The Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) has been requested to give an opinion on the safety of alpha-Hydroxy Acids in cosmetic products.

The attached Position Paper of the SCCNFP has been prepared in this respect.

The Commission services invite interested parties for their comments.

Please send your comments before 15 September 2000 at the following e-mail address :

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

POSITION PAPER

CONCERNING

THE SAFETY OF ALPHA-HYDROXY ACIDS

Adopted by the SCCNFP during the 13th plenary meeting
of 28 June 2000

1. Terms of reference

The safety of α-hydroxy acids in cosmetic products has been questioned by some Member States with respect to their dermal tolerance.

Hydroxy acids have a long history of use in dermatological preparations and recently have become important ingredients in cosmetics. Concerns on both the dermal and systemic safety of these materials has led to calls for their listing in Annex III (List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down) to the Cosmetics Directive 76/768/EEC.

2. Position of the SCCNFP

Definition of AHAs

AHAs are carboxylic acids substituted with a hydroxyl group on the alpha carbon. The AHAs most commonly used in cosmetic products are glycolic acid and lactic acid. Glycolic acid is alpha hydroxy acetic acid, lactic acid is alpha hydroxy propionic acid. Other AHAs used include citric acid (a dihydroxy acid), 2-hydroxyoctanoic acid (alpha hydroxycaprylic acid), and 2-hydroxydecanoic acid (alpha hydroxycapric acid).

Introduction

Since 1992 there have been many products marketed as cosmetics designed to exfoliate the skin [1] [2]. These products most often contain glycolic and lactic acids, which are generally referred to as α-hydroxy acids (AHAs). Market claims for products containing AHAs have included diminished skin wrinkling, evening skin tones, skin softening/smoothing, repair of sun damage, repair of imperfections such as minor scaring and sun damage, and increased elasticity/firmness [3] [4] [5] [6] [7].

AHAs reportedly function as exfoliants by reducing intercorneocyte cohesion and interfering with intercellular ionic bonding which causes an acceleration of cell turnover in the stratum corneum [8] [9] [10] [11]. AHAs are most effective at promoting cell turnover only in the un-ionized form [12] [13]. Maximum cell turnover is obtained at pH 3[14] . Therefore, products containing AHAs stimulate the highest rate of cell turnover at a pH ranging from 2.8-4.8 [9].

A method of determining the concentration of AHAs in cosmetic products is available [15]. A number of **salon** cosmetic products were analysed and their content of acids determined :

Agent	*occurrence %*	*conc. Range %*	*pH range*
glycolic acid	95	3-67	0.2-4.38
lactic acid	15	5-7	2.48-2.81
(salicylic acid)	5	8	not available

In general consumer products the following were found :

Agent	*Occurrence %*	*Conc. Range %*	*pH range*
glycolic acid	67	1-26	2.42-4.26
lactic acid	22	0.4-9	2.67-5.65
(salicylic acid)	13	0.1-5	4.0-7.4
citric acid	4	0.2-4	2.67-5.38
α hydroxyoctanoic acid	11	0.01-0.4	3.47-3.65
α hydroxydecanoic acid	4	0.04-0.3	3.47-3.86

In 1997 the Cosmetic Ingredient Review (CIR) reviewed the safety of glycolic and lactic acids and their salts and simple esters [16]. The panel concluded that in general consumer cosmetics, these ingredients were safe for use at levels up to 10% at pH 3.5 when formulated to avoid increasing sun sensitivity, or when directions for use include the daily use of sun protection. For salon (professional) products, the panel considered the compounds safe at up to 30% at pH 3.0 when designed for brief, discontinuous use followed by thorough rinsing from the skin and when applied by a trained individual and when application is accompanied by directions for the daily use of sun protection.

The FDA has a number of concerns relating to the safe use of AHAs in cosmetic products :

* The safety of long term use has not been established.
* Limited studies in maintenance of barrier integrity.
* Limited information on effects on absorption of other cosmetic ingredients.
* Effects of AHAs on skin's responses to UV exposure.

The FDA has tested the effect of glycolic acid on the absorption of musk xylol and hydroquinone in hairless guinea pigs; no enhanced penetration of either was observed[17]. AHAs have been observed to markedly increase the skin penetration of Benzophenone-3 (oxybenzone) included in a cosmetic formulation[18] There was no disruption of the skin barrier function after skin treatment with a 5% glycolic acid formulation at pH 3.8[19]. Additional studies to measure the effect of AHAs as penetration enhancers are needed. If penetration is enhanced, the safety profile for an ingredient could be altered through increased exposure.

The FDA initiated clinical studies to investigate the effects of AHA application to the skin on the sensitivity of skin to UV exposure. The first study determined changes in the skin sensitivity by determining minimal erythema dose and by measuring the number of sunburn cells following exposure of skin to UV. The second study determined changes in skin sensitivity by measuring the formation of thymine dimers (an indication of DNA damage) following UV exposure. The National Toxicology Program has approved glycolic acid, lactic acid and their salts for toxicity

testing [20]. The study will focus on photo-toxicity and chronic toxicity. It is understood that a study for photo-carcinogenicity is in progress.

FDA studies on short term photo-toxicity

An investigation of the effects of topical treatment with an α-hydroxy acid (AHA) on the sensitivity of human skin to UV-induced damage[21].

The study was designed to furnish information on whether daily treatment with glycolic acid could alter the sensitivity of normal human skin to UV induced damage. A change in UV transmission could result in greater damage to epidermal cells, which can be monitored by the formation of sunburn cells (SBC's), and by a lowering on the Minimal Erythema Dose (MED).

Designated skin sites over the midback were treated either with the AHA preparation or vehicle control. Applications of 2mg/cm^2 were made daily for 4 weeks. At the end of the 4 weeks, MED and SBC production following 1.5x MED were determined. (NB. SBC's are a more sensitive indicator of UV damage than erythema and SBC's are now considered to be markers of damage to DNA). MED and SBC production were reassessed after the end of the 5th week. No treatments were applied during the 5th week

(The test product 10220/1 was declared as containing 10% glycolic acid at pH3.5. Analysis showed it to contain 8.9% glycolic acid; the reason being that commercial grades include diglycolic acid. The pH of the vehicle control was pH3.92. Stability of the samples was confirmed.)

16 subjects completed the study. They had skin types 1-3.

MED using a solar simulator at the end of week 4 gave the following results :

	glycolic acid treated site	*vehicle control site*	*'normal' skin*
mean	11.8	14.4	14.7
standard deviation	3.5	4.6	4.4

MED using a solar simulator at the end of week 5 (1 week after active treatment) gave the following results :

	glycolic acid treated site	*vehicle control site*	*'normal' skin*
Mean	13.4	14.3	14.1
standard deviation	4.6	4.1	4.4

Statistical analysis showed that the reduction in the MED at the end of week 4 following treatment with the glycolic acid preparation was statistically highly significant ($p<0.01$) compared to the vehicle control and 'normal' skin. At the end of week 5, one week after treatment had ceased, there was no statistical difference in MED.
The mean number of SBC's per High Power Field following a single exposure to 1.5 MED's of UVB at the end of week 4 are as follows :

	glycolic acid treated site	*vehicle control site*	*'normal' skin*
Mean	2.97	1.53	1.10
standard deviation	3.36	1.42	0.75

The mean number of SBC's per High Power Field following a single exposure to 1.5 MED's of UVB at the end of week 5 are as follows :

	glycolic acid treated site	*vehicle control site*	*'normal' skin*
Mean	1.30	1.26	0.87
standard deviation	1.28	1.23	0.79

Statistical analysis showed that the elevation in the number of SBC's at the end of week 4 following treatment with the glycolic acid preparation was statistically significant ($p<0.05$) compared to the vehicle control and highly significant ($p<0.01$) compared to 'normal' skin (there was no difference between the vehicle and 'normal' skin $p=0.6971$). At the end of week 5, one week after treatment had ceased, there was no statistical difference in MED between the three groups although the numbers for the glycolic acid and vehicle treated sites were raised

The conclusion of this study was that treatment of the skin daily with a 10% glycolic acid preparation at pH3.5 for 4 weeks resulted in a significant increase in the sensitivity of normal skin to the damaging effects of UVB as judged by a reduction in the MED and an increase in the numbers of SBC's. Sensitivity returned to normal 1 week after cessation of treatment.

The data generated from the above study was reviewed by the FDA[22]. The verity of the statistical treatment and conclusions were confirmed. Additionally, note was made of two earlier studies coded 3800 and 3813. In study 3800, a 5 day mid back exposure to a 10% glycolic acid solution produced statistically significantly higher mean log(SBC's) than exposure to a moisturiser or no treatment. In study 3813, a 12 week mid back exposure to a 10% glycolic acid solution produced statistically significantly higher mean log(SBC's) than exposure to a moisturiser, sponge, vehicle, or no treatment. These results were consistent with the results of study 4275.

All 3 studies showed clear increases in SBC's with application of 10% glycolic acid. The recover phase of study 4275 indicates there are no clear effects of glycolic acid 1 week after cessation of treatment.

An investigation to assess the influence of topical treatment with α hydroxy acid (AHA) on UVB induced pyrimidine dimers in human skin[23].

The study was designed to furnish information on whether daily treatment with glycolic acid can aleter the sensitivity of normal skin to UV induced damage as measured by the yield of pyrimidine dimers in epidermal cells following exposure to a single fixed dose of UV radiation.

Designated sites over the midback region were treated ($2mg/cm^2$) daily with a 10% glycolic acid preparation pH3.5 (see note above) or vehicle control. At the end of the 4 weeks, subsites were exposed to a fixed dose of UVB (1.5 MED's, the mean MED was $57.8mJ/cm^2$) from a filtered bank of FS 20 sunlamp tubes. Shave biopsies from the irradiated subsites were then obtained immediately after the UVB exposure for determination of pyrimidine dimers.

12 subjects with skin types 1-3 finished the study.

There were 4 test sites in each subject: 10% glycolic acid treated, vehicle control site, no treatment but irradiated, no treatment and no UVB. (During the last week of the study, the MED of the individual subject was determined on a nearby area of normal skin.
The shave biopsies, after fixing at 65°C, were sent to the Brookhaven National Laboratory for determination of pyrimidine dimers.

The overall mean number of dimers was highest in the glycolic acid treated sites (mean 42.9), whereas the mean number of the vehicle and irradiation control sites were similar (39.7 and 40.1 respectively). The untreated, unirradiated sites had the lowest mean 3.5. Only this site was significantly different from the other 3 (irradiated) sites. There was no statistical difference between the 3 irradiated sites although the glycolic acid treated sites had higher numbers of dimers.

	10% glycolic acid, 1.5MED	*vehicle, 1.5MED*	*1.5MED*	*no application, no UVB*
mean	42.9	39.7	40.1	3.5
SD	17.7	14.7	9.4	3.8
SEM	5.1	4.2	2.7	1.1

The data and methodology was assessed by K Thompson of Brookhaven National Laboratory. He suggested that although UV clearly increases the pyrimidine dimer formation in all subjects, subjects might react differently to the vehicle and/or AHA and there was evidence for this at the 1% level. Although with only 12 subjects a conclusion could not be made. Further comments by C Barton[24] confirmed no effects of glycolic acid on pyrimidine dimers but the observed mean differences between glycolic acid and vehicle treatments would be statistically different only if the sample size were to be at least 108 subjects.

Saunder reported that twice daily application of 4% glycolic acid at pH 3.8 to the lower back for 3 months led to a statistically significant ($p<0.05$) decrease in MED of 13% [25]. Some of the subjects experienced no change in MED, but three of the subjects experienced 48% to 50% decreases in MED. Marenus et al. Reported no significant effect on MED after twice-daily treatment for 6 months on the volar aspects of the forearms with a 1.4% AHA product containing lactic acid, 2-hydroxyoctanoic acid and 2-hydroxydecanoic acids at pH 4.2 [26].

Skin Irritation

Facial discomfort assays were reported on glycolic acid and lactic acid at concentrations from 2% to 10% and pH from 3.3 to 6.1 [27]. Different glycolic acid creams at 4% pH 3.7 varied in response from nonstinging to moderate stinging. A panel of 100 subjects applied a 0.5% mixture of lactic acid and glycolic acid to the face once a day for 6 weeks. Even with this low concentration, 26% of the subjects perceived some irritation, mostly itching and stinging sensations [28]. Christensen and Kligman investigated the dependence of stinging response on concentrations with 2.5%, 5%, 15% and 20% lactic acid [29]. They reported that a "near-plateau in peak is reached at 10% with only modest increases with 20%". However, 4 of the 10 subjects experienced slight erythema, and slight scaling the next day.

Data on the pH dependence of glycolic acid irritation shows a marked decrease in irritation as the pH is increased from 3 to 7 [30]. Treatment of the legs with 8% lactic acid at pH 3.0 for 3 weeks induced scaling and hyperplasia. An illustration of the effect of pH is that cumulative irritation testing showed that 13% glycolic acid at pH 4.4 was less irritating than 8% glycolic acid at pH 3.25 [31]. The data indicate that pH is the most important factor affecting the irritancy of AHA products and is more important than concentration. However, tests reported in CIR 95-AHA 47 show that factors beyond pH or concentration can alter AHA irritancy. Glycolic acid at 8% pH 3.6 was rated milder than some of the 4%, pH 3.7 formulations, which ranged from slightly to severely irritating. Lactic acid at 8%, pH 4.3 was milder than one of the 6% formulations at the same pH. No formulation details were provided but it is clear that factors other than pH and concentration can affect the biological response [32]

Reports of 17 RIPTs with AHAs obtained from CIR-95-AHA showed no significant signs of irritation (or sensitisation).

In the Federal Republic of Germany, on the basis of information available to the BGVV it has been recommended that glycolic acid may be used at a level of up to 4% and a pH ≥ 3.8 and lactic acid up to a maximum level of 2.5% and a pH ≥ 5 [33].

Discussion

Despite their widespread use, there is concern on the safety of alpha hydroxy acids. The FDA position that studies need to be performed on :

* evaluation of safety of long term use,
* investigation of the maintenance of barrier function integrity of the skin including the effects on absorption of other cosmetic ingredients,
* effects of AHAs on skin's responses to UV exposure,

is indicative of the lack of sufficient data to provide a full scientific assessment of the safety of AHAs with restrictions on use. However, on the precautionary principle, it is suggested that, until the required data are available, it is reasonable to suggest that :

glycolic acid may be used safely at a level of up to 4% and a pH ≥ 3.8
lactic acid up to a maximum level of 2.5% and a pH ≥ 5

Further, it is recommended that their should be appropriate warnings to the consumer of :

* avoiding contact with the eyes
* avoiding / or affording protecting from UV whilst using products containing AHAs because of the suggestion of susceptibility to increased damage from UV whilst cosmetic products containing them are being used.

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