Domiphen Bromide *(BAN, USAN, rINN)*

Bromuro de domifeno; Domifeenibromidi; Domifenbromid; Domiphène, Bromure de; Domipheni Bromidum; NSC-39415; PDDB; Phenododecinium Bromide. Dodecyldimethyl-2-phenoxyethylammonium bromide.

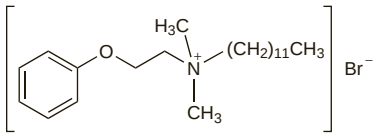
Домифена Бромид

$C_{22}H_{40}BrNO$ = 414.5.

CAS — 13900-14-6 (domiphen); 538-71-6 (domiphen bromide).

ATC — A01AB06.

ATC Vet — QA01AB06.



Pharmacopoeias. In *Br. Chin.* includes the monohydrate.

BP 2008 (Domiphen Bromide). Colourless or faintly yellow, crystalline flakes. Freely soluble in water and in alcohol; soluble in acetone.

Incompatibility. Domiphen bromide is incompatible with soaps and other anionic surfactants.

Profile

Domiphen bromide is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). Preparations containing domiphen bromide are used in the treatment of minor infections of the mouth and throat.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Antiseptique Pastilles; Bronchodex Pastilles; ***Ital.:*** Bradoral; ***Malaysia:*** Domidin; ***Port.:*** Neobradoral.

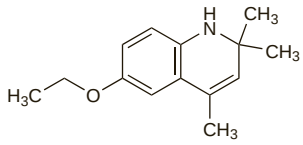
Multi-ingredient: ***Austria:*** Bepanthen; Bradosol; ***Canad.:*** Nupercainal; ***Chile:*** Oralfresh Menta; ***Fr.:*** Fluoselgine; ***Ital.:*** Inalar; ***Pol.:*** Viosept.

Ethoxyquin

Etoxiquina. 6-Ethoxy-1,2-dihydro-2,2,4-trimethylquinoline.

$C_{14}H_{19}NO$ = 217.3.

CAS — 91-53-2.



Profile

Ethoxyquin has been used as an antoxidant for the prevention of common scald of apples and pears during storage and as an additive to animal feeds. Concern has been expressed over the toxicity of ethoxyquin and its residues on foodstuffs and its use is limited or restricted in some countries.

Ethylene Oxide

Dimethylene oxide; Epoxietano; 1,2-Epoxyethane; Etylenu tlenek; Óxido de etileno; Oxirane; Oxirano; Oxirano.

Окись Этилена; Этиленоксид

C_2H_4O = 44.05.

CAS — 75-21-8.

Description. Ethylene oxide is a colourless flammable gas at room temperature and atmospheric pressure.

Stability. Mixtures of ethylene oxide with oxygen or air are explosive but the risk can be reduced by the addition of carbon dioxide or fluorocarbons.

Adverse Effects and Precautions

Ethylene oxide irritates the eyes and respiratory tract and may also cause nausea and vomiting, diarrhoea, headache, vertigo, CNS depression, dyspnoea, and pulmonary oedema. Liver and kidney damage and haemolysis may occur. Fatalities have occurred. Excessive exposure of the skin to liquid or solution causes burns, blistering, irritation, and dermatitis; percutaneous absorption may lead to systemic effects.

Many materials including plastics and rubber adsorb ethylene oxide. If such materials are being sterilised with ethylene oxide all traces of the gas must be removed before the materials can be used; removal may be by ventilation or more active means. Hypersensitivity reactions, including anaphylaxis, have been associated with ethylene oxide-contaminated materials. Ethylene oxide may also react with materials being sterilised to produce substances such as ethylene chlorohydrin (with chloride) or ethylene glycol (with water); these may contribute to any toxicity.

Pharmaceutical manufacturers within the EU have been advised to use ethylene oxide only when there is no alternative. Ethylene oxide has been shown to have carcinogenic and mutagenic properties and there is evidence of increased risk of neoplasms following occupational exposure.

◊ Reviews.

1. WHO. Ethylene oxide. *Environmental Health Criteria 55*. Geneva: WHO, 1985. Available at: http://www.inchem.org/documents/ehc/ehc/ehc55.htm (accessed 15/03/06)
2. WHO. Ethylene oxide health and safety guide. *IPCS Health and Safety Guide 16*. Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg016.htm (accessed 15/03/06)
3. WHO. Ethylene oxide. *Concise International Chemical Assessment Document 54* Geneva: WHO, 2003. Available at: http://www.who.int/ipcs/publications/cicad/en/cicad54.pdf (accessed 15/03/06)

Carcinogenicity. Exposure of workers to ethylene oxide has been associated with the development of lymphatic and haematopoietic cancer and there is concern that it may be linked to breast cancer. In order to evaluate the carcinogenicity of ethylene oxide the National Institute for Occupational Safety and Health (NIOSH), in the mid 1980s, assembled a cohort of about 18 000 workers exposed to ethylene oxide.[1-3] Results of the initial cohort followed up to 1987 showed no overall excess of haematopoietic cancer, but did find a significant excess of non-Hodgkin's lymphoma among men.[1] Based on limited clinical evidence from humans and from significant evidence in *animal* studies, the International Agency for Research on Cancer concluded in 1994 that there was sufficient evidence to classify ethylene oxide as a definite human carcinogen.[4] A later evaluation[3] of the NIOSH cohort from 1987 to 1998 indicated that, despite 2852 deaths as opposed to 1177 deaths in the earlier study, there was little evidence of cancer excesses for ethylene oxide exposed workers versus the general population, with the exception of bone cancer (6 deaths), and no conclusion could be drawn from this small number. However, exposure-response analyses found statistically significant evidence of an association between increased exposure and some types of haematopoietic cancer (non-Hodgkin's lymphoma and lymphocytic leukaemia), particularly for males.[2,3] There was also some evidence for a positive exposure-response for breast cancer. Follow-up of a cohort of 2876 workers exposed to ethylene oxide in the UK[5] found no statistically significant increase in mortality from cancer overall, or from any specific category of tumour. A study[6] of a cohort of 7576 female workers exposed to ethylene oxide suggested that ethylene oxide was associated with breast cancer. However, the authors indicated weaknesses in the study that could have influenced the findings.

1. Steenland K, *et al.* Mortality among workers exposed to ethylene oxide. *N Engl J Med* 1991; **324:** 1402–7.
2. Stayner L, *et al.* Exposure-response analysis of cancer mortality in a cohort of workers exposed to ethylene oxide. *Am J Epidemiol* 1993; **138:** 787–98.
3. Steenland K, *et al.* Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. *Occup Environ Med* 2004; **61:** 2–7.
4. IARC/WHO. Some industrial chemicals. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans volume 60* 1994. Available at: http://monographs.iarc.fr/ENG/Monographs/vol60/volume60.pdf (accessed 23/05/06)
5. Coggon D, *et al.* Mortality of workers exposed to ethylene oxide: extended follow up of a British cohort. *Occup Environ Med* 2004; **61:** 358–62.
6. Steenland K, *et al.* Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes Control* 2003; **14:** 531–9.

Effects on the nervous system. Four men exposed to ethylene oxide at a concentration of greater than 700 ppm developed neurological disorders. One experienced headaches, nausea, vomiting, and lethargy followed by major motor seizures. The others had headaches, limb numbness and weakness, increased fatigue, trouble with memory and thought processes, and slurred speech. Three also developed cataracts, and one required bilateral cataract extractions.[1] Rash, followed a few months later by hand numbness and weakness, headaches, and cognitive impairment, has been reported[2] in a cluster of 12 surgical nurses and technicians after exposure for 5 months to ethylene oxide-contaminated surgical gowns. Several patients showed signs of peripheral and CNS dysfunction and one patient had signs of axonal injury.

1. Jay WM, *et al.* Possible relationship of ethylene oxide exposure to cataract formation. *Am J Ophthalmol* 1982; **93:** 727–32.
2. Brashear A, *et al.* Ethylene oxide neurotoxicity: a cluster of 12 nurses with peripheral and central nervous system toxicity. *Neurology* 1996; **46:** 992–8.

Hypersensitivity. Anaphylactoid reactions in dialysis patients have resulted from the use of dialysis equipment sterilised with ethylene oxide.[1-3] There have also been reports of hypersensitivity[4] and anaphylactoid[5] reactions in plateletpheresis donors caused by residues of ethylene oxide in components of apheresis kits. The most common adverse reactions reported have been dyspnoea, wheezing, urticaria, flushing, headache, and hypotension, but acute severe bronchospasm, circulatory collapse, cardiac arrest, and death have also occurred. It was noted[6] that where severe, sometimes fatal, anaphylactoid reactions have occurred at the beginning of dialysis, ethylene oxide has almost universally been implicated, although exposure to cuprammonium cellulose (cuprophane) dialysis membranes may also have been involved.

It has been reported that there may be an increased risk of ethylene oxide-induced anaphylactic shock in children undergoing surgery for spina bifida.[7] Such children might be at increased risk of sensitisation and anaphylaxis, and came into frequent contact with ethylene oxide through multiple operations and catheterisations.

Occupational asthma and contact dermatitis have been attributed to residual ethylene oxide in surgical gloves.[8]

1. Bommer J, *et al.* Anaphylactoid reactions in dialysis patients: role of ethylene-oxide. *Lancet* 1985; **ii:** 1382–5.
2. Rumpf KW, *et al.* Association of ethylene-oxide-induced IgE antibodies with symptoms in dialysis patients. *Lancet* 1985; **ii:** 1385–7.
3. Röckel A, *et al.* Ethylene oxide hypersensitivity in dialysis patients. *Lancet* 1986; **i:** 382–3.
4. Leitman SF, *et al.* Allergic reactions in healthy plateletpheresis donors caused by sensitization to ethylene oxide gas. *N Engl J Med* 1986; **315:** 1192–6.
5. Muylle L, *et al.* Anaphylactoid reaction in platelet-pheresis donor with IgE antibodies to ethylene oxide. *Lancet* 1986; **ii:** 1225.
6. Nicholls A. Ethylene oxide and anaphylaxis during haemodialysis. *BMJ* 1986; **292:** 1221–2.
7. Moneret-Vautrin DA, *et al.* High risk of anaphylactic shock during surgery for spina bifida. *Lancet* 1990; **335:** 865–6.
8. Verraes S, Michel O. Occupational asthma induced by ethylene oxide. *Lancet* 1995; **346:** 1434–5.

Pregnancy. A study[1] of female staff responsible for sterilising instruments was carried out in all general hospitals in Finland. The incidence of spontaneous abortion (analysed according to employment at the time of conception and corrected for maternal age, parity, decade of pregnancy, smoking, and consumption of alcohol and coffee) was significantly increased in those exposed to ethylene oxide during pregnancy compared with those not so exposed. This study provoked criticism,[2,3] and the authors conceded that the study was not large enough to compare abortion rates and known ethylene oxide concentrations.[4] A retrospective analysis[5] of 32 dental assistants who had been exposed to ethylene oxide during pregnancy suggested that, after adjusting for age, the risk of spontaneous abortions and preterm or post-term births may have been more than doubled.

1. Hemminki K, *et al.* Spontaneous abortions in hospital staff engaged in sterilising instruments with chemical agents. *BMJ* 1982; **285:** 1461–3.
2. Gordon JE, Meinhardt TJ. Spontaneous abortions in hospital sterilising staff. *BMJ* 1983; **286:** 1976.
3. Austin SG. Spontaneous abortions in hospital sterilising staff. *BMJ* 1983; **286:** 1976.
4. Hemminki K, *et al.* Spontaneous abortions in hospital sterilising staff. *BMJ* 1983; **286:** 1976–7.
5. Rowland AS, *et al.* Ethylene oxide exposure may increase the risk of spontaneous abortion, preterm birth, and postterm birth. *Epidemiology* 1996; **7:** 363–8.

Pharmacokinetics

Ethylene oxide gas is rapidly absorbed through the lungs and distributed throughout the body. Percutaneous absorption can occur from aqueous solutions. It is rapidly metabolised by hydrolysis or conjugation with glutathione.

Uses

Ethylene oxide is a bactericidal and fungicidal gaseous disinfectant that is effective against most micro-organisms, including viruses. It is also sporicidal. It is used for the gaseous sterilisation of heat-labile pharmaceutical and surgical materials that cannot be sterilised by other means.

Ethylene oxide forms explosive mixtures with air; this may be overcome by using mixtures containing 10% ethylene oxide in carbon dioxide, or by removing at least 95% of the air from the apparatus before admitting either ethylene oxide or a mixture of 90% ethylene oxide in carbon dioxide. Alternatively, non-flammable