



EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL
Directorate C - Public Health and Risk Assessment
C7 - Risk assessment

SCIENTIFIC COMMITTEE ON CONSUMER PRODUCTS

SCCP

Opinion on

Methyldibromo glutaronitrile

(sensitisation only)

COLIPA n° P77

Adopted by the SCCP during the 3rd plenary meeting
of 15 March 2005

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BACKGROUND

Methyl dibromo glutaronitrile (1,2-Dibromo-2,4-dicyanobutanone) is regulated in the Cosmetic Directive Annex VI, part 1, reference 36. In 2002, the European Commission received a letter from the Chairman of the European Environmental & Contact Dermatitis Research Group (EECDRG) with data demonstrating the rising incidence of contact allergy to methyl dibromo glutaronitrile. At that time methyl dibromo glutaronitrile was authorised up to a maximum concentration of 0.1% in a finished cosmetic product. It was not authorised to be used in cosmetic sunscreen products at a concentration exceeding 0.025%. The European Commission asked the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) to evaluate the data.

In its opinion on Methyl dibromo Glutaronitrile COLIPA¹ n° P77 SCCNFP/0585/02, final, adopted during the 20th plenary meeting of 4 June 2002 the SCCNFP stated that until appropriate and adequate information is available to suggest a level of the preservative in leave-on products that poses an acceptable risk to the consumer (compared with the risk to the consumer from other preservatives), its use should be restricted to rinse-off products at the current maximum permitted level of 0.1%.

Based on this scientific opinion and following the Comitology procedure the Commission adopted Commission Directive 2003/83/EC of 24 September 2003 which restricted the use of methyl dibromo glutaronitrile to rinse-off products only.

In October 2004, the Commission received new scientific papers from Denmark concerning contact allergy to cosmetic products containing methyl dibromo glutaronitrile.

1. TERMS OF REFERENCE

The SCCP is requested to answer the following questions:

- *On the basis of currently available information and taken into account the data provided, the SCCP is asked to assess the risk to consumer of methyl dibromo glutaronitrile when used at the recently recommended maximum concentration in rinse-off products.*
- *Does the SCCP recommend any further restrictions than already recommended in its opinion adopted on 4 June 2002 and updated by opinion SCCNFP/0806/04 adopted on 23 April 2004 with regard to the use of methyl dibromo glutaronitrile as a preservative in cosmetic products?*

¹ COLIPA - European Cosmetics Toiletry and Perfumery Association

2. OPINION

3.1. Chemical and Physical Specifications

3.1.1. Chemical identity

3.1.1.1. Primary name and/or INCI name

Methyldibromo glutaronitrile

3.1.1.2. Chemical names

2-Bromo-2-(bromomethyl) glutaronitrile
 2-Bromo-2-(bromomethyl) pentanedinitrile
 1,2-Dibromo-2,4-dicyanobutane
 Glutaronitrile, 2-bromo-2-(bromomethyl)-
 Pentanedinitrile,-2-bromo-2-(bromomethyl)-

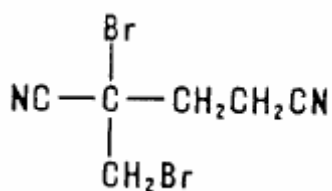
3.1.1.3. Trade names and abbreviations

Merguard 1105

3.1.1.4. CAS / EINECS number

CAS : 35691-65-7
 EINECS : 252-681-0

3.1.1.5. Structural formula



3.1.1.6. Empirical formula

Formula : C₆H₈Br₂N₂

3.1.2. Physical form

Crystals from ethanol

3.1.3. Molecular weight

Molecular weight : 265.94

3.1.4. Purity, composition and substance codes
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3.1.5. Impurities / accompanying contaminants

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3.1.6. Solubility

Very soluble in DMF, acetone, chloroform, ethyl acetate, benzene.
Soluble in methanol, ethanol, ether.
Insoluble in water

3.1.7. Partition coefficient (Log P _{ow})

Log K_{ow} : /

3.1.8. Additional physical and chemical specifications
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Organoleptic properties	:	mildly pungent odour
Melting point	:	51.2-52.5 °C
Boiling point	:	/
Flash point	:	/
Vapour pressure	:	/
Density	:	/
Viscosity	:	/
pKa	:	/
Refractive index	:	/

3.2. Function and uses

MDBGN is used as a preservative and as a biocide.

MDBGN is used as a preservative in cosmetic products at a maximum authorised concentration of 0.1%; as from 24 March 2005 in rinse-off products only (Commission Directive 2003/83/EU, JO 238, 25.9.2003).

MDBGN is used in a wide range of products for consumers and occupational use, e.g. dishwashing liquid, household cleaning products and other detergent products, car care products, wax and other polishing preparations for floors, adhesives, paints, and metal working fluids. It is used in veterinary pharmaceuticals, e.g. in dogs' shampoo.

3.3. Toxicological Evaluation

3.3.1. Acute toxicity

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3.3.2 Irritation and corrosivity

3.3.2.1. Skin irritation

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3.3.2.2. Mucous membrane irritation

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3.3.3. Skin sensitisation

Human Elicitation Studies

A study was carried out to investigate the allergic response elicited, in individuals pre-sensitised to methyl dibromo glutaronitrile (MDBGN), by exposure to a rinse-off product containing the maximum permitted level of MDBGN. 19 subjects with known contact allergy to MDBGN and 9 controls with negative patch test reaction to MDBGN at 0.3% participated. The study was a double blind; randomised repeated open application test (ROAT) using two coded liquid soaps, with and without MDBGN at 0.1%. Areas of 50 cm² on the lower arms were washed with the soaps twice a day for up to 28 days, 2 subjects continued for 34 days. The area was moistened with water, 2 drops of soap were applied, and washed by moving a water-soaked nylon sponge 10 times over the area. The soap was left for a maximum period of 30 s before rinsed off with running water. Soap bottles were weighed every week. A cut-off value for a positive response was erythema covering at least 25% of the test area and infiltration represented by papule(s), regardless of number. The subjects were also patch tested with a dilution series of MDBGN (10 concentrations from 0.2% to 0.001% in ethanol/water, and 0.3 and 0.1% in petrolatum) to determine their patch test threshold values. 7 of 19 subjects with contact allergy to MDBGN (37%) developed allergic contact dermatitis from ROAT with the soap containing MDBGN. The mean dose of MDBGN per application was 2.2 µg cm⁻², and the reactions appeared between days 6 and 34. All controls had negative ROAT. 7 subjects had a positive patch test reaction to the lowest patch test concentration (0.001%) and thus a patch test threshold value <0.001% (10 p.p.m.). The authors concluded that the results indicate that the permitted level of MDBGN in rinse-off products is too high, and that the possibility that sensitisation could occur in an in-use situation with prolonged, frequent use of a rinse-off product containing MDBGN cannot be disregarded.

Ref.: 5

A study was carried out to evaluate if 50 ppm or 100 ppm MDBGN could be safe use concentrations for MDBGN-sensitised individuals. It was also studied if the risk for elicitation of MDBGN allergy was higher with a leave-on product with a high lipid content than with a

product with low lipid content. 18 subjects with known contact allergy to MDBGN and 10 healthy controls participated in the study. Initially, patch testing was carried out to verify the reactivity to MDBGN 0.3% in petrolatum, and to exclude reactivity to the moisturiser without MDBGN. Repeated open application tests (ROATs) were performed on the right and left side of the neck. The two moisturisers, containing 50 ppm MDBGN, were applied to a 5x5 cm area according to a randomisation code, blinded to the investigator and the test subjects. Applications were twice daily for 14 days, or until a positive reaction was seen. If the ROAT was negative after 14 days of application, the application continued for a further 14 days with moisturisers containing 100 ppm MDBGN. Clinical assessment of test reactions was made using a scale for grading the morphology. Assessments were done on days 2, 3, 7, 14, 21 and 28 or when a reaction developed. 11 of the 18 (61%) subjects with allergy to MDBGN developed dermatitis on the test area on the neck (positive ROAT) within 2 to 19 days. 10 (56%) developed a positive ROAT to the moisturiser containing 50 ppm MDBGN, 7 having a positive reaction within 3 days. 7 subjects (39%) with allergy to MDBGN had negative ROAT. Subjects with a positive ROAT had higher patch test score than those with a negative ROAT. All controls had negative ROATs. Reactions to the low-lipid moisturiser were more frequent. All participants had used more of the low-lipid moisturiser than of the high-lipid moisturiser. The authors concluded that 50 ppm MDBGN cannot be regarded as a safe concentration for use.

Ref.: 7

The combined effect of MDBGN and sodium lauryl sulfate (SLS) on the elicitation response of allergic contact dermatitis was studied. 20 volunteers (12 women, 8 men) with contact allergy to MDBGN participated. Persons with a history of atopic dermatitis and persons with current eczema were excluded. The subjects were patch tested with 5 concentrations (10, 50, 100, 500 and 1000 ppm) of MDBGN alone and in combination with 0.25% aqueous SLS on the upper arms for 24h. Reactions were evaluated by clinical scoring on days 1, 3 and 7 and by measurement of transepidermal water loss (TEWL) and skin colour on days 3 and 7. Allergic reactions to MDBGN, as evaluated by clinical assessment, were elicited at lower concentrations when applied in combination with SLS than applied alone. The response was augmented by a factor of 6.4. An increased response to combined exposure to SLS and MDBGN as compared with MDBGN alone was confirmed by TEWL and colour measurements. The authors concluded that the threshold value for elicitation of allergic reactions in MDBGN-sensitised individuals is influenced by the presence of a detergent at low concentration, and that the results are relevant to real-life exposure to many types of products, such as wash-off cosmetics. The presence of detergents needs to be considered in assessing the risk for elicitation of allergic contact dermatitis and in deciding cut-off values for protection of the allergic individual.

Ref.: 8

A study was carried out with the aim to collect cases of primary sensitisation and elicitation to MDBGN due to cosmetic products, and to relate the findings to results from an updated risk assessment model developed by industry. Between January 2002 and September 2002, 807 consecutive dermatitis patients were patch tested with MDBGN 0.3% in petrolatum. 23 patients (2.9%) were found to have a positive patch test to MDBGN 0.3%. The history of each patient was analysed and patch testing performed with leave-on cosmetic products used by the patient. The ingredient labelling of the products was checked for the presence of MDBGN, and if possible, chemical analysis by HPLC was performed. The criteria for a case of primary sensitisation to MDBGN were no previous history of eczema, a clear relationship between the use of a cosmetic product and the onset of disease, exposure to MDBGN established for the

product, and clearance of the eczematous reaction within 2 months after the diagnosis. In 17 patients, the eczematous reaction was located on the hands, in 3 on the arms, in 7 on the legs, in 6 on the face, and in 3 on the trunk. Nearly all of the patients with hand eczema showed a strong clinical reaction. 5 patients were tested with their own products at 100%, with positive test result. In 11 patients, cosmetic products used in relation to the onset of the disease were shown to contain MDBGN. In 8 of the 11 cases primary sensitisation was probable. Chemical analysis of 12 products showed that lotions contained 149-390 ppm of MDBGN, liquid hand soaps 144-399 ppm, a rinsing cream 293 ppm, shampoos 78-79 ppm. After diagnosis, patients were instructed to avoid products with MDBGN, and after a period of 2 months 15 of 17 patients (88%) had recovered completely. The authors stated that applying the updated risk assessment model showed that the concentrations of MDBGN in lotions of 149-390 ppm exceeded the calculated maximum acceptable exposure level for MDBGN, which should be expected to lead to sensitisation in consumers using such products as seen in the study.

Ref.: 10

In 2003, 766 dermatitis patients were patch tested with the European standard series, supplemented with cosmetic allergens including MDBGN 0.3% in petrolatum. Clinical examination, inspection of cosmetic products, and chemical analysis of products by HPLC was performed. 38 patients (4.9%) gave a positive patch test to MDBGN. 2 additional patients with a doubtful patch test were included in the study, as they had relevant exposure. Hand eczema was present in 27 of these 40 patients (68%), and in 33% of the whole group of patch tested patients. Based on product labelling or chemical analysis, MDBGN allergy was judged relevant in 24 of the 27 cases with hand eczema. The predominant exposure was from wash-off products, either liquid soaps or shampoos. In 9 cases with generalised dermatitis and without hand eczema, shampoos seemed to be the predominant exposure. Chemical analysis showed a concentration range of MDBGN from 11 to 473 ppm in wash-off products. In most of the MDBGN-allergic patients, the dermatitis cleared or improved within weeks to months after patch testing and avoidance of products with MDBGN.

Ref.: 9

The frequency of contact allergy to MDBGN among patients seen by dermatologists in private practice in Denmark was studied on behalf of the Danish Contact Dermatitis Group. 2,146 consecutive patients (66% women, 34% men) with contact dermatitis were patch tested with MDBGN in addition to the European standard series. MDBGN 0.3% in petrolatum was used, except in one clinic where Euxyl K 400 1.5% (0.3% MDBGN) was used. The relevance of the patch test reactions and the identified sources of allergen exposure were recorded. 110 (5%) of the patients had positive patch tests to MDBGN, with no difference between sexes. A statistically significant association between hand eczema and MDBGN allergy was seen. Occupational exposure, mainly among health care workers, accounted for 15 (14%) of the cases of MDBGN allergy. In 53 cases (52.4%) the reaction to MDBGN was judged to be of current relevance. Creams and lotions accounted for 31% of the identified causative products, liquid soaps for 23%, and shampoos for 14%. The authors concluded that contact allergy to MDBGN is frequent among patients seen by dermatologists in private practice, that the significant relationship between hand eczema and MDBGN allergy is of concern, and that wash-off products play a significant role in MDBGN allergy.

Ref.: 6

The European Environmental Contact Dermatitis Research Group (EECDRG) initiated two multicentre studies, to define the optimal patch test preparation to diagnose contact allergy to

MDBGN (Refs. 2 and 3). From January 2002 to June 2002, 2,661 consecutively standard-patch-tested dermatitis patients (977 males, 1,684 females) were tested with MDBGN at 11 clinics in 9 European countries. MDBGN was tested at 1.0%, 0.5%, 0.3% and 0.1% in petrolatum, using Finn Chamber® technique or Van der Bend® technique. Patch tests were applied to the back for 2 days. Reactions were read on day 3 or 4, at 5 clinics also on day 6 or 7. Reactions were scored according to ICDRG guidelines. Reactions not fulfilling the criteria to be classified as allergic reaction were carefully differentiated with regard to irritant and doubtful reactions. To the highest patch test concentration (1.0%) a contact allergy rate at 4.4% was noted, while the lower patch test concentrations resulted in contact allergy rates down to 1.1%. Doubtful reactions were noted for all patch test concentrations, from 8.2% down to 0.5%. Irritant reactions were noted, however not for the lowest patch test concentration. The authors summarise that, contact allergy rate and frequency of doubtful and irritant reactions vary with the patch test concentration of MDBGN. The final decision on patch test concentration should rely also on patch test concentrations required to diagnose individual cases with allergic contact dermatitis from MDBGN, and on results of repeated open application tests.

Ref.: 2

The European Environmental Contact Dermatitis Research Group (EECDRG) initiated two multicentre studies, to help determine the optimal patch test preparation for MDBGN (Refs. 2 and 3). From January 2002 to June 2002, 51 dermatitis patients (18 males, 33 females) with a doubtful or a positive patch-test reaction to at least 1 of 4 test preparations with MDBGN in petrolatum (1.0% w/w, 0.5%, 0.3%, 0.1%), were investigated further on the clinical relevance of the reaction. A repeated open application test (ROAT) was performed with 2 moisturisers containing either MDBGN at 0.03%, or methyl paraben at 0.1% and propyl paraben at 0.2% respectively. Applications, on the ventral aspect of the upper arms where an area 5x5 cm was marked, were twice daily for 2 weeks or terminated earlier because of a positive ROAT. The allocation of which moisturiser to be applied to the respective arm was randomised. The patients were instructed to use an approximately 0.5 cm long string of cream for each application (1.4 mg/cm²). Inspection of the upper arm was done on the first day, after 1 and 2 weeks or at the request of the patient. A reaction was considered positive if an erythematous infiltration covered at least 25% of the marked area. 18 of the 51 (35%) patients developed a positive ROAT. There were positive ROATs only to the moisturiser containing MDBGN. A statistically significant association was found between the patch test reactivity to MDBGN and the outcome of the ROAT. The authors summarised that the study demonstrates that patch testing with MDBGN at 0.3% and 0.1% will miss clinically relevant patch test reactions to MDBGN.

Ref.: 3

A recommendation to include MDBGN in the European standard patch test series to trace contact allergy to MDBGN was made, based on gathered experience. 22 previously used patch test preparations were listed (from 34 publications including refs. 5 and 10). Experience from recent studies within the European Environmental Contact Dermatitis Research Group (EECDRG) and elsewhere (including refs. 2-4) was considered when the test preparation to use was determined. It was concluded that MDBGN at 0.5% in petrolatum should be used, in order not to miss clinically relevant allergy; that patch test sensitisation to MDBGN not has been reported; and that use tests may help determine the clinical relevance in the case of doubtful reactions. On behalf of the European Contact Dermatitis Society (ESCD) and the EECDRG, MDBGN at 0.5% w/w in petrolatum is recommended for the European standard patch test series from the year 2005.

Ref.: 1

Petrolatum is the preferred patch test vehicle for most sensitisers. The stability of MDBGN in petrolatum was determined by HPLC analysis. Petrolatum preparations of MDBGN at 1.0%, 0.5%, 0.3% and 0.1% were analysed when fresh and after being stored for one year at 6-8°C. MDBGN in petrolatum was found stable, without any sign of degradation after storage for one year in a refrigerator.

Ref.: 4

3.3.4. Dermal / percutaneous absorption

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3.3.5. Repeated dose toxicity

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3.3.6. Mutagenicity / Genotoxicity

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3.3.7. Carcinogenicity

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3.3.8. Reproductive toxicity

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3.3.9. Toxicokinetics

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3.3.10. Photo-induced toxicity

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3.3.11. Human data

See point 3.3.3. "Sensitisation"

3.3.12. Special investigations

/

3.3.13. Safety evaluation (including calculation of the MoS)**CALCULATION OF THE MARGIN OF SAFETY**

Not applicable

3.3.14. Discussion

The provided human experimental data, clinical patch-test data, results from chemical analysis and product information show that the current usage levels of MDBGN in cosmetic rinse-off products cause elicitation of allergic contact dermatitis and possibly also induction of contact allergy.

The provided experimental data show that the response to MDBGN in sensitised individuals is augmented by the presence of detergents, which is relevant to exposure to rinse-off products.

No safe use-level for MDBGN in cosmetic leave-on or rinse-off products has been shown.

MDBGN is used in a wide range of non-cosmetic consumer products, among them dishwashing liquid and other detergent products, paints, polishing agents, and other products coming into contact with the skin. The exposure to MDBGN from such products is not known and information is required.

The recent consumer exposure to MDBGN has caused a high rate of contact allergy to it. The most frequently used patch test preparation to trace contact allergy to MDBGN (0.3% in petrolatum) has been shown too low and may miss clinically relevant cases of contact allergy. Thus, the prevalence of contact allergy to MDBGN has probably been underestimated. On behalf of the EECDRG and ESCD, it has recently been recommended to include MDBGN at 0.5% in petrolatum in the European standard patch test series.

The control of consumer exposure to MDBGN is important to reduce contact allergy and allergic contact dermatitis.

3. CONCLUSION

In response to the questions asked, the SCCP is of the opinion that:

- MDBGN was shown to cause elicitation of reactions by repeated open exposures with a rinse-off preparation at the maximum concentration allowed in rinse-off products (0.1%).
- No safe use-level for MDBGN in cosmetic leave-on or rinse-off products has been established.
- As no safe use-level for MDBGN in rinse-off products has been established, it is recommended that MDBGN should not be present in any cosmetic products.

Although the mandate requested an opinion on cosmetic use only, the risks to consumer health from the presence of MDBGN in other types of consumer products with relevant skin contact should be assessed. MDBGN has not yet been classified as a skin sensitizer (R43) in Annex I to Directive 67/548/EEC; the attention of the Commission is drawn to this".

4. MINORITY OPINION

Not applicable

5. REFERENCES

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6. ACKNOWLEDGEMENTS

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