OPINION OF THE SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS INTENDED FOR CONSUMERS

CONCERNING

METHYLDIBROMO GLUTARONITRILE

Colipa n° P77

adopted by the SCCNFP during the 20th plenary meeting
of 4 June 2002

1. Terms of Reference

1.1 Context of the question

Methyldibromo glutaronitrile (1,2-dibromo-2,4-dicyanobutane) is regulated in the Cosmetic Directive Annex VI, part 1, reference 36 and can therefore be used as a preservative up to a maximum concentration of 0.1% in the finished product. It shall not be used in cosmetic sunscreen products at a concentration exceeding 0.025%.

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 methyldibromo glutaronitrile.

1.2 Request to the SCCNFP

The SCCNFP was asked to perform an expert review on the basis of the data provided and to answer the following questions :

1. Is methyldibromo glutaronitrile, used at the currently allowed maximum concentration, safe for use in cosmetic products taking into account the data provided?

2. If not, does the SCCNFP consider that a lower concentration is safe for use in cosmetic products and do the data provided indicate such a concentration?

3. And/or does the SCCNFP recommend any further restrictions with regard to the use of methyldibromo glutaronitrile as a preservative in cosmetic products?

1.4 Statement on the toxicological evaluation

The SCCNFP is the scientific advisory body to the European Commission in matters of consumer protection with respect to cosmetics and non-food products intended for consumers.

The Commission's general policy regarding research on animals supports the development of alternative methods to replace or to reduce animal testing when possible. In this context, the SCCNFP has a specific working group on alternatives to animal testing which, in co-operation with other Commission services such as ECVAM (European Centre for Validation of Alternative Methods), evaluates these methods.
The extent to which these validated methods are applicable to cosmetic products and its ingredients is a matter of the SCCNFP.

SCCNFP opinions include evaluations of experiments using laboratory animals; such tests are conducted in accordance with all legal provisions and preferably under chemical law regulations. Only in cases where no alternative method is available will such tests be evaluated and the resulting data accepted, in order to meet the fundamental requirements of the protection of consumer health.

2. Review

A report of the Scientific Committee on Cosmetology expressed an opinion on methyldibromo glutaronitrile on 1st July 1986 based on information submitted in COLIPA dossiers submitted in March 1981 and September 1984 respectively.

"*A skin irritation test in rabbits with 0.5g of undiluted powder produced erythema and oedema. The substance was classified as a moderate irritant. A 0.3% aqueous solution was not irritating to the rabbit skin. A 0.3% dilution in oil was neither irritating nor sensitising when applied to the skin of humans.*

"Although there is adequate information for accepting the use of the substance in cosmetics in general, information on dermal absorption and pharmacokinetics is needed to justify its use in sunscreening agents."

The data referred to in the submission of the EECDRG is a paper accepted for publication in the peer reviewed journal Contact Dermatitis :

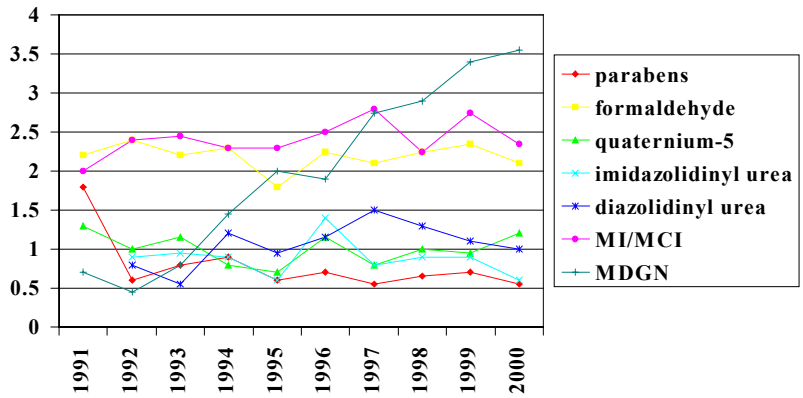
Monitoring levels of preservative sensitivity in Europe: a ten year overview (1991-2000) (Wilkinson JD, Shaw S, Andersen KE, Brandao FM, Bruynzeel DP, Bruze M, Camarasa JMG, Diepgen TL, Ducombs G, Frosch PJ, Goossens A, Lachapelle J-M, Lahti A, Menne T, Seidenari S, Tosti A, Wahlberg JE (ref. 1).

Between 1991-2000, consecutive series of individuals with eczematous skin conditions, attending for diagnostic patch testing in dermatology clinics in geographically different areas in Europe, were routinely tested with methyldibromo glutaronitrile in addition to standard allergens. Within the 15 participating centres in 11 countries the patch test concentration of methyldibromo glutaronitrile varied from 0.1% - 0.3% or was evaluated by testing with Euxyl K400 (containing phenoxyethanol and methyldibromo glutaronitrile) at 0.5% - 1% in petrolatum. There is controversy over the most appropriate concentration at which to test methyldibromo glutaronitrile (ref. 2, 3, 4, 5). Patch testing was based on the ICDRG guidelines (ref. 6) with readings at day 2 and day 3 or 4.

Figure 1 tabulates the average sensitivity rates calculated by combining all the positive patch test results for the preservative from all the participating centres that submitted data for the year in question. Other cosmetics preservatives are included for comparison. The data for methyldibromo glutaronitrile is based on 48,485 individuals tested over the decade with methyldibromo glutaronitrile with 1,064 reacting to it. The majority of positive patch test reactions to methyldibromo glutaronitrile were considered to be of clinical relevance.

Figure 1

Composite data: EECDRG



The incidence of positive patch test reactions to methyldibromo glutaronitrile increased from an average of 0.7% in 1991 to 3.5% in 2000.

The rise in sensitivity to methyldibromo glutaronitrile from other centres is illustrated by the data from St. John's Institute of Dermatology, London which shows a similar trend (ref. 7) (Table 2) :

Table 2:

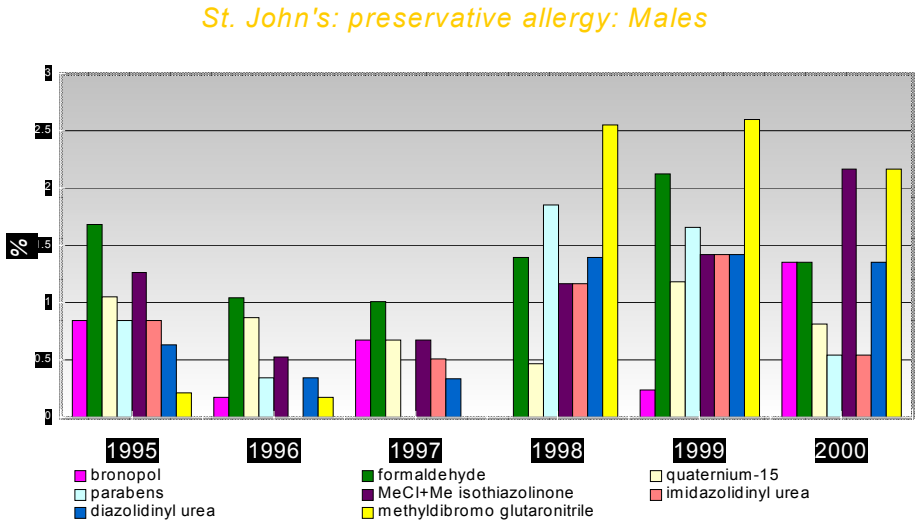
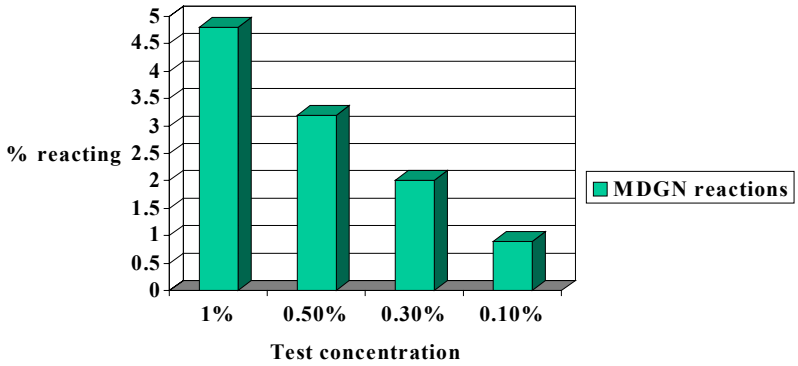


Figure 3 shows recent patch test reactions observed by the EECDRG using different concentrations of methyldibromo glutaronitrile. These data show a clear dose response effect.

Figure 3 Patch test results
January 15 – March 31 2002
n=1364
Source: EECDRG multicentre



Sensitisation rates of contact allergens are dependent not only on the inherent sensitising capacity of the chemical, but also the dose and type of exposure, the amount of allergen per unit area surface of skin (ref. 8), vehicle and the condition of the skin. An approach to allergic contact sensitisation risk has been published (ref. 9).

The rapidly increasing level of contact allergy to methyldibromo glutaronitrile in Europe is of concern. The preservative is now widely used for both leave-on and rinse-off products. In some geographical areas (e.g. Netherlands) the use of methyldibromo glutaronitrile in the early 1990s resulted in a rise in contact allergy during that time (ref. 3).

The data presented represents an estimation of the level of sensitivity to methyldibromo glutaronitrile in individuals with eczema throughout Europe. There is little information about actual exposure levels to the preservative and no information about the level of clinical sensitivity in the general population.

Recent experimental work on the sensitising capacity of methyldibromo glutaronitrile suggests that the guinea pig maximisation test may have failed to detect the true sensitising capacity of methyldibromo glutaronitrile (ref. 10).

3. Opinion

* Is methyldibromo glutaronitrile, used at the currently allowed maximum concentration, safe for use in cosmetic products taking into account the data provided?

The data show a clear rise in the incidence of contact allergy to methyldibromo glutaronitrile throughout Europe. This indicates that the current usage of the preservative – concentration and product types – is responsible for this rise. Maximum consumer exposure will occur from use of leave-on products containing 0.1% (the maximum permitted) of the preservative. Therefore, this use is a risk to the consumer.

* If not, does the SCCNFP consider that a lower concentration is safe for use in cosmetic products and do the data provided indicate such a concentration?

The available data does show a dose response elicitation of allergic contact reactions to the preservative but provides no information on a 'safe level'.

* And/or does the SCCNFP recommend any further restrictions with regard to the use of methyldibromo glutaronitrile as a preservative in cosmetic products?

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), restricting its use to rinse-off products at the current maximum permitted level of 0.1%.

4. References

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