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Formaldehyde-releasers

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Review Article

Formaldehyde-releasers: relationship to formaldehyde contact allergy. Metalworking fluids and remainder. Part 1

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This is part of a series of review articles on formaldehyde-releasers and their relationship to formaldehyde contact allergy. Formaldehyde-releasers used in metalworking fluids (MWF) and a group of releasers not presented in previous articles are discussed. Here, in *Part 1* of the article, there is a short overview of the composition and functions of MWF, the function of biocides in them, and adverse reactions to MWF. In addition, the releasers in MWF that have caused contact allergy are presented with CAS, synonyms, molecular formula, chemical structure, applications, patch test studies, and amount of formaldehyde released by them.

In *Part 2* of the article, the relationship between formaldehyde-releasers used in MWF and formaldehyde contact allergy is discussed as are data on miscellaneous releasers not previously presented, followed by a discussion of *Parts 1* and *2* of the article.

Key words: formaldehyde-releasers; metalworking fluids; formaldehyde; contact allergy © John Wiley & Sons A/S, 2010.

Accepted for publication 17 January 2010

This is part of a series of review articles on formaldehyde and formaldehyde-releasers. Previous publications presented an inventory of formaldehyde-releasers and discussed contact allergy to formaldehyde (1), formaldehyde-releasers in cosmetics (2, 3), and formaldehyde-releasers used in textiles as durable-press chemical finishes (4). The current review is presented in two parts. *Part 1* presents a short overview of the composition and functions of metalworking fluids (MWF), the function of biocides in them and adverse reactions to MWF. In addition, the releasers in MWF that have caused contact allergy are presented with CAS, synonyms, molecular formula, chemical structure, applications, patch test studies, and amount of formaldehyde released by them.

In *Part 2*, the relationship between formaldehyde-releasers used in MWF and formaldehyde contact

Other terminologies used to describe metalworking fluids have included: cutting oils, grinding oils, honing oils, soluble oils, suds, slurry water, lubricants, coolants, neat oils, and mineral oils (5).

allergy is discussed as are data on miscellaneous releasers not previously presented, followed by a discussion of *parts 1* and *2* of the article together.

Formaldehyde-Releasers Used in Metalworking Fluids

Composition and functions of metalworking fluids

The functions of MWF* are primarily those of cooling and lubrication. For these purposes, MWF are applied at the interface of the metal workpiece and the cutting edge of the machine tool. Additional advantages accrued by the use of MWF are improvement of the workpiece surface finish, prolongation of tool life, removal of metal chips which are produced during metalworking operations, and reduction of power consumption (5). Traditionally, MWF may be classified as insoluble (neat) oils or soluble oils. Neat oils are often mineral oils, but can also be of animal, vegetable, or synthetic origin and contain additives. Soluble oils are usually oil in water emulsions, but sometimes true aqueous solutions.

Soluble oils contain a number of additives, such as emulsifiers, buffers, stabilizers, antifog-additives, tensides, solubility enhancers, lubricants, extreme-pressure additives, corrosion inhibitors, coupling agents (which are needed to stabilize the emulsion at high temperatures and increase the ability of the soluble oil to disperse easily in water), anti-foam agents, hard-water stabilizers, dyes, fragrances, and biocides (bactericides and fungicides) (5–7).

Function of biocides in MWF

Biocides, which include the formaldehyde-releasers discussed here, are mixed into water-soluble oils to inhibit the overgrowth of bacterial and fungal populations, including *Pseudomonas* species, anaerobic sulfate reducers (*Desulfovibrio desulfuricans*), and fungi imperfecti including *Fusarium* species, *Cephalosporium* species, and the *Candida* species. Overgrowth of these organisms, which occurs particularly at oil–water interfaces, is responsible for problems of foul odour ('Monday morning stink'), and results in decreased tool life (metal corrosion), loss of cutting oil function, increased frictional heat, increased power consumption, and rust (5). Bacterial growth in these fluids can also cause emulsion breakdown, poor surface finish, excessive solid loads on filters and clarifiers (i.e. slimes and deposits), and discolourations (8).

Adverse reactions to MWF

Occupational hand dermatitis is common in metalworkers exposed to MWF. In several studies, the prevalence or 3-year incidence of hand eczema was found to be 20–25% (9). Irritant contact dermatitis is more frequently observed than allergic contact dermatitis. Skin irritation by MWF is not only caused by wet work but also by the alkaline pH usually ranging from 8.5 to 9.6, and by emulsifiers and biocides in the fluids. Irritant dermatitis promotes and may precede contact sensitization, often caused by biocides, particularly formaldehyde-releasers (6, 7, 10). The occurrence of adverse effects to the worker from overgrowth of spoilage organisms is remarkably infrequent; cellulitis, furunculosis, induction of infectious eczematoid dermatitis, and secondary infection of hand dermatitis have not been found at increased frequency (11). Thus, the purpose of biocides is to preserve cutting fluids rather than to protect the worker (12). Contact with MWF may also induce allergic respiratory diseases (10).

Key Data on Formaldehyde-Releasers Used in Metalworking Fluids

In this section, formaldehyde releasing biocides commonly used in MWF are presented with their

CAS numbers, synonyms, chemical structures, molecular formulas, applications, and frequency of sensitization.

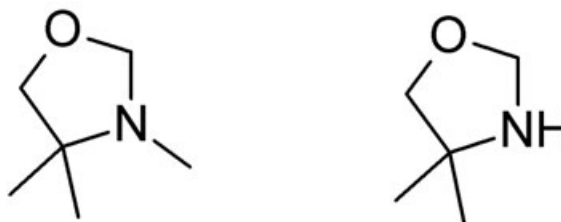
BIOBAN[®] CS-1135

CAS. 81099-36-7 (mixture); 51200-87-4 (4,4-dimethyloxazolidine); 75673-43-7 (3,4,4-trimethyloxazolidine)

Synonyms. Mixture of 4,4-dimethyloxazolidine and 3,4,4-trimethyloxazolidine. The INCI name for 4,4-dimethyloxazolidine is dimethyl oxazolidine.

Molecular formula. C₆H₁₃NO; C₅H₁₁NO

Chemical structure.



Applications. Bioban[®] CS-1135 is used as bactericide in MWF, fluids for oil and gas production, and mineral slurries. It is also used as an in-can preservative for paints, inks, emulsions, non-food contact adhesives, surfactants, and in consumer, household, and institutional products such as dishwashing and laundry detergents, fabric softeners, household and industrial cleaners and polishes. Also it provides quick clean-up for contaminated process water and finished formulations. Typical use concentrations of Bioban[®] CS-1135 range from 400 to 5000 ppm, depending on the type of product. Dimethyl oxazolidine may also be present in cosmetic products and is permitted in the European Union in a maximum concentration of 0.1%, which is also the typical use level.

Frequency of sensitization. There is only one small study in which Bioban[®] CS-1135 has been investigated in consecutive patients patch tested for suspected contact dermatitis (not further selected). Anderson et al. tested 210 such patients with Bioban[®] CS-1135 1% petrolatum and found 13 patients with a positive patch test reaction, a staggering 6.2% (13). As most of the patients co-reacted to formaldehyde, which had a very high 8.1% response rate, most reactions may have been caused by formaldehyde sensitivity (discussed in Part 2). Most of the test reactions were only weakly positive, so some may have been false-positive.

The experience with testing Bioban[®] CS-1135 in selected patient groups is limited in geographic area, most studies having been performed by the IVDK (Informationsverbund Dermatologischer Kliniken, Germany, Austria, Switzerland) (Table 1). In several

Table 1. Frequency of sensitization to Bioban® CS-1135, Bioban® CS-1246, and Bioban® P-1487 in selected patients^a

| Country | Years of study | Bioban CS-1135 | | Bioban CS-1246 | | Bioban P-1487 | | Mode of selection | Reference |
|-------------------|----------------|----------------|---------------------|----------------|---------------------|------------------|---------------------|---|-----------|
| | | Number tested | Percentage positive | Number tested | Percentage positive | Number tested | Percentage positive | | |
| IVDK | 2004–2005 | 139 | 5 | 139 | 2.9 | 95 | 0 | Patients with suspected MWF dermatitis | 14 |
| IVDK | 2002–2003 | 198 | 4.5 | 197 | 2.5 | 37 ^b | 0 | Patients with suspected MWF dermatitis | 6 |
| IVDK | 2000–2002 | | | | | 152 | 1.3 | Patients with present or past occupational exposure to MWF | 15 |
| | | | | | | 182 | 0.5 | | |
| Israel | 1999–2003 | 175 | 1.7 | 175 | 1.1 | 175 ^b | 0 | Patients with suspected occupational contact dermatitis working with oil and cooling fluids | 16 |
| Germany | 1992–2003 | | | 133 | 4.5 | 133 | 3.0 | Metalworkers with suspected occupational contact dermatitis | 17 |
| IVDK | 2000–2002 | 185 | 1.1 | | | | | Patients with present or past occupational exposure to MWF | 15 |
| IVDK | 1999–2001 | 130 | 3.8 | 106 | 0.9 | | | Metalworkers exposed to water-based MWF | 7 |
| IVDK ^c | 1992–1998 | 3486 | 1.4 | 3389 | 0.8 | 3496 | 1.8 | Unknown: 'various occupations' | 18 |
| IVDK ^c | 1992–1995 | 1921 | 1.1 | 1890 | 0.8 | 1920 | 2.0 | NS. Selected from 35062 patients | 20 |
| IVDK ^c | 1990–1994 | 1760 | 1.1 | 1759 | 0.8 | 1754 | 1.9 | NS. Selected from 28349 patients | 21 |
| IVDK ^c | 1990–1994 | 408 | 1.5 | 408 | 2.0 | 408 | 2.2 | Metalworkers with suspected occupational hand dermatitis | 18 |
| IVDK ^c | 1990–1993 | 1112 | 1.4 | 1111 | 1.1 | 1112 | 2.2 | NS. Approximately 30% were patients working with metals and metal objects | 22 |
| Spain | 1991–1993 | | | | | 230 ^d | 3.0 | Metalworkers in contact with MWF suspected of occupational dermatitis | 23 |
| Spain | 1990–1991 | 72 | 1.4 | 72 | 1.4 | | | Metalworkers | 19 |
| UK | 1986–1987 | | | | | 174 ^e | 6.9 | Patients with suspected MWF dermatitis | 24 |

IVDK, Informationsverbund Dermatologischer Kliniken, Germany, Austria, Switzerland; NS, not stated;

^aTest concentration for the Biobans 1% pet. unless otherwise indicated.

^bTest concentration 0.5% pet.

^cIt may be assumed that there is an overlap in the patient populations in these five IVDK studies.

^dTest concentration 1% in olive oil.

^eTest concentration not mentioned.

of these studies, there may have been an overlap in patient population. In eight patch test studies performed in metalworkers having contact with MWF (numbers of patients ranging from 72 to 408), the prevalence of sensitization varied from 1.1% to 5% (6, 7, 14–19). In larger, less selected (and ill defined) groups, 1.1–1.4% had a positive patch test reaction (18, 20–22). The relevance of the reactions was never stated.

BIOBAN[®] CS-1246

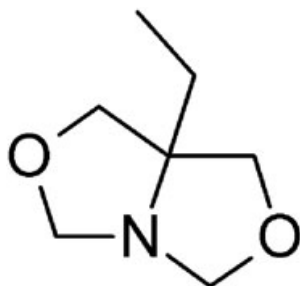
CAS. 7747-35-5

Synonyms. 1-aza-5-ethyl-3,7-dioxabicyclo(3.3.0)octane; 5-ethyl-1-aza-3,7-dioxabicyclo(3.3.0)octane; 7-ethylbicyclooxazolidine;

7a-ethyl-dihydro-1H,3H,5H-oxazolo(3,4-c)oxazole

Molecular formula. C₇H₁₃NO₂

Chemical structure.



Applications. BIOBAN[®] CS-1246 is used as bactericide in adhesives, consumer and household products (including dishwashing and laundry liquids, surface cleaners, and polishes), industrial products, wax and resin emulsions, inks, MWF, non-food contact adhesives, mineral slurries, paints and surfactants. Also used for leather tanning and permitted in cosmetics in the EU in a maximum concentration of 0.3%, which is also the typical maximum use level, depending on the type of product.

Frequency of sensitization to Bioban[®] CS-1246. There is only one small study in which Bioban[®] CS-1246 has been investigated in consecutive patients patch tested for suspected contact dermatitis (not further selected). Anderson et al. tested 210 such patients with Bioban[®] CS-1246 1% pet. and found 13 patients with a positive patch test reaction, a staggering 6.2% (13). As most of the patients co-reacted to formaldehyde, which had a very high 8.1% response rate, most reactions may have been caused by formaldehyde sensitivity (discussed in Part 2). Most of the test reactions were only weakly positive, so some may have been false-positive.

The experience with testing Bioban[®] CS-1246 in selected patient groups is limited in geographic area, most studies having been performed by the IVDK

(Table 1). In several of these studies, there may have been an overlap in patient population. In seven patch test studies performed in metalworkers having contact with MWF (numbers of patients ranging from 72 to 408), the prevalence rates of sensitization varied from 0.9% to 3.0% (6, 7, 14, 16–19). In larger, less selected (and ill defined) groups 0.8–1.1% had a positive patch test reaction (18, 20–22). The relevance of the reactions was never stated.

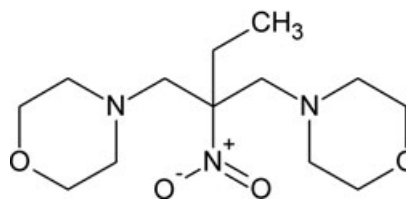
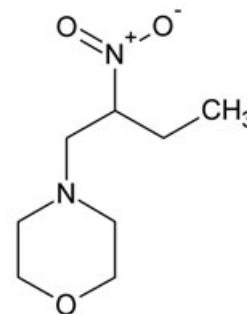
BIOBAN[®] P-1487

CAS. 37304-88-4

Synonyms. morpholine, 4,4'-(2-ethyl-2-nitro-1,3-propanediyl)bis-, mixt. with 4-(2-nitrobutyl)morpholine; mixture of 4-(2-nitrobutyl)morpholine and 4,4'-(2-ethyl-nitrotri-methylene)dimorpholine

Molecular formula. C₁₃H₂₅N₃O₄; C₈H₁₆N₂O₃

Chemical structure.



Applications. Bioban[®] P-1487 is a broad-spectrum bactericidal and fungicidal agent used in MWF, paints, inks, emulsions, slurries, non-food contact adhesives, die cast lubricants, mold-release agents, and also in consumer, household and institutional products.

Typical use concentrations are 100–1000 ppm (0.01–0.1%), depending on the type of product. The concentration used in machines is about 0.1%. When the morpholines in Bioban[®] P-1487 are exposed to high temperatures, there is a risk of formation of nitrosamines, which are well-known carcinogens (25). For this reason, the use of Bioban[®] P-1487 in MWF is prohibited since 1993 in Germany (18, 21).

Frequency of sensitization. In Malmö, Sweden, Bioban[®] P-1487 was tested in 1102 consecutive patients in a concentration of 0.5% w/v in

ethanol/aqua 50/50 vol and 17 patients (1.5%) had a positive reaction. At retesting, the same results were obtained. None of these 17 patients were also allergic to formaldehyde and in only one there was contact with MWF (26). The relevance of the patch test reactions remained unknown in the other 16 patients. Afterwards, 12 of 17 allergic patients were tested with the separate ingredients 4-(2-nitrobutyl)morpholine 0.5% w/v ethanol and 4,4'-(2-ethyl-nitrotrimethylene)dimorpholine 0.76% w/v ethanol, but now only 4 patients reacted, of which 2 reacted to both ingredients. Possible explanations for this discrepancy were given as differences in bioavailability between when the active ingredients were tested separately and when they are present in Bioban[®] P-1487, a sensitizing contaminant in Bioban[®] P-1487, compound allergy, or an additive or synergistic reaction when both ingredients are tested together in Bioban[®] P-1487 (26). Anderson et al. tested 210 consecutive patients with Bioban[®] P-1487 1% pet. and found only one (0.5%) positive reaction (13).

The experience with testing Bioban[®] P-1487 in selected patient groups is summarized in Table 1. Most recent studies have been performed by the IVDK. In several of these studies, there may have been an overlap in patient population. In eight patch test studies performed in metalworkers having contact with MWF (number of patients ranging from 72 to 408), the prevalence of sensitization varied from 0% to 6.9% (6, 14–16, 18, 19, 23, 24). In the past 15 years, prevalences have not exceeded 2.2%. In larger, less selected (and ill defined) groups, 1.8–2.2% had a positive patch test reaction (18, 20–22). The relevance of the reactions was ascertained in one study only: one out of nine (11%) patients was proven to have contact with Bioban[®] P-1487 (18).

Guinea pigs maximization tests have shown that 4,4'-(2-ethyl-nitrotrimethylene) dimorpholine is a stronger sensitizer than 4-(2-nitrobutyl)morpholine. Contact allergy to 4,4'-(2-ethyl-nitrotrimethylene) dimorpholine nearly always results in cross-sensitization to 4-(2-nitrobutyl)morpholine. With primary sensitization to 4-(2-nitrobutyl)morpholine, cross-reactions to the other compounds do occur but probably are less (47).

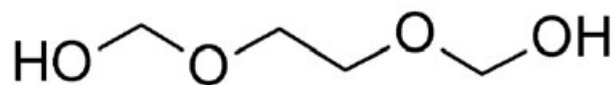
1,6-Dihydroxy-2,5-dioxahexane

CAS. 3586-55-8

Synonyms. dimethylol glycol (INCI); 2,5-dioxahexane-1,6-diol; [1,2-ethanediy] bis(oxy) bismethanol; (ethylenedioxy)dimethanol; ethyleneglycoldiformal; 2-(hydroxymethoxy)ethoxymethanol

Molecular formula. C₄H₁₀O₄

Chemical structure.



Applications. 1,6-Dihydroxy-2,5-dioxahexane is used as biocide and preservative in MWF, paints, and rinse-off cosmetics.

Frequency of sensitization. This biocide is mentioned in only two publications, a multicentre study on contact allergy due to components of MWF of the German Contact Dermatitis Research Group (DKG) (15) and a case report (27). In the DKG study, 1,6-dihydroxy-2,5-dioxahexane 1% pet. was tested in 201 patients, resulting in just one doubtful reaction (15). In the case report, a man working with MWF reacted upon patch testing to his MWF, to several formaldehyde-releasers and (in a second session) to formaldehyde. The manufacturer indicated that the MWF contained 1,6-dihydroxy-2,5-dioxahexane. The biocide itself, however, was not tested (27).

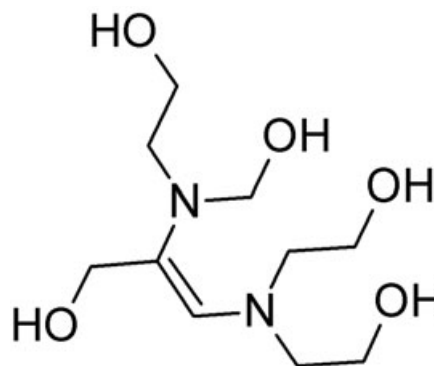
FORCIDE[®] 78 I

CAS. 77044-78-1 (see Table 2 in Ref. 1 for more information)

Synonyms. 2-hydroxymethylaminoethanol-tri-*N*-ethylhydroxy-2-aminomethylene; 3-[bis(2-hydroxyethyl)amino]-2-[(2-hydroxyethyl)(hydroxymethyl)amino]-2-propen-1-ol

Molecular formula. C₁₀H₂₂N₂O₅

Chemical structure.



Applications. FORCIDE[®] 78 I is used as biocide in MWF.

Contact allergy. An engine fitter with hand eczema was sensitized to formaldehyde and a formaldehyde-releaser (described as Parmetol[®] K50). After the biocide had been replaced with Forcicide[®] 78, his hand eczema persisted. A patch test to Forcicide[®] 78 5% oo was positive, as was formaldehyde. Analysis showed formaldehyde to be present in Forcicide[®] 78. However, there were several other strongly positive

Table 2. Frequency of sensitization to *N,N'*-methylenebis(5-methyloxazolidine) in selected patients

| Country | Years of study | Number of patients tested | Test concentration and vehicle | Positive percentage | Current relevance | Mode of selection | Reference |
|-------------------|----------------|---------------------------|--------------------------------|---------------------|-------------------|---|-----------|
| IVDK | 2004–2005 | 102 | 1% pet. | 2.9 | NS | Patients with suspected MWF dermatitis | 14 |
| United Kingdom | 1998–2005 | 318 | 1% pet. | 4.7 | 47% | Patients suspected of occupational dermatitis in contact with MWF | 29 |
| IVDK | 2002–2003 | 198 | 1% pet. | 4.5 | NS | Patients with suspected MWF dermatitis | 6 |
| Germany | 1992–2003 | 134 | 1% pet. | 6.7 | NS | Metalworkers with suspected occupational contact dermatitis | 17 |
| IVDK | 1999–2001 | 130 | 1% pet. | 2.3 | NS | Metalworkers exposed to water-based MWF | 7 |
| IVDK ^a | 1992–1995 | 1786 | 1% pet. | 3.1 | NS | NS. Selected from 35 062 patients | 20 |
| IVDK ^a | 1990–1994 | 1522 | 1% pet. | 3.0 | NS | NS. Selected from 28 349 patients | 21 |
| IVDK ^a | 1990–1993 | 940 | 1% pet. | 3.5 | NS | NS. Approximately 30% were patients working with metals and metal objects | 22 |

^aIt may be assumed that there is an overlap in the patient populations in these three IVDK studies; IVDK, Informationsverbund Dermatologischer Kliniken, Germany, Austria, Switzerland; NS, not stated.

patch test reactions (risk of false-positivity because of excited skin syndrome); the test was not repeated and no controls were performed (28).

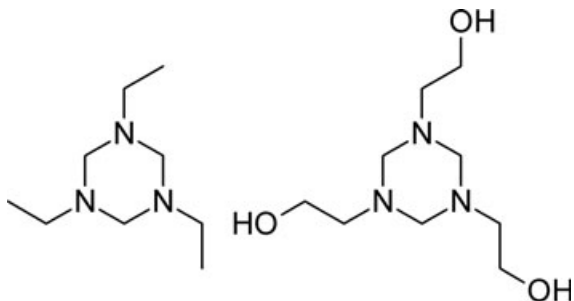
FORCIDE 78 II

CAS. 4719-04-4 [tris(*N*-hydroxyethyl)hexahydro-triazine] and 7779-27-3 (hexahydro-1,3,5-triethyl-1,3,5-triazine). Forcide 78 (II) is a mixture of tris(*N*-hydroxyethyl)hexahydrotriazine (see below) and hexahydro-1,3,5-triethyl-1,3,5-triazine.

Synonyms. hexahydro-1,3,5-triethyl-s-triazine; triethyl-trimethylenetriamine (see Table 2 in reference (1) for additional information).

Molecular formula. C₉H₂₁N₃

Chemical structure.



Applications. FORCIDE 78 II is used as a preservative.

Relationship to formaldehyde contact allergy. At Gentofte Hospital, Denmark, in 1982/1983 Forcide[®] 78 (II) 2% pet. was tested on 678 consecutive patients and 4 (0.6%) gave a positive reaction. All four were also allergic to formaldehyde and three also reacted to other formaldehyde-releasers. The source of sensitization was not mentioned,

but it was stated that these patients had not been sensitized by MWF (30).

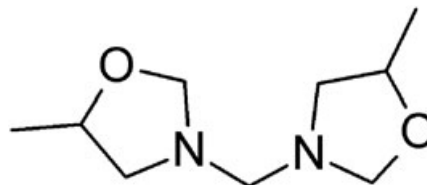
N,N'-methylenebis(5-methyloxazolidine)

CAS. 66204-44-2

Synonyms. 3,3'-methylenebis(5-methyloxazolidine)

Molecular formula. C₉H₁₈N₂O₂

Chemical structure.



Applications. *N,N'*-methylenebis(5-methyloxazolidine) is used as biocide in MWF, in nylon spin finish (31), technical emulsions, and system cleansers.

Frequency of sensitization. In five patch test studies performed in metalworkers having contact with MWF (numbers of patients ranging from 102 to 318), the prevalence of sensitization varied from 2.3% to 6.7% (Table 2) (6, 7, 14, 17, 29). In larger, less selected (and ill defined) groups 3.0–3.5% had a positive patch test reaction (20–22). The relevance of the reactions was stated in only one study and was found to be 47% (7 of 15 patients) in an investigation from the United Kingdom among 318 patients suspected of occupational dermatitis in contact with MWF (29).

At the Finnish Institute of Occupational Health, there were 7 positive patch test reactions to *N,N'*-methylenebis(5-methyloxazolidine) 1% pet. among

1166 patients suspected of occupational contact dermatitis tested between 2001 and 2007, but it was not stated how many patients had been tested with the releaser. Two of these patients were exposed to an MWF containing *N,N'*-methylenebis(5-methyloxazolidine) (32).

4,4'-Methylenedimorpholine

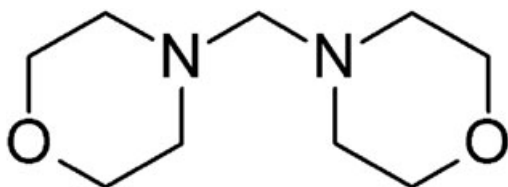
CAS. 5625-90-1

Synonyms. bismorpholinomethane; dimorpholinomethane; 4,4'-methylenebis-morpholine; *N,N'*-methylenebismorpholine

Applications. biocide in MWF

Molecular formula. C₉H₁₈N₂O₂

Chemical structure.



Frequency of sensitization. There appear to be no reports of testing 4,4'-methylenebis(morpholine) in consecutive dermatitis patients. One hundred and forty-four metalworkers exposed to MWF were patch tested by the members of the IVDK in 2004–2005 with 4,4'-methylenebis(morpholine) 1% w/w pet. and 7 (4.9%) had a positive reaction (14). The maximum formaldehyde concentration in the patch test preparation was calculated to be about 0.16% (1600 ppm). Because of this low concentration and the fact that only two of seven patients reacted to formaldehyde, it was considered unlikely that the positive patch test reactions indicated formaldehyde allergy only. The relevance of the positive reactions was not ascertained (14). At the Finnish Institute of Occupational Health, there were 6 positive patch test reactions to 4,4'-methylenebis(morpholine) 1% pet. among 1166 patients suspected of occupational contact dermatitis tested between 2001 and 2007, but it was not stated how many patients had been tested with the releaser. One of these patients was exposed to an MWF containing 4,4'-methylenebis(morpholine) (32).

Propyleneglycol hemiformal

CAS, synonyms, applications, molecular formula, chemical structure. no data available.

In a group of 1536 patients tested with an industrial biocide test series, 10 (0.7%) had a positive patch test reaction to propyleneglycol hemiformal 1% pet. (21). In an earlier IVDK data analysis including 951 of these patients, 8 (0.8%) had a

positive patch test reaction to propyleneglycol hemiformal 1% pet. (22). In both studies, all positive patients co-reacted to formaldehyde.

This compound, for which we could not find any information on CAS, synonyms, molecular formula, or chemical structure, was patch tested as part of the DKG industrial biocide test series until spring 1995. It was removed because all patients reacting to propyleneglycol hemiformal also reacted to formaldehyde and/or benzylhemiformal and it was no longer available as patch test preparation. Most likely, this compound is no longer in use.

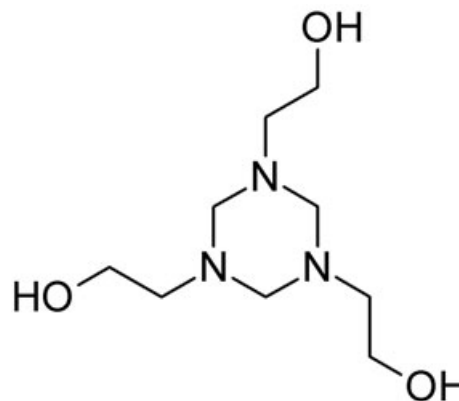
Tris(N-hydroxyethyl)hexahydrotriazine

CAS. 4719-04-4

Synonyms. triazinetriethanol; hexahydro-1,3,5-tris(hydroxyethyl)triazine; 1,3,5-triazine-1,3,5(2H,4H,6H) triethanol; trihydroxyethylhexahydro s-triazine; 1,3,5-trihydroxyethylhexahydrotriazine; Grotan[®] BK.

Molecular formula. C₉H₂₁N₃O₃

Chemical structure.



Applications. *Tris(N-hydroxyethyl)hexahydrotriazine* is used as bactericide and fungicide in adhesives, industrial cleaning systems, polymer emulsions, latex emulsions, soluble lubricants, paints and MWF, in oilfield water systems, drilling muds, and in workover and completion fluids. Also used in in-can preservation of water-based products such as paints, glues, emulsions, inks, pigment dispersions, cutting oils and water-soluble cleaners, as well as in fuel protection during storage.

Frequency of sensitization. In four studies tris(*N*-hydroxyethyl)hexahydrotriazine (in varying concentrations and vehicles) has been patch tested in patients suspected of contact dermatitis (Table 3) (33–36). Sensitization rates ranged from 0.3% to 4.5%. The latter high rate may be caused by a high rate of formaldehyde sensitization in the United States patch test population (discussed in Part 2) (33). In one study from the United

Table 3. Frequency of sensitization to tris(*N*-hydroxyethyl)hexahydrotriazine in patients suspected of contact dermatitis

| Country | Years of study | Number of patients | Test concentration and vehicle | Positive percentage | Current relevance percentage | Comments/setting | Reference |
|-----------------|----------------|--------------------|--------------------------------|---------------------|------------------------------|--------------------------|-----------|
| United States | 2001–2005 | 3709 | 1% pet. | 4.5 | 60 | Mayo Clinic, 3 locations | 33 |
| The Netherlands | 1985 | 501 | 1% aqua | 0.6 | NS | Multicentre study | 34 |
| Denmark | 1983–1984 | 671 | 2% pet. | 0.3 | NA | | 35 |
| Denmark | 1976–1977 | 694 | 2% aqua | 2 | NA | Multicentre study | 36 |

NA, not ascertained; NS, not specified.

States, relevance was claimed for 60% of the cases (without specification) (33).

The data on patch testing in *selected* groups of patients are summarized in Table 4. In six patch test studies performed in metalworkers having contact with MWF (numbers of patients ranging from 39 to 230), the prevalence of sensitization varied from 0% to 8.1% (Table 4) (6, 7, 14, 16, 17, 23). The high prevalences were limited to a very small study of 39 patients (14) and a study of over 25 years ago, when the patch test preparations were prepared by authors themselves (23). These were also the only two studies where a patch test preparation of tris(*N*-hydroxyethyl)hexahydrotriazine in water was used. In larger, less selected (and ill defined)

groups, 0.6–3.4% had a positive patch test reactions (20–22, 37, 38). The relevance of the reactions was never stated.

At the Finnish Institute of Occupational Health, there were 24 positive patch test reactions to tris(*N*-hydroxyethyl)hexahydrotriazine tested 1% in water among 1166 patients suspected of occupational contact dermatitis tested between 2001 and 2007, but it was not stated how many patients had been tested with the releaser. Two of these patients were exposed to a MWF containing tris(*N*-hydroxyethyl)hexahydrotriazine (32).

The literature from before 1978 has been reviewed by Rycroft (8). Contact allergy from tris(*N*-hydroxyethyl)hexahydrotriazine (which at that time was almost invariably called Grotan®)

Table 4. Frequency of sensitization to tris(*N*-hydroxyethyl)hexahydrotriazine in selected patients

| Country | Years of study | Number of patients tested | Test concentration and vehicle | Positive percentage | Current relevance percentage | Mode of selection | Reference |
|-------------------|----------------|---------------------------|--------------------------------|---------------------|------------------------------|---|-----------|
| IVDK | 2004–2005 | 99 | 1% pet. | 0 | NS | Patients with suspected metalworking | 14 |
| | | 37 | 1% aqua | 8.1 | NS | Fluid dermatitis | 14 |
| IVDK | 2002–2003 | 199 | 1% pet. | 1.5 | NS | Patients with suspected MWF dermatitis | 6 |
| Israel | 1999–2003 | 175 | 1% aqua | 1.7 | NSP | Patients with suspected occupational contact dermatitis working with oil and cooling fluids | 16 |
| Germany | 1992–2003 | 134 | 1% pet. | 2.2 | NS | Metalworkers with suspected occupational contact dermatitis | 17 |
| IVDK | 1999–2001 | 137 | 1% pet. | 0.7 | NS | Metalworkers exposed to water-based MWF | 7 |
| USA | 1998–2000 | 713 | 1% pet. | 3.4 | NS | NS. Selected from 1324 patients | 37 |
| IVDK ^a | 1992–1995 | 2081 | 1% pet. | 0.9 | NS | NS. Selected from 35 062 patients | 20 |
| IVDK ^a | 1990–1994 | 1722 | 1% pet. | 1.0 | NS | NS. Selected from 28 349 patients | 21 |
| IVDK ^a | 1990–1993 | 1120 | 1% pet. | 1.4 | NS | NS. Approximately 30% were patients working with metals and metal objects | 22 |
| Spain | 1981–1983 | 230 | 1% aqua | 7.0 | NS | Metalworkers with possible occupational dermatitis | 23 |
| France | 1981 (?) | 465 | 1% pet. | 0.6 | NS | Patients suspected of allergy to cosmetics, drugs, industrial products, or clothes | |

IVDK, Informationsverbund Dermatologischer Kliniken, Germany, Austria, Switzerland; NS, not stated; NSP, not specified for individual allergens.

^aIt may be assumed that there is an overlap in the patient populations in these three IVDK studies.

BK) was first reported in 1964 from West Germany. Of 2156 workers in contact with the biocide, 144 reacted to a mixture of 1% Grotan® BK in water with another triazine bactericide. These 144 were later tested with Grotan® BK at patch test concentrations of 0.5% and 1% in water and 22 gave positive reactions to the lower concentration, whereas 38 (1.8%) of the total exposed population reacted to the 1% test substance (39). In the same year, Rietschel (40) reported on 152 grinders with or without dermatitis of the hands who were patch tested with Grotan® BK 0.15% in water. He found six positive reactions in each group, representing 12% of those with dermatitis and 6% of those without. On the other hand, Schneider et al. reported patch tests carried out in a total of over 200 workers in contact with Grotan® BK in soluble oil emulsions, 18% of who had dermatitis. Patch tests concentrations of 0.1–1% Grotan® BK in water gave negative results in all subjects (41).

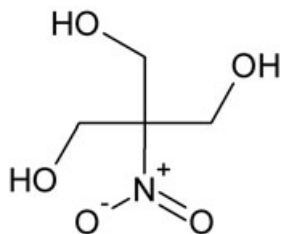
Tris(hydroxymethyl)nitromethane

CAS. 126-11-4

Synonyms. 2-(hydroxymethyl)-2-nitro-1,3-propanediol; nitromethylidynetrimethanol; trimethylolnitromethane; tris nitro

Molecular formula. C₄H₉NO₅

Chemical structure.



Applications. *Tris(hydroxymethyl)nitromethane* is used as antimicrobial agent in industrial applications such as household and institutional products, oil field water systems and drilling muds, recirculating water systems, chemical toilets, and MWF. The chemical structure of *tris(hydroxymethyl)nitromethane* is similar to that of 2-bromo-2-nitropropane-1,3-diol; it differs from 2-bromo-2-nitropropane-1,3-diol only by the substitution of a methoxy group at position 2 for a bromine atom. *Tris(hydroxymethyl)nitromethane* is a possible decomposition product of 2-bromo-2-nitropropane-1,3-diol (together with formaldehyde and bromonitroethanol). Heat and alkaline solutions hasten this process (12, 42).

Frequency of sensitization. There appear to be no reports of testing *tris(hydroxymethyl)nitromethane* in consecutive dermatitis patients. In five studies

in *selected* patients (in three studies patients with suspected MWF dermatitis) prevalence rates were very low with 0–0.6% (Table 5) (6, 14, 16, 20, 22).

Two machinists with hand eczema in contact with the preservative had positive patch test reactions to *tris(hydroxymethyl)nitromethane* 1% pet. One patient also reacted to formaldehyde, but at retesting the reaction could not be reproduced. Nevertheless, this patient also reacted to a number of other formaldehyde-releasers including benzylhemiformal, imidazolidinyl urea, *tris(N-hydroxyethyl)hexahydrotriazine* and 2-bromo-2-nitropropane-1,3-diol (12). The use of *tris(hydroxymethyl)nitromethane* in MWF has been prohibited since 1993 in Germany because it promotes the generation of carcinogenic nitrosamines (21).

The Amount of Formaldehyde Released by Formaldehyde Donors Used in MWF

There is very little data available on the amount of formaldehyde that will be released by formaldehyde donors used in MWF. This amount depends on the nature of the releaser, its concentration, the pH of the product, the temperature (the higher the temperature the more formaldehyde is present in solution after constant time) (43), the age of the product (upon storage increased levels of formaldehyde will be observed), the level of microbial contamination, and the other constituents of the products containing the releaser (7, 20, 44, 45).

MWF often circulate in machines for many weeks and may be heated for short periods of time. This may influence the amount of formaldehyde drastically, so investigations with fresh unaged preparations will give results not representative for the actual usage conditions. In addition, biocides may also be added later in the work process.

Bioban® CS-1135 can liberate one molecule formaldehyde/mol Bioban® CS-1135 and Bioban® CS-1246 can liberate two. Bioban® P-1487, *tris(hydroxymethyl)nitromethane*, and *N-methylolchloroacetamide* are said to release little formaldehyde, especially at higher pH levels (20).

In a hand cleanser preserved with 0.2% *tris(N-hydroxyethyl)hexahydrotriazine*, 350 ppm free formaldehyde was found (43). Andersen et al. (30) analysed the materials they used for guinea pigs maximization tests for the presence of formaldehyde and found the amounts shown in Table 6. It is clear that aqueous preparations contain far more (up to a factor 15) free formaldehyde than their pet. counterparts, which is to be expected, as formaldehyde is released by hydrolysis. If the amount of *releasable* formaldehyde in 1% pet. test substances of *tris(N-hydroxyethyl)hexahydrotriazine* and *N,N'-methylenebis(5-methyloxazolidine)* is in

Table 5. Frequency of sensitization to tris(hydroxyethyl)nitromethane in selected patients

| Country | Years of study | Number of patients tested | Test concentration and vehicle | Positive percentage | Current relevance percentage | Mode of selection | Reference |
|-------------------|----------------|---------------------------|--------------------------------|---------------------|------------------------------|---|-----------|
| IVDK | 2004–2005 | 101 | 1% pet. | 0 | NS | Patients with suspected MWF dermatitis | 14 |
| IVDK | 2002–2003 | 153 | 1% pet. | 0 | NS | Patients with suspected MWF dermatitis | 6 |
| Israel | 1999–2003 | 175 | 1% pet. | 0.6 | NSP | Patients with suspected occupational contact dermatitis working with oil and cooling fluids | 16 |
| IVDK ^a | 1992–1995 | 2021 | 1% pet. | 0.2 | NS | NS. Selected from 35 062 patients | 20 |
| IVDK ^a | 1990–1993 | 1113 | 1% pet. | 0.3 | NS | NS. Approximately 30% were patients working with metals and metal objects | 22 |

IVDK, Informationsverbund Dermatologischer Kliniken, Germany, Austria, Switzerland; NS, not stated; NSP, not specified for individual allergens.

^aIt may be assumed that there is an overlap in the patient populations in these two IVDK studies.

Table 6. Analysis of formaldehyde release from test substances with formaldehyde donors used for maximization tests (30)

| Compound | Concentration | Vehicle | Percentage free formaldehyde (30) |
|--|---------------|---------|---|
| Forcide [®] 78 (II) [tris(<i>N</i> -hydroxyethyl)hexahydrotriazine + hexahydro-1,3,5-triethyl-1,3,5-triazine] ^a | 1% | aqua | 0.27 (2700 ppm) |
| | 1% | pet. | 0.02 (200 ppm) |
| Grotan BK [®] [80% tris(<i>N</i> -hydroxyethyl)hexahydrotriazine] | 'as is' | | 28.6 |
| | 25% | aqua | 7.76 |
| | 1% | saline | 0.30 (3000 ppm) |
| | 1% | pet. | 0.14–0.19 (1400–1900 ppm) (various batches) |
| | 0.5% | saline | 0.13 (1300 ppm) |
| | 0.1% | saline | 0.02 (200 ppm) |
| Grotan [®] OX [<i>N,N'</i> -methylenebis(5-methyloxazolidine)] ^a | 'as is' | | 46.6 |
| | 10% | aqua | 4.03 |
| | 1% | saline | 0.40 (4000 ppm) |
| | 0.5% | saline | 0.17 (1700 ppm) |
| | 0.1% | saline | 0.04 (400 ppm) |
| KM [®] 200 [tris(<i>N</i> -hydroxyethyl)hexahydrotriazine] ^a | 1% | aqua | 0.30 (3000 ppm) |
| | 1% | pet. | 0.02 (200 ppm) |
| | 1% | aqua | 0.30 (3000 ppm) |
| Preventol [®] D2 (mixture of hydroxymethylene and polyhydroxymethylene monobenzyl ether) ^a | 1% | aqua | 0.30 (3000 ppm) |
| | 1% | pet. | 0.24 (2400 ppm) |

^aConcentration active ingredients unknown, estimated to be approximately 60%.

the order of the concentration of free (*released*) formaldehyde in their aqueous counterparts, these would be high enough to induce positive patch test reactions in a number of patients allergic to formaldehyde (1). In Finland, in 2008 17 samples of MWF concentrates were analysed for skin sensitizers. Formaldehyde was detected in all 17. Three concentrates contained less than 0.01% of total formaldehyde. The others contained 0.08–1.3% of total formaldehyde ('free and easily released'). Four commercial formaldehyde releasing biocides containing *N,N'*-methylenebismorpholine (Acticide[®] EF), 4,4-dimethyl- and 3,4,4-trimethyloxazolidine (Bioban[®] CS-1135) and *N,N'*-methylenebis(5-methyloxazolidine) (Grotan[®] OX, Biocide[®] OX) and tris(*N*-hydroxyethyl)hexahydrotriazine

(Grotan[®] BK) were analysed for formaldehyde content and proved to contain 16–41% total formaldehyde (free formaldehyde was not measured) (46). We have not found data on the free formaldehyde content in fresh and used MWF in use dilutions.

Discussion

The data presented here will be discussed in a *Part 2* of this article.

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