been recommended[1] that if the period of use would exceed 6 weeks, PVC bottles should not be used for storing or dispensing: Chloroform and Morphine Tincture, or aqueous mixtures containing more than 5% thereof; mixtures or dispersions in which chloroform is present in excess of its aqueous solubility; aqueous mixtures containing chloroform and high concentrations of electrolytes; or of mixtures containing chloroform water.

1. Anonymous. Plastics medicine bottles of rigid PVC. *Pharm J* 1973; **210:** 100.

Adverse Effects and Precautions

Chloroform depresses respiration and produces hypotension. Cardiac output is reduced and arrhythmias may develop. Poisoning can lead to respiratory depression and cardiac arrest. Delayed hepatotoxic and nephrotoxic reactions have occurred 6 to 24 hours after a dose; symptoms may include abdominal pain, vomiting, and, at a later stage, jaundice.

Liquid chloroform is irritant to the skin and mucous membranes and may cause burns if spilt on them. Suitable precautions should be taken to avoid skin contact with chloroform as it can penetrate skin and produce systemic toxicity. Chloroform is not flammable. Care should be taken not to vaporise chloroform in the presence of a flame because of the production of toxic gases.

In the UK medicinal products are limited to a chloroform content of not more than 0.5% (w/w or v/v as appropriate) of chloroform. Exceptions include supply by a doctor or dentist, or in accordance with his prescription, to a particular patient, and supply for anaesthetic purposes.

In the USA the FDA has banned the use of chloroform in medicines and cosmetics, because of reported carcinogenicity in *animals*. It has also been withdrawn from systemic use in other countries.

The sale within or import into England and Wales and Scotland of food containing any added chloroform is prohibited.

See also Adverse Effects and Precautions for General Anaesthetics, p.1779.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving chloroform, and the American Academy of Pediatrics[1] considers that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 25/05/04)

Porphyria. Chloroform has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Uses and Administration

Chloroform is a volatile halogenated anaesthetic that was used by inhalation, but safer drugs are now preferred in general anaesthesia.

Chloroform is used as a carminative and as a flavouring agent and preservative. For these purposes it is usually employed as Chloroform Spirit (BP 2008) or Double-strength Chloroform Water (BP 2008) but doubts have been cast on the safety of the long-term use of chloroform in mixtures.

Externally, chloroform has a rubefacient action.

Chloroform is also used as a solvent.

Anaesthesia. An historical review of the use of chloroform in clinical anaesthesia.[1]

1. Payne JP. Chloroform in clinical anaesthesia. *Br J Anaesth* 1981; **53:** 11S–15S.

Preparations

BP 2008: Chloroform and Morphine Tincture; Chloroform Spirit; Double-strength Chloroform Water.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Dentophar; ***Rus.:*** Eludril (Элюдрил); Espol (Эспол); ***S.Afr.:*** Diphenhydramine Expectorant Syrup; Mrs Johnsons American Soothing Syrup; SB Toothache Drops; Tandpyndruppels; Vicks Acta Plus; ***Venez.:*** Fiometil†; Gamasol†; Iodex†; Rubefric†.

Cyclopropane *(rINN)*

Ciclopropano; Cyclopropanum; Trimethylene.

Циклопропан

C_3H_6 = 42.08.

CAS — 75-19-4.

Pharmacopoeias. In *US.*

USP 31 (Cyclopropane). A colourless highly flammable gas with a characteristic odour and pungent taste. Freely soluble in alcohol; soluble in fixed oils. One volume dissolves in about 2.7 volumes of water at 15°.

Stability. CAUTION. Mixtures of cyclopropane with oxygen or air at certain concentrations are explosive. Cyclopropane should not be used in the presence of an open flame or of any electrical apparatus liable to produce a spark. Precautions should be taken against the production of static electrical discharge.

Storage and supply. Cyclopropane is supplied compressed in metal cylinders. National standards are usually in operation for the labelling and marking of such cylinders.

Adverse Effects and Precautions

Cyclopropane depresses respiration to a greater extent than many other anaesthetics. Laryngospasm, cardiac arrhythmias, or hepatic injury may occur. Cyclopropane increases the sensitivity of the heart to sympathomimetic amines. Malignant hyperthermia has also been reported. Postoperative nausea, vomiting, and headache are frequent.

Cyclopropane should be used with caution in patients with bronchial asthma and cardiovascular disorders. Premedication with atropine may be advisable to reduce vagal tone.

See also Adverse Effects and Precautions for General Anaesthetics, p.1779.

Abuse. Two of 4 deaths from abuse of volatile anaesthetics in operating rooms were attributed to cyclopropane.[1]

1. Bass M. Abuse of inhalation anesthetics. *JAMA* 1984; **251:** 604.

Malignant hyperthermia. Malignant hyperthermia was associated with cyclopropane.[1]

1. Lips FJ, *et al*. Malignant hyperthermia triggered by cyclopropane during cesarean section. *Anesthesiology* 1982; **56:** 144–6.

Interactions

Care is advised if adrenaline or other sympathomimetics are given during cyclopropane anaesthesia. Potentiation of competitive neuromuscular blockers occurs after use of cyclopropane.

See also Interactions for General Anaesthetics, p.1779.

Uses and Administration

Cyclopropane is an anaesthetic that has been given by inhalation for analgesia and induction and maintenance of general anaesthesia. It produces skeletal muscle relaxation, is non-irritant, and induction and recovery are rapid, but it is difficult to use and handle and other anaesthetics are generally preferred. Because of the risk of explosion, it has usually been given by means of a closed circuit. It has a minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) of 9.2%.

Desflurane *(USAN, rINN)*

Desfluraani; Desfluran; Desflurano; Desfluranum; I-653. (±)-2-Difluoromethyl 1,2,2,2-tetrafluoroethyl ether.

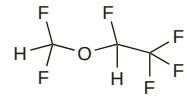
Десфлуран

$C_3H_2F_6O$ = 168.0.

CAS — 57041-67-5.

ATC — N01AB07.

ATC Vet — QN01AB07.



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

Ph. Eur. 6.2 (Desflurane). A clear, colourless, mobile, heavy liquid. B.p. about 22°. Practically insoluble in water; miscible with anhydrous alcohol. Store in a glass bottle fitted with a polyethylene-lined cap. Before opening the bottle, cool the contents to below 10°.

USP 31 (Desflurane). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Replace cap securely after each use. Protect from light.

Adverse Effects and Precautions

As with other halogenated anaesthetics, respiratory depression, hypotension, and arrhythmias may occur. Desflurane may rarely precipitate malignant hyperthermia in susceptible individuals. It appears to sensitise the myocardium to sympathomimetics to a lesser extent than halothane or enflurane. Nausea and vomiting have been reported in the postoperative period.

Desflurane is irritant to the airways and may provoke breath holding, apnoea, coughing, increased salivation, and laryngospasm. It is therefore not recommended for induction of anaesthesia in paediatric patients.

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with desflurane. Desflurane may increase CSF pressure and should therefore be used with caution in patients with, or at risk from, raised intracranial pressure.

In order to minimise the risk of developing elevated carboxyhaemoglobin levels carbon dioxide absorbents in anaesthetic apparatus should not be allowed to dry out when delivering volatile anaesthetics such as desflurane (see below).

See also Adverse Effects and Precautions of General Anaesthetics, p.1779.

Carbon dioxide absorbents. Significant carboxyhaemoglobinaemia may develop rarely during anaesthesia with volatile anaesthetics given by circle breathing systems containing carbon dioxide absorbents.[1] The effect is only seen when the absorbent has become excessively dried out. The use of barium hydroxide lime (which is not available in the UK) as an absorbent produces more carbon monoxide than soda lime, particularly at low water content. No cases of this complication had been reported to date in the UK.

1. CSM/MCA. Safety issues in anaesthesia: volatile anaesthetic agents and carboxyhaemoglobinaemia. *Current Problems* 1997; **23:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)

Effects on the cardiovascular system. A review[1] of *animal* and human studies concluded that the cardiorespiratory effects of desflurane were similar to those of isoflurane but that there might be better control of arterial pressure with desflurane during stressful stimuli. A study[2] in patients undergoing coronary artery bypass surgery showed that a state of haemodynamic stability suitable for patients at risk of myocardial ischaemia could be maintained when desflurane was used with the opioid analgesic fentanyl.

1. Warltier DC, Pagel PS. Cardiovascular and respiratory actions of desflurane: is desflurane different from isoflurane? *Anesth Analg* 1992; **75:** S17–S31.
2. Parsons RS, *et al*. Comparison of desflurane and fentanyl-based anaesthetic techniques for coronary artery bypass surgery. *Br J Anaesth* 1994; **72:** 430–8.

Effects on the liver. Although considered to be less hepatotoxic than some other halogenated anaesthetics (see under Adverse Effects of Halothane, p.1784), delayed hepatotoxicity has occurred in a 65-year-old woman after maintenance anaesthesia involving desflurane.[1] She had received halothane on two previous occasions which may have caused sensitisation. Investigation of

hepatocellular integrity (by measuring glutathione transferase alpha) in 30 women given desflurane indicated a mild subclinical disturbance.[2]

1. Martin JL, *et al.* Hepatotoxicity after desflurane anesthesia. *Anesthesiology* 1995; **83:** 1125–9.
2. Tiainen P, *et al.* Changes in hepatocellular integrity during and after desflurane or isoflurane anaesthesia in patients undergoing breast surgery. *Br J Anaesth* 1998; **80:** 87–9.

Effects on the respiratory tract. The irritant effect of desflurane on the lungs limits its role in the induction of anaesthesia, especially in children. Pre-operative use of nebulised lidocaine 4% failed to alleviate the response[1] although pretreatment with intravenous opioids may reduce the irritation.[2]

1. Bunting HE, *et al.* Effect of nebulized lignocaine on airway irritation and haemodynamic changes during induction of anaesthesia with desflurane. *Br J Anaesth* 1995; **75:** 631–3.
2. Kong CF, *et al.* Intravenous opioids reduce airway irritation during induction of anaesthesia with desflurane in adults. *Br J Anaesth* 2000; **85:** 364–7.

Interactions

The effects of competitive neuromuscular blockers such as atracurium are enhanced by desflurane (see p.1904). Lower doses of desflurane are required in those receiving opioids, benzodiazepines or other sedatives. Care is advised if adrenaline or other sympathomimetics are given to patients during desflurane anaesthesia.

See also Interactions of General Anaesthetics, p.1779.

◊ References.

1. Dale O. Drug interactions in anaesthesia: focus on desflurane and sevoflurane. *Baillieres Clin Anaesthesiol* 1995; **9:** 105–17.

Pharmacokinetics

Desflurane has a low blood/gas partition coefficient and on inhalation its absorption, distribution, and elimination are reported to be more rapid than for other halogenated anaesthetics such as isoflurane or halothane. It is excreted mainly unchanged through the lungs. A small amount diffuses through the skin. About 0.02% of inhaled desflurane is metabolised in the liver and trichloroacetic acid has been detected in the serum and urine of patients given desflurane.

◊ References.

1. Caldwell JE. Desflurane clinical pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1994; **27:** 6–18.
2. Eger EI. Physicochemical properties and pharmacodynamics of desflurane. *Anaesthesia* 1995; **50** (suppl): 3–8.
3. Wissing H, *et al.* Pharmacokinetics of inhaled anaesthetics in a clinical setting: comparison of desflurane, isoflurane and sevoflurane. *Br J Anaesth* 2000; **84:** 443–9.
4. Lu CC, *et al.* Pharmacokinetics of desflurane uptake into the brain and body. *Anaesthesia* 2004; **59:** 216–21.

Uses and Administration

Desflurane is a volatile halogenated anaesthetic administered by inhalation. It is structurally similar to isoflurane and has anaesthetic actions similar to those of halothane (p.1785). The minimum alveolar concentration (MAC) value (see Uses of General Anaesthetics, p.1779) ranges from about 6% in the elderly to about 11% in infants. It is non-flammable and non-explosive in clinical concentrations but, because of its low boiling-point, it must be delivered by a special vaporiser, preferably within a closed circuit system.

Desflurane is used for induction and maintenance of general anaesthesia (p.1780), but because of its pungency is not recommended for induction in children. Concentrations of 4 to 11% v/v have been used for induction and usually produce surgical anaesthesia in 2 to 4 minutes. Concentrations of 2 to 6% v/v with nitrous oxide or 2.5 to 8.5% v/v in oxygen or oxygen-enriched air may be used to maintain anaesthesia. Higher concentrations of desflurane have been used but it is important to ensure adequate oxygenation; concentrations in excess of 17% v/v are not recommended. For concentrations used in patients with hepatic or renal impairment, see below.

As with other volatile halogenated anaesthetics supplemental neuromuscular blockers may be required. Recovery from anaesthesia is reported to be more rapid than with other halogenated anaesthetics.

Administration in hepatic or renal impairment. Desflurane concentrations of 1 to 4% v/v in oxygen and nitrous oxide have been used in patients with chronic renal or hepatic impairment and during renal transplantation surgery.

Anaesthesia. The characteristics of desflurane have been discussed in a number of reviews.[1-6] Its advantages are considered to include rapid induction and emergence from anaesthesia, and minimal metabolism makes end-organ toxicity unlikely. Emergence from anaesthesia and recovery of psychomotor and cognitive skills with desflurane is more rapid than after anaesthesia with other halogenated volatile anaesthetics such as isoflurane and possibly than after the intravenous anaesthetic propofol. This is considered to be of particular advantage for outpatient treatment, but studies so far have found no difference in time to discharge with desflurane or other general anaesthetics. Furthermore, the incidence of nausea and vomiting with desflurane is significantly greater than after the use of propofol. Desflurane's pungency may also limit its use for induction especially in children, although it is suitable for maintenance in this group and may be particularly suitable for neonates.[4]

1. Caldwell JE. Desflurane clinical pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1994; **27:** 6–18.
2. Patel SS, Goa KL. Desflurane: a review of its pharmacodynamic and pharmacokinetic properties and its efficacy in general anaesthesia. *Drugs* 1995; **50:** 742–67.
3. Young CJ, Apfelbaum JL. Inhalational anesthetics: desflurane and sevoflurane. *J Clin Anesth* 1995; **7:** 564–77.
4. Hatch DJ. New inhalation agents in paediatric anaesthesia. *Br J Anaesth* 1999; **83:** 42–9.
5. Umbrain V, *et al.* Desflurane: a reappraisal. *Acta Anaesthesiol Belg* 2002; **53:** 187–91.
6. Sakai EM, *et al.* Inhalation anesthesiology and volatile liquid anesthetics: focus on isoflurane, desflurane, and sevoflurane. *Pharmacotherapy* 2005; **25:** 1773–88.

Status epilepticus. For mention of the use of desflurane in the management of refractory status epilepticus, see p.469.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Suprane; ***Austral.:*** Suprane; ***Austria:*** Suprane; ***Canad.:*** Suprane; ***Cz.:*** Suprane; ***Denm.:*** Suprane; ***Fin.:*** Suprane; ***Ger.:*** Suprane; ***Gr.:*** Suprane; ***Hong Kong:*** Suprane; ***Hung.:*** Suprane; ***Indon.:*** Suprane; ***Israel:*** Sulorane; ***Ital.:*** Suprane; ***Malaysia:*** Suprane; ***Mex.:*** Suprane†; ***Neth.:*** Suprane; ***NZ:*** Suprane; ***Philipp.:*** Suprane; ***Pol.:*** Suprane; ***Port.:*** Suprane; ***S.Afr.:*** Suprane; ***Spain:*** Suprane; ***Swed.:*** Suprane; ***Switz.:*** Suprane; ***Thai.:*** Suprane; ***UK:*** Suprane; ***USA:*** Suprane; ***Venez.:*** Suprane†.

Enflurane *(BAN, USAN, rINN)*

Anaesthetic Compound No. 347; Compound 347; Enfluraani; Enfluran; Enflurano; Enfluranum; Methylfluorether; NSC-115944. 2-Chloro-1,1,2-trifluoroethyl difluoromethyl ether; 2-Chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane.

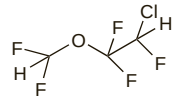
Энфлуран

$C_3H_2ClF_5O$ = 184.5.

CAS — 13838-16-9.

ATC — N01AB04.

ATC Vet — QN01AB04.



Pharmacopoeias. In *Jpn* and *US*.

USP 31 (Enflurane). A clear colourless volatile liquid having a mild sweet odour. Non-flammable. Distilling range 55.5° to 57.5°. Slightly soluble in water; miscible with organic solvents, with fats, and with oils. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Adverse Effects

As with other halogenated anaesthetics, respiratory depression, hypotension, and arrhythmias have been reported although the incidence of arrhythmias is lower with enflurane than with halothane. It sensitises the myocardium to sympathomimetics to a lesser extent than halothane. Compared with halothane, enflurane has a stimulant effect on the CNS and convulsions may occur when concentrations of enflurane are high or hypocapnia is present. Malignant hyperthermia has also been reported. Asthma and bronchospasm may occur. There have been reports of elevated serum-fluoride concentrations although resulting renal damage appears to be rare. There have been changes in measurements of hepatic enzymes and a number of reports of liver damage. Shivering, nausea, and vomiting have been reported in the postoperative period.

See also Adverse Effects of General Anaesthetics, p.1779.

Effects on the blood. The development of carboxyhaemoglobinaemia in patients anaesthetised with volatile anaesthetics is discussed under Precautions, below.

Effects on the kidneys. The nephrotoxicity of volatile anaesthetics has been reviewed.[1] Although enflurane released inorganic fluoride it appeared to be safe in patients with normal renal function. It had also been given to patients with mild to moderate renal impairment without any further deterioration. There was an increase in serum-fluoride concentrations when enflurane was given to a group of patients who had been receiving isoniazid, but there was no change in kidney function. Pretreatment of patients with a single dose of disulfiram before anaesthesia was found to produce a consistent and almost complete inhibition of enflurane metabolism as shown by substantial reductions in plasma-fluoride concentrations and urinary excretion of fluoride.[2]

1. Mazze RI. Nephrotoxicity of fluorinated anaesthetic agents. *Clin Anaesthesiol* 1983; **1:** 469–83.
2. Kharasch ED, *et al.* Clinical enflurane metabolism by cytochrome P450 2E1. *Clin Pharmacol Ther* 1994; **55:** 434–40.

Effects on the liver. A review[1] of 58 cases of suspected enflurane hepatitis considered enflurane to be the likely cause of the liver damage in 24. There was biochemical evidence of liver damage in 23 of these cases. Histology reports were available for 15 patients and all showed some degree of hepatocellular necrosis and degeneration.

While the incidence of liver damage from enflurane seemed to be lower than from halothane, the character of the injury was similar.

Another review[2] of the same cases plus an additional 30 (88 in all) came to different conclusions; the main author was a consultant to the manufacturer of enflurane. Of the 88 patients with suspected enflurane hepatitis, 30 were rejected because of insufficient evidence and 43 were considered to have other factors known to produce liver injury. This left 15 possible cases of enflurane hepatitis compared with the 24 identified by the first review. While agreeing that in the rare patient unexplained liver damage follows enflurane anaesthesia, it was considered that the incidence was too small to suggest an association. No consistent histological pattern was identified in this study.

See also under Adverse Effects in Halothane, p.1784.

1. Lewis JH, *et al.* Enflurane hepatotoxicity: a clinicopathologic study of 24 cases. *Ann Intern Med* 1983; **98:** 984–92.
2. Eger EI, *et al.* Is enflurane hepatotoxic? *Anesth Analg* 1986; **65:** 21–30.

Effects on respiration. Overall, enflurane is considered to produce more respiratory depression than halothane or isoflurane.[1,2]

1. Quail AW. Modern inhalation anaesthetic agents: a review of halothane, isoflurane and enflurane. *Med J Aust* 1989; **150:** 95–102.
2. Merrett KL, Jones RM. Inhalational anaesthetic agents. *Br J Hosp Med* 1994; **52:** 260–3.

Precautions

Enflurane should be used with caution in patients with convulsive disorders. High concentrations of enflurane may cause uterine relaxation. In order to minimise the risk of developing elevated carboxyhaemoglobin levels, carbon dioxide absorbents in anaesthetic apparatus should not be allowed to dry out when delivering volatile anaesthetics such as enflurane.

As with other halogenated anaesthetics, patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetised with enflurane.

See also Precautions for General Anaesthetics, p.1779.

Abuse. Report[1] of a fatality in a 29-year-old student nurse anaesthetist who had applied enflurane to the herpes simplex lesions of her lower lip. She was found with an empty 250 mL bottle of enflurane.

1. Lingenfelter RW. Fatal misuse of enflurane. *Anesthesiology* 1981; **55:** 603.

Carbon dioxide absorbents. Significant carboxyhaemoglobinaemia may develop rarely during anaesthesia with volatile anaesthetics given by circle breathing systems containing carbon dioxide absorbents.[1] The effect is only seen when the absorbent has become excessively dried out. The use of barium hydroxide lime (which is not available in the UK) as an absorbent produces more carbon monoxide than soda lime, particularly at low water content. No cases of this complication had been reported to date in the UK.

1. CSM/MCA. Safety issues in anaesthesia: volatile anaesthetic agents and carboxyhaemoglobinaemia. *Current Problems* 1997; **23:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 16/05/06)