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Recommendation to include methyldibromo glutaronitrile in the European standard patch test series

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The preservative methyldibromo glutaronitrilc (MDBGN) is used non-occupationally and occupationally. High contact allergy rates have been reported when tested in consecutive dermatitis patients as well as clinical cases with allergic contact dermatitis. Up till now there has been no agreement on which patch test preparation to use to trace contact allergy to MDBGN. From the year 2005 on, MDBGN at 0.5% w/w in petrolatum is recommended for the European standard patch test series. The choice of 0.5% is based on consideration of rates of contact allergy, doubtful and irritant reactions, as well as on information on clinical relevance represented by results of a repeated open application test, and patch test concentrations to diagnose allergic contact dermatitis from MDBGN in individual cases.

Key words: 1,2-dibromo-2,4-dicyanobutane; allergic contact dermatitis; CAS 35691-65-7; clinical relevance; contact allergy; Euxyl K400; methyldibromo glutaronitrile; preservative; Tektamer 38.

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A contact sensitizer should fulfil certain requirements to justify inclusion in a standard patch test series (1). Its exposure should not be confined to small groups or special occupations, and the contact allergy rate in routinely tested dermatitis patients should equal or exceed approximately 1% (1). Furthermore, the contact allergy should be clinically relevant in a substantial number of those with demonstrated contact allergy. Thus, thimerosal and gold are currently not candidates for the standard series, although being sensitizers with high contact allergy rates. On the other hand, the preservative methyldibromo glutaronitrile (MDBGN) is used non-occupationally and occupationally and high allergy rates have been reported, as well as clinical cases with allergic contact dermatitis.

However, there has been no agreement on which patch test preparation to use to trace contact allergy to MDBGN. In Table 1, 22 patch test preparations (2–35) to be used to trace contact allergy to and allergic contact dermatitis from MDBGN are listed. Recent studies within the European and Environmental Contact Dermatitis Research Group (EECDRG) and elsewhere have contributed results that have helped determine which test preparation to use. From the year 2005 on, MDBGN at 0.5% w/w in petrolatum (pet.) is therefore on behalf of the European Contact Dermatitis Society (ESCD) and the EECDRG recommended for the European standard patch test series (Table 2). The reasons for choosing this preparation follow.

For practical and stability reasons, pet. is often the preferable patch test vehicle for most sensitizers. Stability studies have shown that MDBGN in pet. at concentrations in the range 0.1–1.0% w/w is stable over a period of 12 months (36). Furthermore, chemical analysis at the Department of Occupational and Environmental Dermatology in Malmö (unpublished observation) has demonstrated that soya lecithin, recommended for addition to pet. (33), does not require addition to increase an even distribution of MDBGN.

The choice of 0.5% is based on consideration of rates of contact allergy, doubtful and irritant reactions, as well as on information on clinical relevance represented by results of a repeated

Table 1. Test preparations used to diagnose allergic contact dermatitis and trace contact allergy to methyldibromo glutaronitrile (MDBGN)

Chemical	Vehicle	Concentration (%)	References
Tektamer 38®	Petrolatum (pet.)	0.1	(2)
Euxyl K400	Pet.	2.5	(3–5)
Euxyl K400	Pet.	1	(3, 6, 7–10)
Euxyl K400	Pet.	1–0.5	(11)
Euxyl K400	Pet.	0.5	(6, 12–18)
Euxyl K400	Pet.	0.2	(16)
Euxyl K400	Pet.	0.1	(19, 20)
Euxyl K400	Propylene glycol	2	(21)
Euxyl K400	Propylene glycol	0.15	(21)
Euxyl K400	Ethanol	2.5	(5)
Euxyl K400	Water	1	(22, 23)
Euxyl K400	Water	0.5	(4)
Euxyl K400	Water/ethanol	0.2	(24)
Euxyl K400	Water/propylene glycol (50/50)	1.5	(4)
MDBGN	Pet.	0.5	(4, 25)
MDBGN	Pet.	0.3	(9, 12, 25, 26, 34, 35)
MDBGN	Pet.	0.3–0.1	(11)
MDBGN	Pet.	0.1	(15, 16, 22, 25, 27–30)
MDBGN	Pet.	0.05	(31, 32)
MDBGN	Pet.	0.04	(16)
MDBGN	Pet./soya lecithin	0.3	(33)
MDBGN	Water	0.1	(10)

open application test (ROAT), and patch test concentrations required to diagnose allergic contact dermatitis from MDBGN in individual cases (37–39). Besides the concentration, the elicitation of a patch test reaction in a given individual depends upon the dose, the patch test technique and the occlusion time (1). The dose is determined by the concentration and the volume/amount of the test preparation applied. Thus, when the same amount/volume of a test preparation is applied with the same test technique, it is appropriate to use concentration as a parameter for the dose. However, with pet. as the vehicle, it is impossible to repeatedly apply an exact volume/amount. An experienced and trained person can, however, keep variation within a limited range (40). For the 2 EECDRG studies on MDBGN (37, 39), the same occlusion time was used and the 2 patch test techniques gave equivalent results. Furthermore, at the participating clinics a major interest is focused on contact allergy, and patch testing is frequently performed by experienced and trained personnel.

With a patch test concentration of 0.1% w/w, and virtually also for 0.3% w/w, no irritant reactions were obtained (37). Above 0.3%, the frequencies of irritant reactions were obtained at 0.9 and 1.5% for patch test concentrations at 0.5 and 1.0%, respectively. However, in a way, reactions with a clearly irritant morphology do not constitute a problem as they need not be confused with and misinterpreted as allergic reactions (1). There might, though, be a problem with these reactions if they hid a simultaneous allergy or if the irritant reaction facilitated sensitization. However, so far, patch test sensitization to MDBGN has not been reported.

On the other hand, doubtful reactions constitute a different problem as they can represent either weak allergic or irritant reactions and should hence not be routinely registered as irritant reactions. Doubtful reactions will appear for any MDBGN patch test concentration but, at least from 0.1% and higher, not only the absolute percentages will increase but also the relative percentages, i.e. the higher the patch test concentration the larger proportion of all test reactions will be doubtful reactions. Individually, this means that a doubtful reaction to a low test concentration, e.g. 0.1 and 0.3%, more likely represents an allergic and clinically relevant reaction than a doubtful reaction to a higher concentration, e.g. 0.5 and 1.0% (37, 38). Therefore, in the case that there is a doubtful reaction, re-testing with the same test preparation and preferably, if possible, with MDBGN at a higher test concentration is recommended. For some sensitizers, intracutaneous testing and/or *in vitro* methods may help establish contact allergy. However, currently, neither intracutaneous testing nor any *in vitro* methods that can be used for establishing of contact allergy to MDBGN have been reported.

In individuals with doubtful patch test reactions to MDBGN, a use test with a leave-on product preserved with MDBGN at a high but realistic concentration could also be performed, although a positive use test rather gives information on the clinical relevance rather than on the nature of the test reactivity. In individual cases, a patch test concentration of 0.5% has been required to enable a diagnosis of allergic contact dermatitis from MDBGN in leave-on products (39). Furthermore, a randomized and controlled ROAT with MDBGN at 0.03% w/w in a moisturizer applied 2× daily for 2 weeks elicited a statistically significant positive response in MDBGN-hypersensitive persons testing positively to 0.5% and lower on patch testing (38). Therefore, convincing reasons favour a patch test concentration for MDBGN of 0.5% in order not to miss clinically relevant allergy.

Considering the facts that MDBGN has been allowed at 0.1% in leave-on products and still

Table 2. The European standard series with the addition of methyldibromo glutaronitrile

Compound	Concentration % (w/w) in petrolatum*	Concentration in mg/cm^2 in hydrophilic dried-in vehicle
Potassium dichromate	0.5	0.023
4-Phenylenediamine base	1.0	0.090
Thiuram mix	1.0	0.025§
Tetramethylthiuram monosulfide (TMTM)	0.25	
Tetramethylthiuram disulfide (TMTD)	0.25	
Tetraethylthiuram disulfide (TETD)	0.25	
Dipentamethylenethiuram disulfide (PTD)	0.25	
Neomycin sulfate	20.0	0.23
Cobalt chloride	1.0	0.020
Benzocaine	5.0	0.63¶
Nickel sulfate	5.0	0.20
Clioquinol (Chinoform and Vioform)	5.0	0.19**
Colophonium	20.0	0.85
Parabens	16.0	1.00††
Methyl-4-hydroxybenzoate	4.0	
Ethyl-4-hydroxybenzoate	4.0	
Propyl-4-hydroxybenzoate	4.0	
Butyl-4-hydroxybenzoate	4.0	
N-Isopropyl-*N*-phenyl-4-phenylenediamine	0.1	0.075‡‡
Lanolin alcohol	30.0	1.00
Mercapto mix	2.0	0.075§§
N-Cyclohexylbenzothiazyl sulfenamide	0.5	
Mercaptobenzothiazole	0.5	
Dibenzothiazyl disulfide	0.5	
Morpholinylmercaptobenzothiazole	0.5	
Epoxy resin	1.0	0.050
Myroxylon pereirae resin	25.0	0.80
4-tert-Butylphenol formaldehyde resin	1.0	0.040
Mercaptobenzothiazole (MBT)	2.0	0.075
Formaldehyde	1.0†	0.18
Fragrance mix	8.0‡	0.43¶¶
Cinnamic alcohol	1.0	
Cinnamic aldehyde	1.0	
Hydroxycitronellal	1.0	
α-Amylcinnamic aldehyde	1.0	
Geraniol	1.0	
Eugenol	1.0	
Isoeugenol	1.0	
Oakmoss absolute	1.0	
Sesquiterpene lactone mix	0.1	NA
Alantolactone	0.033	
Dehydrocostus lactone + Costunolide	0.067	
Quaternium-15 (Dowicil 200)	1.0	0.10
Primin	0.01	NA
Cl + Me-isothiazolinone (Kathon CG, 100 p.p.m.)	0.01†	0.004
Budesonide	0.01	NA
Tixocortol pivalate	0.1	NA
Methyldibromo glutaronitrile	0.5	NA

NA, not available.
*Concentration is not given in mg/cm^2 as different patch test systems (different size chambers, different volumes, etc.) may be used.
†In water.
‡Emulsifier: Sorbitan sesquioleate 5%.
§Equal parts of TMTM, TMTD, TETD and PTD.
¶Benzocaine, tetracaine hydrochloride, dibucain hydrochloride (5 : 1 : 1).
**Clioquinol, chlorquinaldol (1 : 1).
††Methyl-4-hydroxybenzoate, ethyl-4-hydroxybenzoate, propyl-4-hydroxybenzoate, butyl-4-hydroxybenzoate, benzyl-4-hydroxybenzoate (1 : 1 : 1 : 1 : 1).
‡‡*N*-Isopropyl-*N*-phenyl-4-phenylenediamine, *N*-cyclohexyl-*N*-phenyl-phenylenediamine, *N*,*N*-diphenyl-4-phenylenediamine (2 : 5 : 5).
§§*N*-Cyclohexylbenzothiazyl sulfenamide, dibenzothiazyl disulfide, morpholinylmercaptobenzothiazole (1 : 1 : 1).
¶¶Cinnamic alcohol, cinnamic aldehyde, hydroxycitronellal, α-amylcinnamic aldehyde, geraniol, eugenol, isoeugenol, oakmoss absolute (4 : 2 : 4 : 1 : 5 : 2 : 1 : 5).

Table 3. Ratios between patch test concentration and maximal previously allowed concentration in cosmetics for methyldibromo glutaronitrile (MDBGN) and the preservatives included in the European standard series

Preservative	Test concentration (%)	Maximum allowed concentration in cosmetics (%)	Ratio
Methylchloroisothiazolinone/ methylisothiazolinone	0.01	0.0015	6.7
Formaldehyde	1.0	0.2	5
Parabens	16.0	0.8	20
Quaternium-15	1.0	0.2	5
MDBGN	0.5	0.1*	5

*From July 2004, forbidden in cosmetics of leave-on type and allowed in rinse-off cosmetic products at a maximum of 0.1%. Still exposure to leave-on products with MDBGN at 0.1% may occur, if manufactured before that date.

may be used at this concentration (0.025% in sunscreen products), the enhanced significance of the use of leave-on products over longer periods than 2 weeks (41, 42) and, possibly on damaged skin, make it highly likely that the patch testing with MDBGN at 0.5% will still miss some clinically relevant contact allergy to MDBGN. Therefore, in the case that there is a strong suspicion of contact allergy to MDBGN and the patient tests negatively or with a doubtful reaction to 0.5%, patch testing with MDBGN at the same and at a higher concentration, e.g. 1.0%, is recommended. Again, in this situation a use test may help determine the clinical relevance.

Results

With regard to previously used patch test concentrations to trace contact allergy to and allergic contact dermatitis from MDBGN, the recommended concentration of 0.5% may seem high. However, in comparison with patch test concentrations of other preservatives included in the European standard test series (Table 3), 0.5% is not a high test concentration. The recommended MDBGN test concentration is 5× higher than the previous highest allowed MDBGN concentration in leave-on products. For the other preservatives, the corresponding ratio between patch test concentration and highest allowed concentration in leave-on products varies between 5 and 20 (Table 3).

Discussion

The authors are concerned about the high number of reactions to MDBGN at 0.5%. These reactions might even be read as positive and the patient be instructed to avoid any products containing MDBGN. In some patients, this may not be necessary. However, based on the data obtained by the studies, the authors conclude that the risk of missing clinically relevant cases of sensitization by testing only with MDBGN at 0.3% is unacceptably high. MDBGN seems to be a very special sensitizer where the eliciting concentration for a clinically relevant allergic reaction shows definite overlap with irritancy. Further quantitative studies on proven cases of allergic contact dermatitis caused by MDBGN are needed to determine the optimal patch test concentration.

Conclusion

In conclusion, MDBGN in pet. at 0.5% w/w is recommended for inclusion in the European standard patch test series. As for other standard test preparations, this MDBGN preparation should be subjected to constant considerations with regard to modifications needed and justified by new information, such as changes in rates of contact allergy, allergic contact dermatitis and adverse reactions, particularly patch test sensitization.

References

1. Bruze M, Conde-Salazar L, Goossens A, Kanerva L, White I R. Thoughts on sensitizers in a standard patch test series. The European Society of Contact Dermatitis. *Contact Dermatitis* 1999: 41: 241–250.
2. Mathias C G T. Contact dermatitis to a new biocide (Tektamer 38®) used in a paste glue formulation. *Contact Dermatitis* 1983: 9: 418–435.
3. Jackson J M, Fowler J F. Methyldibromoglutaronitrile (Euxyl K400): A new and important sensitizer in the United States? *J Am Acad Dermatol* 1998: 38: 934–937.
4. Tosti A, Vincenzi C, Trevisi P, Guerra L. Euxyl K 400: incidence of sensitization, patch test concentration and vehicle. *Contact Dermatitis* 1995: 33: 193–195.
5. Tosti A, Guerra L, Bardazzi F, Gasparri F. Euxyl K 400: a new sensitizer in cosmetics. *Contact Dermatitis* 1991: 25: 89–93.
6. Geier J, Schnuch A, Brasch J, Gefeller O. Patch testing with methyldibromoglutaronitrile. *Am J Contact Dermat* 2000: 11: 207–212.

7. Marks J G, Belsito D V, DeLeo V A et al. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J Am Acad Dermatol* 1998: 38: 911–918.
8. Kelterer D, Kaatz M, Bauer H I, Thiele J, Elsner P. Contact allergy to methyldibromo glutaronitrile in Euxyl K 400 in a cosmetic cream for protection against a permanent wave solution. *Contact Dermatitis* 2002: 46: 250.
9. Erdmann S M, Sachs B, Merk H F. Allergic contact dermatitis due to methyldibromo glutaronitrile in Euxyl K 400 in an ultrasonic gel. *Contact Dermatitis* 2001: 44: 39–40.
10. Senff H, Exner M, Görtz J, Goos M. Kontaktallergie auf einen neuen Konservierungsstoff. *Dermatosen* 1989: 37: 45–46.
11. Wilkinson J D, Shaw S, Andersen K E et al. Monitoring levels of preservative sensitivity in Europe. A 10-year overview (1991–2000). *Contact Dermatitis* 2002: 46: 207–210.
12. McFadden J P, Ross J S, Jones A B, Rycroft R J G, Smith H R, White I R. Increased rate of patch test reactivity to methyldibromoglutaronitrile. *Contact Dermatitis* 2000: 42: 54–55.
13. Guimaraens D, Hernández M I, Gonzalez M A, Conde-Salazar L. Contact allergy to Euxyl K 400 in consecutively patch-tested patients. *Contact Dermatitis* 2000: 43: 55–56.
14. Schnuch A, Geier J, Uter W, Frosch P J. Patch testing with preservatives, antimicrobials and industrial biocides. Results from a multicentre study. *Br J Dermatol* 1998: 138: 467–476.
15. Okkerse A, Geursen-Reitsma A M, van Joost Th. Contact allergy to methyldibromoglutaronitrile and certain other preservatives. *Contact Dermatitis* 1996: 34: 151–152.
16. Fuchs Th, Enders F, Przybilla B et al. Contact allergy to Euxyl K 400. *Dermatosen* 1991: 39: 151–153.
17. Wong C S M, Beck M H. Occupational contact allergy to methyldibromo glutaronitrile in abrasive cleansers and work creams. *Contact Dermatitis* 2001: 44: 311–312.
18. Gebhart M, Stuhlert A, Knopf B. Allergic contact dermatitis due to Euxyl® K 400 in an ultrasonic gel. *Contact Dermatitis* 1993: 29: 272.
19. O'Donnell B F, Foulds I S. Contact dermatitis due to dibromodicyanobutane in cucumber eye gel. *Contact Dermatitis* 1993: 29: 99–100.
20. Silvestre J F, Rodriguez-Serna N, Miquel J F, Gauchia R, Aliaga A. Allergic contact dermatitis from Euxyl K 400 in a sunscreen cream. *Contact Dermatitis* 1996: 35: 315.
21. Motolese A, Seidenari S, Truzzi M, Giannetti A. Frequency of contact sensitization to Euxyl K 400. *Contact Dermatitis* 1991: 25: 128.
22. Torres V, Soares A P. Contact allergy to dibromodicyanobutane in a cosmetic cream. *Contact Dermatitis* 1992: 27: 114–115.
23. Ross J S, Cronin E, White I R, Rycroft R J G. Contact dermatitis from Euxyl K 400 in cucumber eye gel. *Contact Dermatitis* 1992: 26: 60.
24. Corazza M, Mantovani L, Roveggio C, Virgili A. Frequency of sensitization to Euxyl K 400 in 889 cases. *Contact Dermatitis* 1993: 28: 298–299.
25. Diba V C, Adisesh A, Statham B N. Occupational allergic contact dermatitis in hospital workers caused by methyldibromoglutaronitrile in a work soap. *Contact Dermatitis* 2003: 48: 118–119.
26. Armstrong D K B, Smith H R, Rycroft R J G. Contact allergy to methyldibromo glutaronitrile presenting as severe scalp seborrhoeic eczema. *Contact Dermatitis* 1999: 40: 335.
27. Vigan M, Brechat N, Girardin P et al. Un nouvel allergène: Le dibromodicyanobutane. Compte rendu d'une étude portant sur 310 malades de janvier à décembre 1994. *Ann Dermatol Venereol* 1996: 123: 322–324.
28. Van Ginkel C J W, Rundervoort G J. Increasing incidence of contact allergy to the new preservative 1,2-dibromo-2,4-dicyanobutane (methyldibromoglutaronitrile). *Br J Dermatol* 1995: 132: 918–920.
29. Fernández E, Navarro J A, Del Pozo L, Fernándes de Corrès L. Allergic contact dermatitis due to dibromodicyanobutane in cosmetics. *Contact Dermatitis* 1995: 32: 109–110.
30. Pigatto P D, Bigardi A, Legori A, Altomare G F, Carminati G. Allergic contact dermatitis from Tektamer 38® (dibromocyanobutane). *Contact Dermatitis* 1991: 25: 138–139.
31. de Groot A C, Weyland J W. Contact allergy to methyldibromoglutaronitrile in the cosmetics preservative Euxyl K 400. *Am J Contact Dermat* 1991: 2: 31–32.
32. de Groot A C, Bruynzeel D P, Coenraads P J et al. Frequency of allergic reactions to methyldibromoglutaronitrile (1,2-dibromo-2,4-dicyanobutane) in The Netherlands. *Contact Dermatitis* 1991: 25: 270–271.
33. De Groot A C, De Cock P A J J M, Coenraads P J et al. Methyldibromoglutaronitrile is an important contact allergen in The Netherlands. *Contact Dermatitis* 1996: 34: 118–120.
34. Zachariae C, Rastogi S, Devantier C, Menné T, Johansen J D. Methyldibromoglutaronitrile: clinical experience and exposure-based risk assessment. *Contact Dermatitis* 2003: 48: 150–154.
35. Jensen C D, Johansen J D, Menné T, Andersen K E. Methyldibromoglutaronitrile in rinse-off products causes allergic contact dermatitis: an experimental study. *Br J Dermatol* 2004: 150: 90–95.
36. Gruvberger B, Bjerkemo M, Bruze M. Stability of patch test preparations of methyldibromo glutaronitrile in petrolatum. *Contact Dermatitis* 2004: 51: 317.
37. Gruvberger B, Andersen K E, Brandao F M et al. Patch testing with methyldibromo glutaronitrile, a multicentre study within the EECDRG. *Contact Dermatitis* 2005: 52: 14–18.
38. Gruvberger B, Andersen K E, Brandao F M et al. Repeated open application testing with methyldibromo glutaronitrile, a multicentre study within the EECDRG. *Contact Dermatitis* 2005: 52: 19–23.
39. Bruze M, Goossens A, Gruvberger B, Hindsén M, Pontén A. Allergic contact dermatitis from methyldibromo glutaronitrile. (Submitted).
40. Fischer T, Maibach H I. Finn Chamber patch test technique. *Contact Dermatitis* 1984: 11: 137–140.
41. Andersen K E, Johansen J D, Bruze M et al. The time-dose-response relationship for elicitation of contact dermatitis in isoeugenol allergic individuals. *Toxicol Appl Pharmacol* 2001: 170: 166–171.
42. Bruze M, Johansen J D, Andersen K E et al. Deodorants: an experimental provocation study with cinnamic aldehyde. *J Am Acad Dermatol* 2003: 48: 194–200.

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