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

Methyldibromoglutaronitrile

(sensitisation only)

COLIPA N° P77

Adopted by the SCCP during the 8th plenary meeting
of 20 June 2006

TABLE OF CONTENTS

1. BACKGROUND

The Scientific Committee on Consumer Products (SCCP), which, following Commission Decision 2004/210 of 4 March 2004 replaces the Scientific Committee on Cosmetic and Non Food Products intended for consumers (SCCNFP) has delivered several opinions on Methyldibromo glutaronitrile (MDBGN)[1]:

- SCCNFP/0585/02, final, of 04 June 2002;
- SCCNFP/0806/04, of 23 April 2004;
- SCCP/0863/05, of 15 March 2005.

In its last opinion on MDBGN, the SCCP concluded that:

"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."

In the light of this opinion, the Commission as risk-manager initiated the necessary steps to ban the use of MDBGN in cosmetic products.

However, the Commission's attention was drawn to the fact that in its most recent opinion on MDBGN the SCCP did not take some important aspects into consideration.

2. TERMS OF REFERENCE

In the light of the submission received by the European Commission in response to opinion SCCP/863/05, does the SCCP alter its opinion set out therein?

[1] The opinions of the SCCP and the SCCNFP can be found via the links under http://europa.eu.int/comm/health/ph_risk/committees/04_sccp/04_sccp_en.htm

3. 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)-

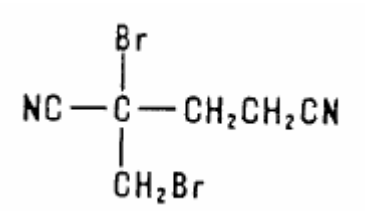
3.1.1.3. Trade names and abbreviations

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: $C_6H_8Br_2N_2$

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

/

3.1.5.	Impurities / accompanying contaminants

/

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

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 products, e.g. in dogs' shampoo.

3.3. Toxicological Evaluation

3.3.1. Acute toxicity

Not applicable

3.3.2. Irritation and corrosivity

3.3.2.1. Skin irritation

Not applicable

3.3.2.2. Mucous membrane irritation

Not applicable

3.3.3. Skin sensitisation

Local Lymph Node Assay (LLNA)

Guideline:	OECD 429
Species/strain:	mice/not given
Group size:	not given
Test substances:	Iodopropynyl butylcarbamate (IPBC), 10%, 5%, 1% and 0.1% in Acetone/olive oil (AOO 3+1 v/v) Positive controls: Methyldibromo glutaronitrile (MDBGN) 10% and 5-chloro-2-methyl-4-isothiazolin-3-one/2-methyl-4-isothiazolin-3-one (CMI/MI) 0.1% in AOO. Negative control: the vehicle AOO.

The LLNA was used to determine the sensitization potential for the preservative IPBC. MDBGN and CMI/MI were used as positive controls. A stimulation index (SI) was calculated for each concentration: for IPBC 0.1%, 1%, 5%, 10% the SI was 0.7, 3.4, 4.2, and 12.0 respectively; for MDBGN 10% the SI was 6.1; and for CMI/MI 0.1% the SI was 8.7. An EC3 value for IPBC was theoretically derived by linear interpolation and found to be 0.87%.

In the reference, attention is drawn to the increasing use of IPBC in cosmetic leave on products as a substitute for MDBGN, and it is commented that the widespread presence of IPBC in moist tissues for personal care incurs further risk, as witnessed by its predecessor MDBGN.

Comment
This paper submitted by industry as part of its support for methyldibromo glutaronitrile is irrelevant.

Ref.: 4

3.3.4. Dermal / percutaneous absorption

Not applicable

3.3.5. Repeated dose toxicity

Not applicable

3.3.6. Mutagenicity / Genotoxicity

Not applicable

3.3.7. Carcinogenicity

Not applicable

3.3.8. Reproductive toxicity

Not applicable

3.3.9. Toxicokinetics

Not applicable

3.3.10. Photo-induced toxicity

Not applicable

3.3.11. Human data

Use tests with MDBGN

Method:	Open patch test on arm and provocative use test on scalp (shampoo use test)
Subjects:	12 volunteers (4 males and 8 females) who had previously shown positive patch test reactions to Euxyl K400 and MDBGN, and in 8 cases also to other patch test substances.
Test substances:	*Shampoo A* preserved with DMDM hydantoin, without MDBGN, 10% in distilled water; *Shampoo B* the same composition as in shampoo A, with 0.02% MDBGN added Supplied by Procter & Gamble Technical Centres Ltd, UK
Dosages:	*Shampoo A*: open patch test, details not given; *Shampoo B*: participants were instructed to shampoo the hair in the normal manner at least 3 times per week for 9-13 weeks, details not given.

All 12 subjects were initially patch tested with Shampoo A to ensure that no subject had a pre-existing allergy to any other component of the formulation. No reaction was recorded. All 12 subjects started the provocative use test, 11 subjects completed the study. No cutaneous reactions to the shampoo were evinced, no itching and/or dermatitis was reported.

Conclusions

Under the conditions of the provocative use test, no reactions to the shampoo containing 0.02% (200 ppm) MDBGN were recorded in 11 volunteers with known contact allergy to MDBGN. The authors concluded that the shampoo containing 0.02% MDBGN was safe without the risk of eliciting cutaneous reactions.

Ref.: 5

Comment
The description of the method and results is limited. No control subjects or control substance were used in the shampoo use test and thus the study was not "blind". The actually applied dose, the actual number of applications per week and the number of weeks are not given. 3 applications per week of a shampoo, the rate according to the instructions, is considered too little compared to normal use of shampoo, and other rinse-off products. The number of exposed subjects (11) is too low to allow conclusions concerning safety.
Accordingly, it cannot be concluded from the study that rinse-off products containing MDBGN at 0.02% are safe to use.

Method:	Patch test and use test by repeated open application
Subjects:	19 patients (17 women, 2 men) sensitized to MDBGN who had no dermatitis or mild dermatitis outside the test area in the trial period. A control group of 12 individuals (10 women, 2 men) with negative patch test reaction to 0.3% MDBGN in petrolatum.
Test substances:	*Patch test solutions*: MDBGN at 0.2% through 0% (16 concentrations) in ethanol/aqua. *Use test solutions*: 0.04%, 0.01%, 0% MDBGN in ethanol/aqua 20:80 in glass droplet bottles. The concentration of MDBGN in solutions was analysed by HPLC. The preparations were manufactured by the pharmacy at Odense University Hospital
Dosages:	*Patch test*: 15 µl of each test solution on filter paper of small Finn Chambers. *Use test*: randomized sets of 2x2 droplet bottles containing eth./aq. solutions to be applied to a 3x4 cm^2 area on the inside of their forearms for up to 3 weeks. 2 solutions on each arm 2 drops applied once daily of a solution containing 0.04% MDBGN and three times a day of a solution containing no MDBGN; or 4 times a day of a solution containing 0.01% MDBGN.

The patch test threshold value was determined by patch test with exposure 2 days, reading on D3 and D7.

A provocative use test with randomized sets droplet bottles was performed. Application of an approximately equal amount of MDBGN on both arms, applied either in 1 application of 0.04% or distributed by 4 applications of 0.01%, blinded and randomized. The number of applications prior to a positive use test was recorded. A positive response was erythema covering at least 25% of the test area and infiltration presented by papules regardless of number.

14/19 subjects developed dermatitis on both arms while 5 were completely negative on both arms at the termination of the study after 3 weeks. They developed dermatitis after application of

an average total of 8.3 or 7.9 µg/cm^2 MDBGN from the 0.04% and 0.01% solution respectively. Most patients developed dermatitis on both arms within 4 days. Controls were negative. A correlation was demonstrated between the patch test threshold value and the amount of MDBGN needed to elicit a reaction in the use test.

Conclusion
The application of 0.04% (400 ppm) MDBGN once daily, or 0.01% (100 ppm) MDBGN 4 times daily in a use test, had approximately equal capability of provoking allergic contact dermatitis. The accumulated total dose of MDBGN from multiple exposures over short time is of considerable importance.

Ref.: 2

Method:	Use test by repeated open application test (ROAT) and patch test
Subjects:	40 dermatitis patients (30 women, 10 men) with at least a + reaction to MDBGN/PE (methyldibromo glutaronitrile/phenoxyethanol) at reading D3 on routine patch testing.
Test substance:	*Use test*: Ointment containing 10-15% glyceryl stearate in water as vehicle and test substance Euxyl K 400® MDBGN/PE in 3 concentrations equivalent to 0.005, 0.01 and 0.025% (50, 100 and 250 ppm) of MDBGN. *Negative control*: The vehicle without Euxyl K 400. The products were prepared by Schülke & Mayr. *Patch test*: MDBGN 0.1, 0.2, 0.3 and 0.5% in petrolatum, by Hermal/Trolab.
Dosages:	*Use test*: 5x5 cm^2 on the volar side of each forearm. 2 preparations (one with and one without Euxyl K400), 0.5 ml applied 2 times daily, continued for 2 weeks. If no reaction after 2 weeks, the next higher concentration was used for another 2 weeks, etc. *Patch test*: applied to the back for 1 day or 2 days. Reading was performed at D3.

13/39 patients reacted to the lowest ROAT concentration (0.005% or 50 ppm MDBGN), 8/39 to the middle (100 ppm) and 3 to the highest concentration (250 ppm) only. One patient did not complete the study. From those 13 reacting to the lowest concentration (50 ppm), dermatitis developed after a very short exposure (within 1 day in 2 patients; or within 1 through 7 days in 12 patients). Reactions to the control preparation were not observed.

A confirmatory patch test with MDBGN at different concentration was done in 24 patients at the end of the ROAT, to find the best patch test concentration for MDBGN.
The strength of the initial patch test results with Euxyl K400, the confirmatory patch test results with MDBGN and the outcome of ROAT were associated.

Conclusions
It was concluded that MDBGN at 50 ppm in a leave-on product can elicit contact dermatitis in sensitized persons. The authors state that they were unable to find a safe, still microbiocidal, concentration for leave-on products.

Ref.: 3

3.3.12. Special investigations

Not applicable

3.3.13. Safety evaluation (including calculation of the MoS)

Not applicable

3.3.14. Discussion

In its submission, industry suggests a lowering of the maximum use concentration of MDBGN in rinse-off products from 1,000 ppm to 200 ppm, with particular reference to results from a shampoo use test (ref. 5).

It cannot be concluded from the shampoo use test study (ref. 5) that shampoos or other rinse-off products containing MDBGN at 0.02% are safe to use. The description of the study and the results is limited. The study did not include controls or blinding. The application frequency (at least 3 times per week) is considered too low compared to normal use of shampoo and other rinse-off products, and the number of exposed subjects (n=11) was too low to allow for conclusions concerning safety of use.

The concept of rinse-off products covers soaps, shampoos and other products. In its submission, industry makes reference to the use of shampoo as typical use of rinse-off cosmetics. In the shampoo use-tests included in the submission (refs. 1, 5), shampoo was used at least 3 times per week or every other day, which is a low use, compared to existing COLIPA cosmetic exposure data and the Notes of guidance (SCCNFP/0321/02)where the application frequency of shampoo is set to 1/day and shower gel 2/day. In the submission, the usual frequency of hand-washing seen in many common occupations, as well as at home, is called “exaggerated hand washing”.

In its submission, industry makes reference also to a use test with shampoos preserved with 15 ppm CMI/MI or 0.3% imidazolidinyl urea, respectively (ref. 1). The study was a randomized, double-blind, 2-period crossover study with 2 shampoos in 27 CMI/MI-sensitive patients. The participants were instructed to wash the hair every other day for 2 weeks. This study is considered to be irrelevant in the present risk assessment of MDBGN.

In its submission, industry did not supply the study on repeated open application comparing two concentrations of MDBGN (ref. 2). This important study provides new knowledge, showing that the accumulated total dose of MDBGN from multiple exposures of low doses over short periods of time has a similar potential for elicitation of allergic contact dermatitis compared with a single higher exposure.

The submission by industry (refs. 1, 3-5) does not allow for the conclusion that it is safe to use MDBGN in rinse-off products.

4. CONCLUSION

In response to the question asked by the European Commission, the SCCP is of the opinion that no safe use-level for methyldibromo glutaronitrile in cosmetic rinse-off products has been established.

In light of the submission, the SCCP does not alter its previous opinion stating that no safe use-level for methyldibromo glutaronitrile in rinse-off products has been established.

5. MINORITY OPINION

Not applicable

6. REFERENCES

1. Frosch PJ, Lahti A, Hannuksela M, Andersen KE, Wilkinson JD, Shaw S, Lachapelle JM. Chloromethylisothiazolone/methylisothiazolone (CMI/MI) use test with a shampoo on patch-test-positive subjects. Results of a multicentre double-blind crossover trial. Contact Dermatitis 1995; 32: 210-217
2. Jensen CD, Johansen JD, Menné T, Andersen KE. Methyldibromo glutaronitrile contact allergy: effect of single versus repeated daily exposure. Contact Dermatitis 2005; 52: 88-92
3. Schnuch A, Kelterer D, Bauer A et al. Quantitative patch and repeated open application testing in methyldibromo glutaronitrile-sensitive patients. Contact Dermatitis 2005; 52: 197-206
4. Siebert J. The sensitizing potential of iodopropynyl butylcarbamate in the local lymph node assay. Contact Dermatitis 2004; 51: 318-319
5. Tosti A, Vincenzi C, Smith KA. Provocative use testing of methyldibromo glutaronitrile in a cosmetic shampoo. Contact Dermatitis 2000; 42: 64-67

7. ACKNOWLEDGEMENTS

Members of the working group are acknowledged for their valuable contribution to this opinion. The members of the working group are:

Dr. C. Chambers
Prof. R. Dubakiene
Dr. R. Grimalt
Dr. B. Jazwiec-Kanyion
Prof. V. Kapoulas
Prof. J. Krutmann
Prof. C. Lidén (Rapporteur)
Prof. J.-P. Marty
Dr. S.C. Rastogi
Prof. J. Revuz
Prof. V. Rogiers
Prof. T. Sanner
Dr. I.R. White (Chairman)