

ASPECTS ON BIOCIDES USE

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Synopsis

To achieve what is technically necessary with the optimum economy with a simultaneous reduction of human and eco-toxicological risks, important secondary conditions in the selection and use of chemical preservatives have to be considered.

Nevertheless, the use of preservatives in cosmetic preparations always bears a slight remaining risk from the dermatological/allergological point of view. For this reason a specific dermatological/allergological evaluation of observed incompatibilities is extraordinarily important.

I think that our experience, as well as many discussions with dermatologists allows us to conclude that even in future, no preservative of the required microbiological efficiency will become available which at the same time has an absolutely zero potential for sensitizing of the human.

Talking about preservatives with a proven minimum sensitization potential, such as Euxyl K 400, all side effects in the course of the monitoring should be estimated.

This estimation has to lead to a risk/benefit ratio which does not endanger the user more than necessary considering all available experience.

Premature and non-proven publications can discredit active agents quicker than new ones can be developed.

Riassunto

L'attenta selezione dei conservanti per uso cosmetico è molto importante per evitare i rischi eco-tossicologici connessi con il loro impiego, impiego che comunque, presenta rischi di carattere sia allergologico che dermatologico. Per questi motivi è molto importante valutare preventivamente gli eventuali effetti allergo-dermatologici.

Secondo la nostra esperienza suffragata anche dal parere di molti dermatologi, credo si possa affermare che neanche in un prossimo futuro sarà possibile reperire sul mercato conservanti che attivi dal punto di vista microbiologico, siano non sensibilizzanti per l'uomo.

Parlando di conservanti come l'Euxyl K 400, di cui si conosce il potenziale di sensibilizzazione, è necessario studiarne a fondo tutti gli eventuali effetti collaterali. L'approfondita conoscenza di questi

dati è necessaria per valutare il rapporto rischio-beneficio del composto da noi selezionato per l'uso. Spesso la pubblicazione affrettata di dati ritenuti negativi perchè non attentamente valutati, può compromettere l'uso di nuovi derivati ancor prima del tempo occorrente per sviluppare nuovi prodotti.

1. Introduction

The Council of Europe adapted the laws of the member states on cosmetic preparation by creating the guide-line 76/768/EWG.

Article 2 says:

“Cosmetic preparations within the European Community must be harmless to human health in normal usage”

Article 6 paragraph 1 c. defines the stability of a cosmetic product as follows:

“The period of time the product keeps its original function when stored appropriately and remains stable especially with article 2.”

Cosmetic products with a period of stability of less than 30 months have to show the expiry time.

Both articles demonstrate the necessity of avoiding unlimited growth of micro-organisms in cosmetic products for technical as well as for health reasons.

In demands for improved microbiological purity of cosmetic products, the prime arguments, of course, are those for safety with regard to health. However, it should not be forgotten that contaminated or spoiled goods which are no longer able to be sold are expensive to dispose of. Therefore, environmental aspects of no little importance are also arguments in favour of good microbiological quality.

The numbers of adverse reactions to cosmetic products reported in practice are very low in relation to the numbers of pack units sold (IKW: over 13 years 1/1.9 million pack units). This is most certainly attributable to the increasing effort to improve microbiological quality by more hygienic production and an optimised use of chemical preservatives.

2. Preservation

Preservation means the inclusion of temporarily limited protecting mechanisms in the products

to keep the initial quality.

An uninhibited growth of micro-organisms in cosmetic products may have consequences:

- for products in container
- for technical plant
- for the production
- for the environment

e.g. - odour

- health risks
- increasing complaints on skin irritation

Some aspects will be reviewed.

Contaminating organisms

- may metabolize components of the formulation
- secrete material which may react with components
- microbial cellular components and/or metabolic by-products may serve as nutrients for other organisms
- microbial endo- and exo-toxins may cause adverse reactions in consumers, e.g. lipopolysaccharide (LPS) cell envelope of gram negative organisms is pyrogenic
- microbial toxins such as staphylococcal enterotoxins are mutagenic and increase the rate of cell division of lymphocytes

A long term protection against microbial growth by physical methods is practically impossible, because of the actual compositions and handling of the cosmetic products. Products that can always be recontaminated cannot be protected by physical methods.

By the use of chemical preservatives, the growth of bacteria, yeasts and moulds can be inhibited and spoilage can be avoided while the product is in the trade channel and in the hands of consumers. The users are protected from possible health risks caused by microbial toxins and other products of metabolism.

As common practice shows: preservatives are essential, and only a chemical preservative guarantees permanent protection of cosmetic products.

3. Requirements for chemical preservatives

“Preservatives are defined as chemical substances or mixtures with low toxicity and good skin tolerance which in low concentrations, generally 0.1 - 5000 µg/ml or g, destroy or inhibit the development of micro-organisms and exhibit good compatibility with the product that they are to protect.” (Wallhäußer)

A modern preservative has to be an optimal compromise of the required profile:

A. Microbiology

- broad spectrum of effect against micro-organisms
- biocidal = rapid onset of effect
- biostatic = prolonged effect

B. Application

- compatibility with other ingredients
- temperature stability
- stability at different pH values
- resistance to light
- no problem of incorporation during the manufacturing process.
- specific solubilizing properties -> water
- no additional corrosion
- non unpleasant smell
- high degree of economy

C. Toxicology

- low toxicity potential to human being
- > subject of appendix VI EEC cosmetic regulation

D. Environment

- no adverse effect on the environment
- environment friendly = acceptable risk assessment

Needless to say, no antimicrobial agent fulfils all of these criteria.

So it is a duty of companies like Schülke & Mayr to develop multicomponent preservative systems for the following reasons:

- to increase the spectrum of antimicrobial activity
- to benefit from possible synergistic or additive antimicrobial effect
- to reduce the toxicological hazard by use of lower concentrations of each component preservative
- to reduce the likelihood of the development of adapted organisms
- to obtain possible cost savings as a result of using lower concentrations.

4. Toxicology of preservatives

The most important objectives of the EEC Cosmetic Directive is consumer safety, that means to protect the consumer from health risks and from misleading information.

To meet this objective the guide-line (76/768/EEC) includes a huge list of prohibited materials as well as various positive lists, e.g. the positive list of approved preservatives (Appendix VI).

This list includes only antimicrobial substances checked according to the guide-lines of the Scientific Committee for Cosmetology (SCC) of the EEC commission. The expert opinions on toxicity and compatibility are evaluated by the members of the committee - all independent scientists of all EEC states - and judged as harmless for the recommended application.

The registration also stipulated the maximum concentrations considered to be safe for application in cosmetics.

Today the consumer often is irritated by the endless discussion about preservatives which are always identified as poisonous. In this negative discussion, especially in the cosmetic field, slightly biased arguments are used, in many cases.

From the view point of marketing products free of preservatives are often desired. But the idea that all skin incompatibilities could be avoided with such products is an error.

The argument "free of preservatives" is often true in the legal sense only of the relevant paragraphs, because non of the preserving agents mentioned in appendix VI has been applied. Preservatives - if not applied mainly for the purpose of preservation - or other antimicrobial substances in formulations of cosmetic products may lead to the following statements created by clever advertising agents;

- "free of chemical preserving agents"
- "contains no synthetic preservative"
- "unpreserved"
- "free of preservatives"
- "free of preserving agents"

So the question may be asked if, for example, it is better for the customer, from a toxicological/dermatological point of view, to use a body lotion preserved with 2% of phenethyl alcohol instead of 1% of phenoxy ethauol.

Or what about the increased risk of incompatibilities by the use of preserving substances of "natural origin" like benzoin tiucture, hinokitol, propolis extract or thyme oil? In this case the following should be born in mind:

Many of the most potent toxins are derived from natural sources. Many ingredients of natural products are not yet identified. Their harmlessness is drawn from innumerable reports over centuries of experience which cannot be completely validated from the present scientific point of view.

According to the old law of nature: if natural materials have no side effects and are completely harmless, might not they also be completely ineffective?

To minimize the human and environment risks in the use of chemical preservatives which is absolutely essential for technical reasons, these preparations must be applied only in the technically necessary amounts.

In practice this means

- as little as possible
- as much as technically necessary.

5. Biovalidation - challenge testing

Using the technically necessary amount of a preservative means avoiding a too high as well as a too low dosage.

This means no

Underdosing

which leads e.g. to inadequate effects, a false feeling of security or adaption of the micro-organisms.

as well as no

Overdosing

which leads e.g. to uneconomical work, greater toxicity, greater environmental pollution.

In practice, this means that the evaluation of the concentration necessary for effective safety is of extreme importance.

Preservatives are tested to determine the type and miuimum (optimal) effective concentrations which meet acceptance criteria and documenting for the microbiological safety and stability of cosmetic products.

Chemical preservatives in the concentration recommended for use are only effective, if they are bioavailable.

The amount of free unbonded preservative and its efficacy must thus be determined by meaus of a suitable test. As the amount of preservative detected by analysis is not always identical with the bioavailable amount, due perhaps to absorption, instability and so forth, a preservation load test is the most valuable procedure for determining the preservative effect (long term ef-

fect) in the substrate to be preserved. The most useful results are obtained when the test is carried out in the final container after specified storage times, but this is expensive in practice.

S & M is doing a repetitive challenge test with six inoculation cycles which simulate conditions encountered in practice. Thus, in the S & M Koko test, in various series different concentrations of the preservative to be tested are added to the unpreserved samples. A constant microorganism load is achieved by periodic inoculation (inoculation cycles) of the test preparations. Immediately before inoculation, samples of the individual preparations are streaked out onto nutrient media. The preserving effect is evaluated from the extent of the growth of the micro-organism on the nutrient media. The longer the time to the appearance of the growth, the more effective is the preservative.

In tab. 1 an example is given of the system of evaluation and documentation of the result obtained with a body lotion.

If such results are obtained with actual products, if possible ones coming directly from the production line, it can be assumed that the stability period of 30 months stipulated by the Cosmetics Decree will be achieved.

Because of the current public debate about preservation, and thus about the preservatives used, there are many people who want to reduce the requirements for the preservation of cosmetic products and thus the requirements of such load tests. For example, there is debate about having only microbistatic effectiveness, no multiple load, inoculation with lower numbers of organisms, and other matters.

Based on our fifteen years of experience with load tests for cosmetic products, we believe that minimising the requirements in preservation load tests would put in jeopardy the standards of microbial purity and stability achieved in the last few years. For example, in the majority of cosmetic products, a preservative with only a microbistatic effect is not sufficient even to maintain the initial microbial situation. For pra-

Table I.

INOCULATION CYCLES

Product	Conc. (%)	1 BY+F	2 BY+F	3 BY+F	4 BY+F	5 BY+F	6 BY+F
Blank reading	0	2+ 2+	3+ 3+	3+ 3+	3+ 3+		
	0.05	- -	- 2+	- 2+	3+ 3+	3+ 3+	
	0.10	- -	- +	+ +	+ +	+ +	+ 2+
	0.20	- -	- -	- -	- -	- -	- -

B = Bacteria

Y = Yeasts

F = Fungi

*Euxyl K 400

tical requirements, the preservative chosen must have microbicidal properties.

6. Sensitization potential of Euxyl K 400

Incompatibilities with preservatives, especially to skin, are discussed again and again by experts such as dermatologists, as well as less professionally by the public.

In the course of a toxicological evaluation of a preservative special attention is paid to the dermatological tests, especially the sensitization potential.

Euxyl K 400 used since 1984 has been increasingly applied in cosmetics since 1987 as an alternative to the isothiazolinones.

sen. None of the studies showed any sensitization potential of Euxyl K 400. It is well known that results of animal tests cannot directly be applied to humans. Thus it is impossible to draw the conclusion that the tested substance will definitely not lead to allergies in human beings from the negative results of animal tests.

It can only be stated that a substance which showed negative results in e.g. the Magnusson/Kligman test is likely to have only a very slight sensitization potential for humans.

So it makes sense to monitor the sensitization effects of a substance in future applications due to the possibility of allergic reactions.

Up to now more than 8000 consecutive patients with suspected allergic contact dermatitis have been patch-tested with Euxyl K 400 in more than 20 different hospitals.

Let me repeat that these tests have been carried out on patients already suffering from certain

Table II.

	Number of patients	Test conc. Euxyl K 400	posit. react with clinical relevance	
DKG*	3.762	0.5% pet	19	0.5%
Bologna	2.057	2.5% pet/eth	11	1.1%
Modena	1.033	2 % PG	21	2 %
Göttingen	816	0.5% pet	4	0.5%
Hamburg	482	0.5%pet	2	0.4%

* DKG: Deutsche Kontaktdermatitis-Gruppe
(German Contact Dermatitis Group)

In the following let me give you some details on the sensitization potential of this preservative.

In several laboratories Euxyl K 400 has been independently investigated for sensitizing potential in animal tests. The maximization test after intradermal and repeated topical application to the guinea pig (OECD guide lines) according to B. Magnusson and A.M. Kligman has been cho-

skin diseases to answer the question whether an irritating effect could be caused by Euxyl K 400. Persons with healthy skin cannot be compared with these patients.

The results of some finished patch tests are shown in the following table

In Contact Dermatitis 1991: 25, 1-18 the Euro-

pean Environmental and Contact Dermatitis Research Group recommends for dibromo dicyanobutane a test concentration of 0.1% (corresponding to 0.5% of Euxyl K 400) for patch testing.

When estimating the sensitization potential of a preservative the number of applications must always be viewed in relation to the numbers of cases of proven side effects over an observation period of several years. Only on the basis of this risk/benefit ratio can the sensitization potential be evaluated fairly.

It may be assumed that there were in 1988 about 2×10^9 , in 1989 6×10^9 , and in 1990 6×10^9 applications by cosmetic users in the form of rinse off and stay on products preserved with Euxyl K 400.

If the patch test results are considered against

the above figures, the allergenic potential of Euxyl K 400 is apparently only low.

According to statements of well-known dermatologists Euxyl K 400 is a preservative with an extremely small sensitization potential and thus is a very good alternative to isothiazolinones and other preservatives. This judgement is based on the results of the monitoring the side effects of Euxyl K 400 for several years, showing a very good risk/benefit ratio.

This is clearly demonstrated by a comparison of the results of Euxyl K 400 shown in figure 2 with those of other preservatives evaluated in the DKG, Bologna and Modena studies.

The next table shows the information drawn from personal communications.

Table III.

		Positive react. with clinical RELEVANCE
DKG* study	formaldehyde	2.4%
parabens	3%	
isothiazolinones	5.2%	
Bologna	isothiazolinones	4-6%
Modena	parabens	2.8%

* DKG: Deutsche Kontaktdermatitis-Gruppe

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