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

OPINION

CONCERNING

UPDATE OF ENTRY N° 39 OF ANNEX VI TO DIRECTIVE 76/768/EEC ON COSMETIC PRODUCTS :

MIXTURE OF 5-CHLORO-2-METHYL-ISOTHIAZOLIN-3(2H)-ONE AND 2-METHYLISOTHIAZOLIN-3(2H)-ONE

COLIPA n° P56

Adopted by the SCCNFP during the 24th plenary meeting
of 24-25 June 2003

1. Terms of Reference

1.1 Context of the question

The Cosmetic Directive 76/768/EEC, adopted on 27 July 1976 (published in the OJEC on 27 September 1976) has been amended six times and at present covers more than 25 adaptations to technical progress. Technical Annexes (II – VII) are a set of lists, qualifying the use of certain ingredients for the safety of the final preparation.

In Annex VI, a positive list of preservatives which may be used is laid down. The mixture of 5-Chloro-2-methyl-isothiazolin-3(2H)-one and 2-Methylisothiazolin-3(2H)-one with magnesium chloride and magnesium nitrate is currently listed in Annex VI, part 1 and consequently allowed for use in cosmetic products under the conditions and restriction laid down in the Annex. According to Annex VI, only magnesium chloride and magnesium nitrate may be used as stabilisers.

Since modern manufacturing processes and formulation techniques have made it possible to reduce the amount of magnesium nitrate and chloride stabiliser needed, or even replace it entirely with other alternative stabilisers, e.g. copper sulfate, the European Commission was asked to allow the use of copper sulfate as stabilising system, or to delete from the entry n° 39 of Annex VI any reference to stabilisers.

1.2 Requests to the SCCNFP

The SCCNFP was asked to answer the following questions, accompanying two consecutive submission (VIII and IX) regarding the entry n° 39 of Annex VI to the Cosmetics Directive :

On the requests of Submission VIII, the SCCNFP was asked to answer the following questions :

* Does the SCCNFP agree that entry n° 39 in Annex VI of the Cosmetics Directive can be changed to the following wording?

Ref. n°	Substance	Maximum authorised concentration
39	Mixture of 5-Chloro-2-methyl-isothiazolin-3(2H)-one and 2-Methylisothiazolin-3(2H)-one with magnesium chloride and magnesium nitrate or copper sulfate	0.0015% (of a mixture of 5-Chloro-2-methyl-isothiazolin-3(2H)-one and 2-Methylisothiazolin-3(2H)-one)

On the requests of Submission IX, the SCCNFP was asked to answer the following questions:

* Does the safety profile documented in the attached submission support that using different stabilisers in the mixture of 5-Chloro-2-methyl-isothiazolin-3(2H)-one and 2-Methylisothiazolin-3(2H)-one does not alter the toxicological profile of this mixture?
* Does the SCCNFP propose any restrictions or conditions for the use of stabilisers in the mixture of 5-chloro-2-methyl-isothiazolin-3(2H)-one and 2-methylisothiazolin-3(2H)-one?

1.3 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. Toxicological Evaluation and Characterisation

Introductory Remarks

1. The chloromethylisothiazolone/methylisothiazolone mixture is hereafter abbreviated, for convenience, as MCI/MI or by its COLIPA identification number P56.

2. The present opinion of the SCCNFP is limited to answering to the specific questions regarding the authorised stabilisers for the MCI/MI mixture; it is not a re-evaluation and safety assessment of the preservative, whose authorisation in the EU is still based on the respective opinion of the SCC (1) adopted during the plenary session of 1 July 1986 (evaluation report: January 1984, Submissions VI and VII: November 1984). In its opinion, the SCC expressed no objection for including this preservative in the list of "preservatives whose use in cosmetic products can be maintained for the time being, but concerning which the Committee would like to obtain additional data". For P56, "data on the stability of the compound under test conditions should have been provided (1). Some additional data in the CIR report (4), included in the last Submission IX, in which 51 (out of 84) of the cited references are dated between 1984 and 1990. Its final conclusion is that the MCI/MI mixture may be safely used in "rinse-off" products at a concentration not to exceed 15 ppm, and in "leave-on" cosmetic products at a concentration not to exceed 7.5 ppm. These permissive levels have been approved by regulations in the USA and Poland, as well as by manufacturers in countries where no regulatory approval is required, while in Japan no approval has been sought for "leave-on" products (23).

3. According to information provided with Submissions VIII and IX, the problems arising from the inherent instability of MCI/MI mixtures are mainly connected with water-based technical concentrates (concentration >20-25%), stock solutions (5%), and dilutions commonly

used by the cosmetics industry (1.5%); once the mixture is added to a final cosmetic formulation, the stabilising system has no function.

2.1. Evaluation of submission VIII

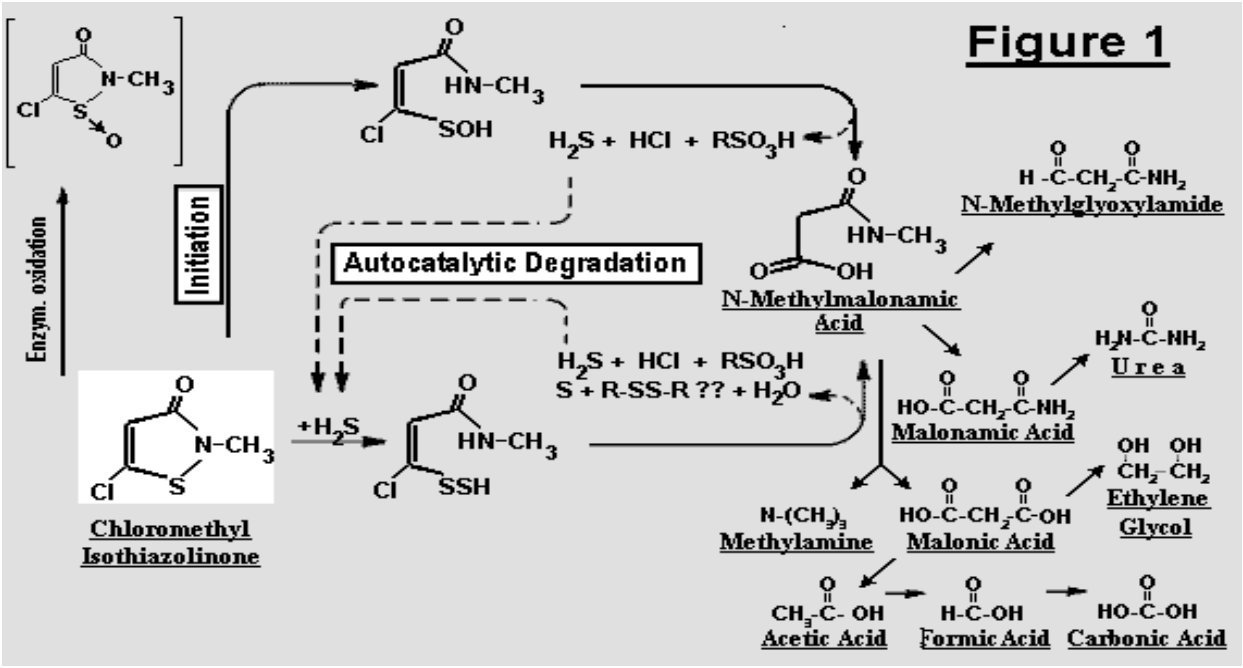
The use of copper sulfate as an alternative stabiliser is requested in order to diminish or even wholly avoid the content of salt stabilisers, the presence of which allows unpredictable decomposition of certain dispersions or emulsions and, promoted by poor mixing, formation of precipitates or coagulates, which may enclose the biocidal active ingredient.

According to information provided with submission VII, a mixture of 5-Chloro-2-methyl-isothiazolin-3(2H)-one and 2-Methylisothiazolin-3(2H)-one with low concentrations of copper sulfate (up to 100ppm expressed as Cu^{2+}) has been developed in order to avoid the above-mentioned disadvantages. The active ingredients as well as their ratio remained unchanged. Assuming that the maximum authorised concentration 0.0015% is used, the final level of cupric ions is 150 ppb (parts per billion). This concentration is negligible, much lower than the acceptable heavy-metal impurities, while more than 10 cosmetic ingredients included in the Cosmetics Inventory are copper salts for which there is no quantitative restriction.

2.2. Evaluation of submission IX

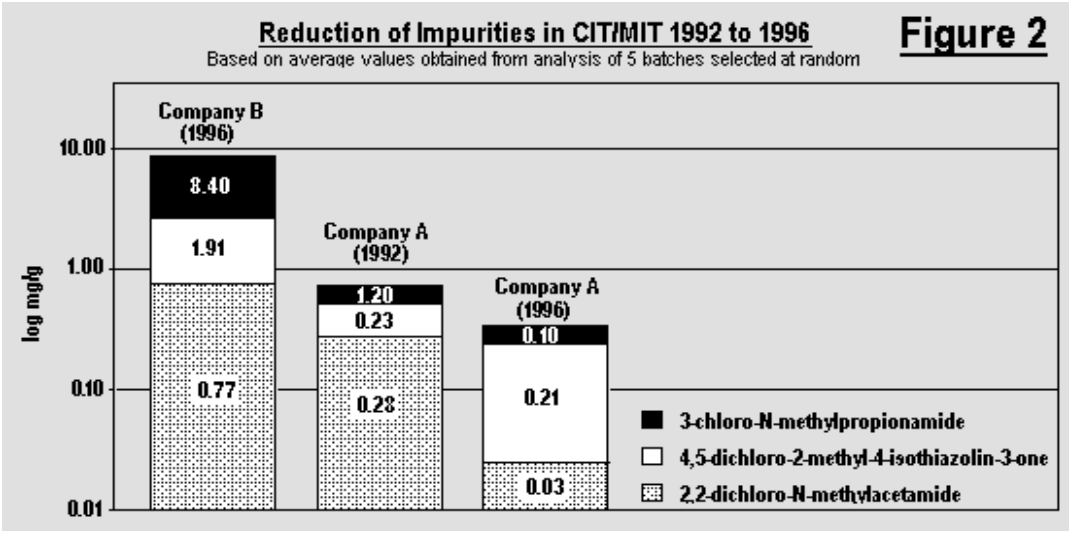
2.2.1. Technical aspects on the impurities

According to the information provided in the dossier, the instability of commercial MCI/MI mixtures is due to two factors, i.e. the inherent instability of the isothiazolinone molecules, and residual impurities of the manufacturing processes.
The sulphur-nitrogen bond of the isothiazolinone ring represents an electrophilic centre that may react easily with nucleophilic substances (20,21). In the MCI molecule, a further electrophilic centre, the vinyl-activated chlorine atom in the neighbourhood of the sulphur-nitrogen bond is responsible for increasing the instability of MCI in comparison to MI molecule (22).
Deactivation is thought to proceed by means of a cascade of reactions, initiated by ring opening, loss of chlorine and sulfur, and subsequent formation of *N*-methylmalonamic acid. The degradation then proceeds through malonamic, malonic, acetic, and formic acids to carbon dioxide and methylamine, accompanied by several side products (*N*-methylglyoxylamide, ethylene glycol, urea). Isothiazolinone-l-oxides are also derived by enzymic oxidation of isothiazolones and further interactions lead to formation of other intermediates including disulphanes, elemental sulphur (as a result of breakdown of sulphurous acids) and hydrogen sulphide. This is a strong nucleophile attacking the ring and accelerating the decomposition in a self-perpetuating autocatalytic sequence of reactions, which is more rapid at higher concentrations of the MCI/MI solutions.



In pure aqueous solutions the ring opening is initiated by simple hydrolytic cleavage of the S-N bond, which is the reaction occurring in the presence of strong nucleophiles such as primary and, secondary amines and particularly thiol derivatives. Thus, residual impurities from the manufacturing process is the second factor of importance for the stability characteristics of the commercial MCI/MI mixtures. Its importance was recognised by industry after 1990 and since then, as stated in the report (3) :

* Knowledge of isothiazolinone chemistry has improved and advances have been made in their manufacture and purification, and there has been a consequent reduction in the amount of nucleophilic impurities present, as illustrated in the figure below.



* The use of purer isothiazolinones has the advantage of reducing the risk of exposure to contaminants of MCI/MI. Earlier production processes yielded concentrated MCI/MI containing 14% active ingredient. High levels of impurities led to instability and the requirement to add

additional stabilisers (up to 23%) to prevent deactivation when diluting with water. Modern, pure mixtures do not have this requirement.

* It is no longer necessary to be so heavily reliant on stabilisers to prevent degradation and manufacturers are able to reduce the concentration of magnesium nitrate salts and develop alternative stabilised mixtures.

Remarks

1. The sums of the 3 impurities in the illustrated examples are 10.68, 1.71 and 0.34 mg/kg (or 1.068 %, 0.171 % and 0.034 %) respectively, indicating that some marketed MCI/MI mixtures may contain about 30-fold amounts of impurities than the technically feasible contents.

2. There is no indication whether the above percentages are related to the dry matter or to the solutions of 14% (or higher) resulting by the manufacturing processes, as stated above. In the latter case, the above impurity content, e.g. of the samples of company B, corresponds to about 7.5 % on a dry matter basis.

3. There is no information indicating the route of synthesis used in the production of the respective batches, i.e. whether they have been produced by the older process based on the chlorine-induced cyclization of 3,3-dithio-dipropionamide, or by the more specific process based on amidation of methyl-3-mercaptopropionate (4) or, eventually, by another process. The same three impurities reported for all above examples may indicate differences only in the purification steps of crude products derived by the same synthetic route and, therefore, even higher amounts of impurires may occur in products manufactured by the old synthetic route.

4. No further information is provided about the "known sensitisers generated in the manufacturing process" (and included in the marketed MCI/MI mixtures), which is revealed for the first time.

2.2.2. Technical aspects on the stabilising agents

The introductory report included in the dossier (3) provides the following information :

* The exact mechanism of how stabilisers work is not clear.

* That residual magnesium chloride already present may have resulted in the original preference for magnesium nitrate, though the salts of other polyvalent metals such as calcium, copper, manganese, nickel and zinc have also been used successfully.

* It is also known that the stability of isothiazolinones is closely dependant on redox potential.

* Some substances such as hydrogen peroxide, which may be used to stabilize isothiazolinones, have an additional function in final cosmetic formulations where, by reacting rapidly with, and neutralizing substances such as sulphites present in the finished product, prevent them from reacting with the isothiazolinone molecule.

* A survey of the patent literature reveals that several such stabilizers have been suggested (5-19). Many of these, such as hydrogen peroxide (5), bronopol (8), iron (11), cupric ion and an oxidant (14), formaldehyde and formaldehyde donors (16), alkyl hydantoins (17) some halogenated organics (methyldibromo glutaronitrile) (18) and surfactants (19) have already been assessed for safety in use as cosmetic ingredients.

* The concentration at which these stabilisers are effective is extremely low.

* The need for alternatively stabilised isothiazolinones is due to technical concerns associated with the stabilisation of isothiazolinones with magnesium nitrate (5-19).

* A review of documentation available (5-9) shows that the stabilisers are effective in preventing degradation of the actives.

* The pathways for degradation of MCI/MI are the same whatever the stabiliser.

Remarks
In concentrated solutions of MCI/MI, some unstable (chemically active) intermediates of its degradation may result in products that have not been considered in earlier assessments. Therefore, the above statements on the toxicological profile of the mixtures may be uncertain when the mode of stabilisation is unknown.

2.2.3 Conclusions

Prior to any further consideration, it should be pointed out that the practical significance of any restrictive reference to stabilisers in entry n° 39 of Annex VI, without any quantitative limitation in particular, is questionable if their content in the finished cosmetic product is unknown.

Provided that there is no interaction between the stabiliser and degradation intermediates, and that only authorised cosmetic ingredients are used for this purpose, the use of different stabilisers is not expected to alter toxicological profiles in general.

The provided information concerning the qualitative and quantitative composition of the impurities present in currently marketed MCI/MI mixtures is inadequate. Any further consideration on the use of different stabilisers should rely on a proper re-evaluation of the safety of the MCI/MI mixture itself on the basis of complete data on its impurities, as well as on the toxicological studies accumulated since 1986.

3. Opinion

Taking into account that the active ingredients and their ratio remain unchanged and that the concentration of the stabiliser system in the finished cosmetic products is negligible, the SCCNFP is of the opinion that :

* the replacement of magnesium chloride and magnesium nitrate by copper sulfate or any other authorised cosmetic ingredient as a stabiliser system in the mixture of 5-Chloro-2-methyl-

isothiazolin-3(2H)-one and 2-Methylisothiazolin-3(2H)-one does not alter the toxicological profile of this mixture.

4. Other considerations

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5. Minority opinions

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6. References

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