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

OPINION

CONCERNING

THE DETERMINATION OF CERTAIN FORMALDEHYDE RELEASERS IN COSMETIC PRODUCTS

Adopted by the SCCNFP during the 22nd plenary meeting
of 17 December 2002

1. Background

The EU working party (WP) on Methods of Chemical Analysis of Cosmetic Products has observed that certain formaldehyde releaser in aqueous/polar solvents release some or all of the formaldehyde they contain, and they do not remain as a single compound. The working party has identified 4 such formaldehyde releasers, which are permitted to be used as preservatives in cosmetic products, according to Directive 76/768/EC: imidazolidinyl urea, diazolidinyl urea, sodium hydroxymethyl glycinate and benzylhemiformal (entries 27, 46, 51 and 55 respectively in Annex VI, part 1 of the Directive). As these compounds did not remain intact during various analytical conditions employed, WP concluded that it may not be possible to develop method(s) of analysis of these compounds. One of the approaches to overcome the analytical problem, suggested by working party, is that these 4 formaldehyde releasers may be regulated on the basis of their formaldehyde content.

2. Request to the SCCNFP

With reference to above-mentioned background the SCCNFP was requested to answer following questions :

- Does the SCCNFP consider it possible to amend the above mentioned entries 27, 46, 51and 55 so that the maximum authorised concentration could be expressed as a concentration of total formaldehyde without prejudicing the safety of cosmetic products?

- If so, can the SCCNFP propose maximum authorised concentrations of these preservatives, expressed as total formaldehyde, in cosmetic products?

3. Legislation on formaldehyde content of cosmetic products

According to Annex VI of the Cosmetic Directive 76/768/EC, the maximum authorised concentration of free formaldehyde is 0.2%. In addition, the provisions of Annex VI state that, *All finished products containing formaldehyde or substances in this Annex and which release formaldehyde must be labelled with the warning "contains formaldehyde" where the concentration of formaldehyde in the finished product exceeds 0.05%.*

The legislation is thus dependent upon the ability of analytical methods to differentiate free formaldehyde from the bound, inert form. The official EC method (1) for analysis determines the level of free formaldehyde in the presence of its donor compound.

4. Analytical problem

According to the Cosmetic Directive, official EU methods should be used to check the compliance of cosmetic products. The EU WP on Methods of Chemical Analysis of Cosmetic Products developed and validated a method for the determination of free formaldehyde in the presence of formaldehyde releasers (1). The method has been used since 1990 as the official EU method for the determination of free formaldehyde. During the development of method(s) for the analysis of formaldehyde releasers imadozolidinyl urea, diazolidinyl urea, sodium

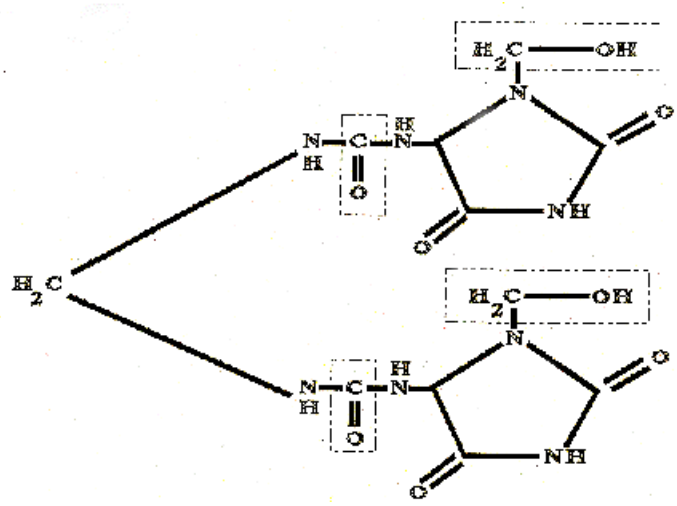
hydroxymethyl glycinate and benzylhemiformal, it was observed that these compounds decompose very rapidly to release formaldehyde when dissolved in aqueous/ polar solvents. Therefore, identification and determination of these compounds in cosmetic products may not be possible with the present state of knowledge. There is no information on the stability of these compounds in cosmetic products.

5. The formaldehyde releasers

5.1 Imidazolidinyl urea : 3,3-Bis(1-hydroxymethyl-2,5-dioxoimidazolidin-4-yl)-1-1'-methyldiurea

Empirical formula	:	$C_{11}H_{16}N_8O_8$
MW	:	388
CAS Reg. No.	:	39236-46-9

Soluble in water, propylene glycol, glycerine
Maximum authorised concentration in cosmetic products : 0.6%



Imidazolidinyl urea is soluble only in polar solvents. In aqueous solution, it is decomposed to release formaldehyde. The formaldehyde release from imidazolidinyl urea in an aqueous solution increases with the increase in pH and temperature of the solution as well as with the increase in storage period (2). One molecule of imidazolidinyl urea can release 4 molecules of formaldehyde under rigorous conditions. The total free formaldehyde content in a product containing 0.6% imidazolidinyl urea will thus correspond to 0.186%.

A method for analysis imidazolidinyl urea in cosmetic products was published in 1994 (3). This method employs determination of the compound by micellar electrokinetic chromatography (MEKC). However, it was not established that the chromatographic peak obtained by the analysis of imidazolidinyl urea was in fact the intact compound. Furthermore, this method could not be reproduced in another laboratory (4). The research in the later laboratory also indicated that it would not be possible by the MEKC to discriminate between imidazolidinyl urea and diazolidinyl urea, even if this method worked properly. It is possible that a common

decomposition product (an allantoin derivative) of both imidazolidinyl urea and diazolidinyl urea is seen as a single peak in MEKC. Further attempts to develop a method for the analysis of imidazolidinyl urea failed (4), because it was not possible to verify the identity of the parent compound under experimental conditions (as the compound degrades spontaneously in the solution). It has been shown by high performance liquid chromatography (HPLC), capillary zone electrophoresis (CZE) and nuclear magnetic resonance spectrometry (NMR) that the solution of imidazolidinyl urea contains several entities (2,4). It has not been established whether all molecules present in a solution of imidazolidinyl urea are decomposition products of the parent compound or the parent compound itself is a mixture of isomers. In any case, several of these molecules will contain formaldehyde. It is also expected that such molecules exist in the aqueous phase of water-containing cosmetics such as shampoos as well as in emulsion type cosmetics.

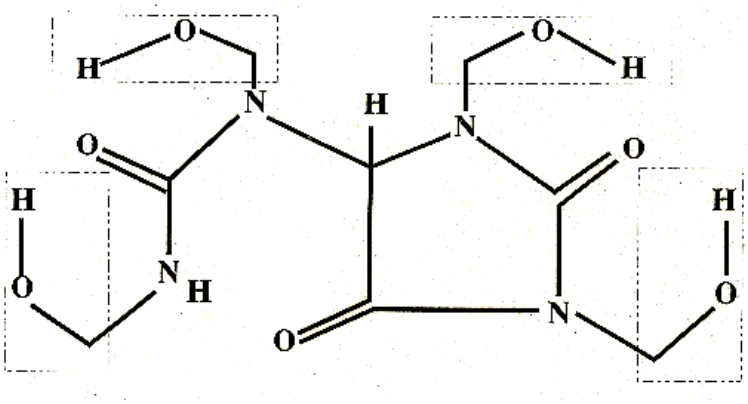
The latest Opinion on imidazolidinyl urea dates back to 1 July 1986. The Scientific Committee on Cosmetology (SCC) in its Opinon of 1 July 1986 stated that, "*The available information suggests the substance to be of relatively low toxicity. Details of the Ames test are required and a chromosome aberration test in mammalian cells in vitro. However, the Committee sees no objection to maintaining the use of this substance as a preservative in cosmetic products for the time being at a maximum level of 0.6%".*

The SCC did not consider the release of formaldehyde from imidazolidinyl urea when the safety of this compound was assessed. The toxic profile of decomposition product(s) of imidazolidinyl urea may be different than that of parent compound, which appears to be a mixture of isomers. However, it may be considered that the decomposition products of imidazolidinyl urea were present in the test solutions used in experiments performed for the elucidation of toxicity of the compound.

5.2 Diazolidinyl Urea : N-[1,3-bis(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]-N,N'-bis (hydroxymethyl)urea

Empirical formula	:	$C_8H_{14}N_4O_7$
MW	:	278
CAS Reg. No.	:	78491-02-8

Soluble in water, insoluble in most organic solvents
Maximum authorised concentration in cosmetic products: 0.5%



In aqueous solution, diazolidinyl urea is decomposed to release formaldehyde. One molecule of diazolidinyl urea can release 4 molecules of formaldehyde under rigorous conditions. The total free formaldehyde content in a product containing 0.5% diazolidinyl urea will thus correspond to 0.215%.

A HPLC method for the analysis of diazolidinyl urea in an experimental cream was published in 1997 (5). This method involves UV detection of the compound at 214 nm, while the λ_{max} of diazolidinyl urea is 236nm. It was not established that the chromatographic peak obtained by the analysis of diazolidinyl urea was in fact the intact compound. The applicability of the method has not yet been demonstrated to any cosmetic product available in the market. Attempts to develop a method for the analysis of diazolidinyl urea failed (4), because it was not possible to verify the identity of the parent compound under experimental conditions (as the compound degrades spontaneously in the solution). HPLC, CZE and NMR studies have shown that diazolidinyl urea solution contains several entities (4). It has not been established whether all molecules present in a solution of diazolidinyl urea are decomposition products of the parent compound or the parent compound itself is a mixture of isomers. In any case, several of these molecules will contain formaldehyde. It is also expected that such molecules exist in the aqueous phase of water-containing cosmetics such as shampoos as well as in emulsion type cosmetics.

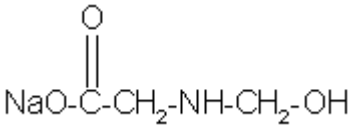
The latest Opinion on imidazolidinyl urea dates back to 10-11October 1990. The SCC in its Opinon of 10-11October 1990 concluded that, *"The Committee had requested a study using the oral route, since this would have provided much more information on the teratogenic potential of Germal II* (diazolidinyl urea) *than the dermal study actually carried out. It is likely that (eg. from physicochemical considerations) the compound is poorly absorbed through the skin, although there is little data on this aspect. The results do however indicate that compound is unlikely to give rise to any concern regarding teratogenic effect".*

The SCC did not consider the release of formaldehyde from diazolidinyl urea when the safety of this compound was assessed. The toxic profile of decomposition product(s) of diazolidinyl urea may be different than that of parent compound, which appears to be a mixture of isomers. However, it may be considered that the decomposition products of diazolidinyl urea were present in the test solutions used in experiments performed for the elucidation of toxicity of the compound

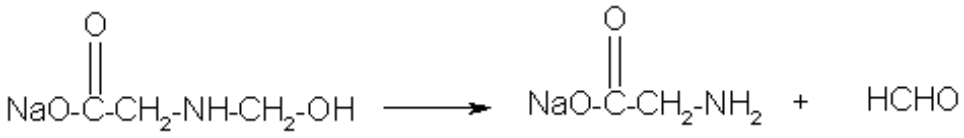
5.3 Sodium hydroxymethyl glycinate : Sodium hydoxymethylamino acetate

Empirical formula	:	$C_3H_6NO_3Na$
MW	:	127
CAS Reg. No.	:	70161-44-3

Highly soluble in water, soluble in methanol propylene glycol, glycerine, but insoluble in most organic solvents.
Maximum authorised concentration in cosmetic products: 0.5%



In an aqueous solution, sodium hydroxymethyl glycinate is decomposed to release formaldehyde. One molecule of formaldehyde is formed by the decomposition of each molecule of sodium hydroxymethyl glycinate, as described below.



The total free formaldehyde content in a product containing 0.5% sodium hydroxymethyl glycinate corresponds to 0.118%.

Attempts to develop a method for the analysis of sodium hydroxymethyl glycinate failed because the parent compound could not be identified under experimental conditions (6).

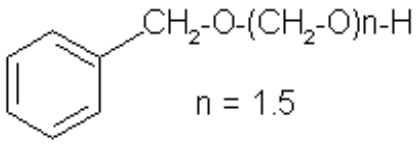
The latest Opinion on sodium hydroxymethyl glycinate is from 1995 (SPC/1254/95 Rev. 1). The SCC concluded that, "*According to the control that we have done on all reports to secure validity of the previous assessment, and to the negative results obtained with the in vivo – in vitro UDS assay, a safety margin of 70 is still applicable. Nevertheless, it is strongly recommended to the industry to define accurately if Suttocide A* (sodium hydroxymethyl glycinate) *is a powder or a 50% aqueous solution of the powder. No further assays appear to be necessary at the present time. Experimental data demonstrate that this compound is a potential allergen according to the guinea pig maximisation test. At the current usage levels, there is no evidence of unacceptable risk of sensitisation to the consumers. However, any background of sensitivity to the compound may be assessed at the later date if it becomes more widely used as cosmetic preservative".*

The SCC did not consider the release of formaldehyde from sodium hydroxymethyl glycinate, when the safety of this compound was assessed. However, the decomposition product of sodium hydroxymethyl glycinate, e.g. sodium glycinate cannot be considered harmful.

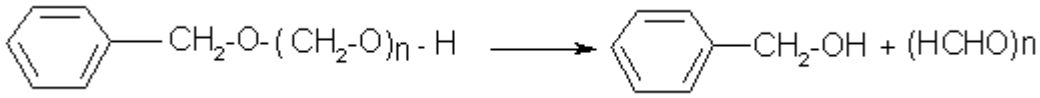
5.4 Benzylhemiformal

Empirical formula	:	
MW	:	153 for 1.5 mol/per mol of benzylhemiformal
CAS Reg. No.	:	14548-60-8

Soluble in organic solvents; solubility in water 25 g/L (at 20°C)
Maximum authorised concentration in cosmetic products: 0.15% in "rinse-off" products



Benzylhemiformal in an aqueous solution is decomposed to formaldehyde and benzyl alcohol. The decomposition of benzylhemiformal releases all formaldehyde it contains, as described below.



The total free formaldehyde content in a product containing 0.15% benzylhemiformal corresponds to 0.044%

A method for the analysis of benzylhemiformal is not possible, because the parent compound cannot be identified under experimental conditions (7).

The latest Opinion on benzylhemiformal is from 1998 (SCCNFP/0033/98)). The SCCNFP concluded that, *"Under the assumption of a complete release of HCHO out of the Benzylhemiformal (P21) molecule and the given maximal product concentration of 0.15% a HCHO content of less than 0.05% is to be expected.In real figures related to the use of Benzylhemiformal as a preservative in "rinse-off"-cosmetic products with a maximum concentration of 0.15% means that the maximum possible exposure of ……."* Classification: 1 at a maximum concentration of 0.15% in rinse-off products

6. Summary

It is demonstrated that in aqueous solutions, imidazolidinyl urea, diazolidinyl urea sodium hydroxymethyl glycinate and benzylhemiformal release some or all of the formaldehyde they contain, and thus, they may not be available for analysis as parent compounds in cosmetic products.

A MEKC method is published for the analysis of imidazolidinyl urea, in which it was not established that the chromatographic peak obtained by the analysis of imidazolidinyl urea was in fact the intact compound. The method could not be reproduced in another testing laboratory. Similarly, a HPLC method is published for the analysis of diazolidininyl, in which it was not established that the chromatographic peak obtained by the analysis of diazolidinyl urea was infact the intact compound. Furthermore, the applicability of the HPLC method validated for the analysis of diazolidinyl urea in an experimental cream has not been demonstrated for the analysis of this compound in the marketed cosmetics. HPLC, CZE and NMR studies have indicated that both imidazolidinyl urea and diazolidinyl urea may be a mixture of isomers. It appears that it is impossible, with present state of knowledge, to develop a method(s) for the analysis of imidazolidinyl urea and diazolidinyl urea as parent compounds in cosmetic products.

Sodium hydroxymethyl glycinate and benzylhemiformal, present in a cosmetic product, theoretically should release all of the formaldehyde they contain. Thus, an analytical method(s) for the identification and quantification of these preservatives in cosmetic products is not necessary.

The maximum authorised concentrations of imidazolidinyl urea, diazolidinyl urea, sodium hydroxymethyl glycinate and benzylhemiformal in cosmetic products are based on the Opinions of SCC/SCCNFP. Only in the case of benzylhemiformal, SCCNFP considered complete decomposition of the preservative releasing total formaldehyde of the compound as free formaldehyde. The decomposition product of Sodium hydroxymethyl glycinate, e.g. sodium glycinate cannot be considered harmful. As regards the decomposition products of imidazolidinyl urea and diazolidinyl urea, it may be considered that they were present in the test solutions used in the experiments performed for the elucidation of toxicity of the parent compounds. And thus, the safety profile of the decomposition products has been elucidated together with that of parent compounds.

A possibility to overcome the unavailability of the analytical method(s) for these 4 formaldehyde releasers may be to determine total formaldehyde content in a product and relate this amount to the amount of the formaldehyde releaser. But this approach can only be used when the formaldehyde releaser in a product can be unequivocally identified, and when it is guaranteed that there is only one source of formaldehyde in the product. Both of these conditions appear to be impractical.

7. Opinion

SCCNFP has reviewed the previous SCC/SCCNFP Opinions on imidazolidinyl urea, diazolidinyl urea, sodium hydroxymethyl glycinate and benzylhemiformal (entries 27, 46, 51and 55 respectively in Annex VI of Cosmetic Directive) and analytical problems associated with the determination of these compounds. The SCCNFP does not recommend a general amendment of these entries, so that the maximum allowed concentration could be expressed as a concentration of total formaldehyde.

In the absence of analytical methods to check the compliance of cosmetic products with respect to the content of the four preservatives, consumer safety may be ascertained by adequately assessing the presence of formaldehyde in the cosmetic products; the total content of formaldehyde in the finished cosmetic product must not exceed 0.2%

8. References

1. Commission Directive 90/207/EEC. *Off. J. Eur. Commun*. L108, 92 (1990)
2. Engelhardt H and Klinkner R (1990) Determination of free formaldehyde in the presence of donators in cosmetics by HPLC and post-column derivation. *Chromatographia* 20, 559-566.
3. Michalakis GM and Barry EF (1994) Determination of imidurea in cosmetic products by capillary zone electrophoresis and miscellar electrokinetic chromatography. *J. Soc. Cosmet. Chem*. 45, 194-202
4. Schouten A, Van Osenbruggen WA, De Vries AJ and Verhoef A (1996) Methods of determination of preservatives mentioned in the EC Council Directive regarding cosmetic products. 122. Progress report on the " Selection and development of methods for the determination of Germall 115, Germall II and hexetidine in cosmetic products". TNO report V.96.619, TNO Nutrition and Food Research Institute, Netherlands

5. Williams RO, Mahaguna V and Sriwongjanya M (1997) Determination of diazolidinyl urea in a topical cream by high performance liquid chromatography. *J. chromatogr*. B 696, 303-306.
6. Gevers EchTh (1994) Methods of determination of preservatives mentioned in the EC Council Directive regarding cosmetic products. 114 determination of sodium hydroxymethyl aminoacetate in cosmetic products. TNO report V.94.479, TNO Nutrition and Food Research Institute, Netherland
7. EU Commission, Proposal Future Research DG Enterprise. Document 00/Enter/COS/18

Annex

Free formaldehyde equivalent to maximum authorised concentration of certain formaldehyde releasers

Nr.	Compound	Maximum authorised concentration	Formaldehyde equivalent
VI,1,55	Benzylhemiformal, (containing 1.5 mole formaldehyde)	0.15%	0.044%
VI,1,51	Sodium Hydroxymethylglycinate	0.5%	0.118%
VI,1,46	Diazolidinyl Urea	0.5%	0.215%
VI,1,27	Imidazolidinyl Urea	0.6%	0.186%