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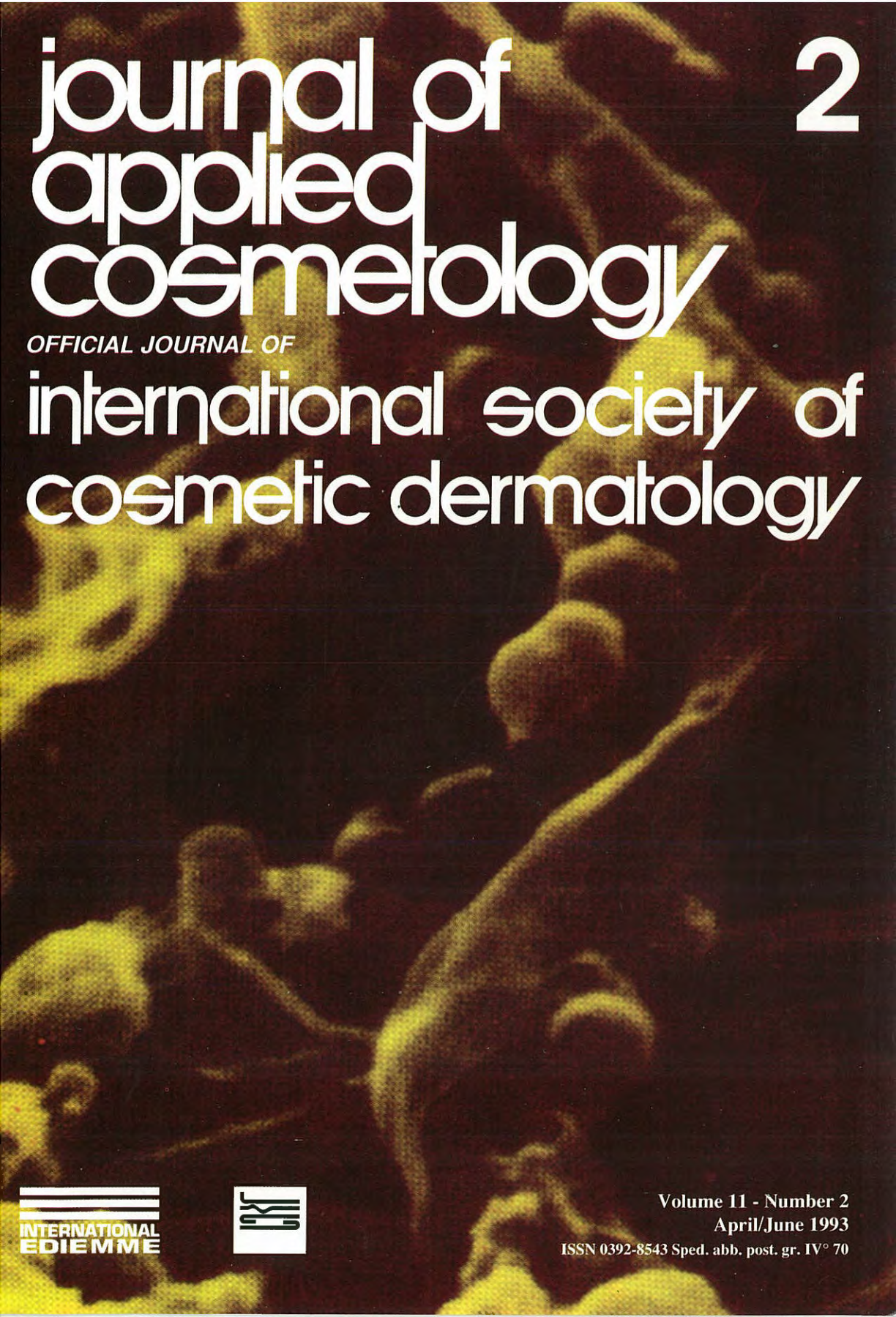

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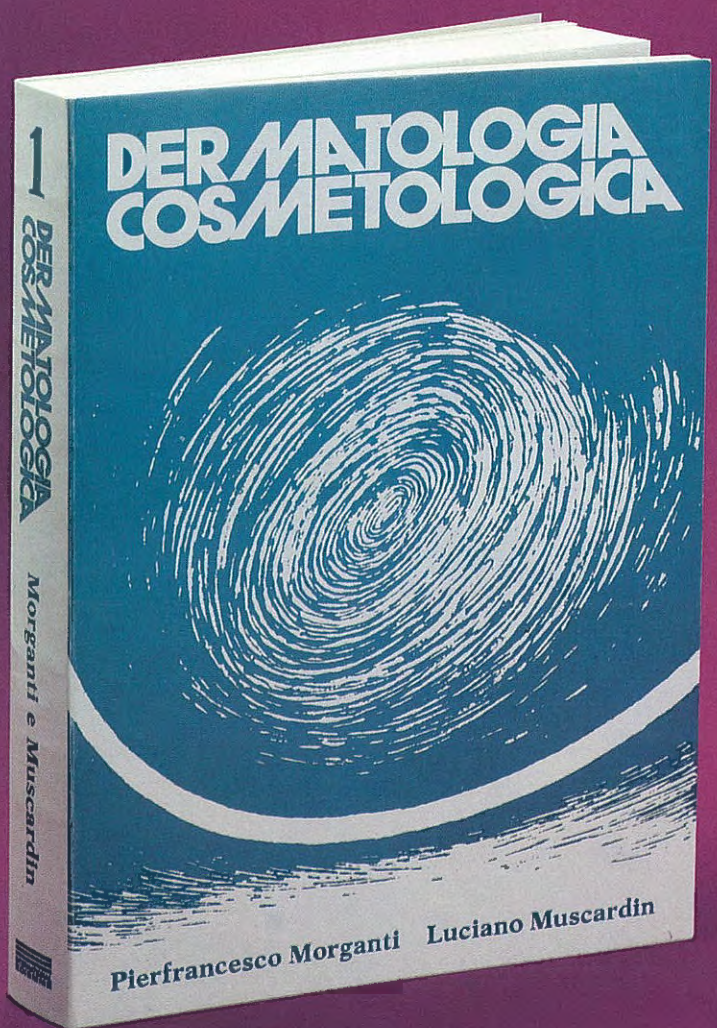

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J. Appl. Cosmetol. 11, 49-53 (April - June 1993)

THE ROLE OF PRESERVATIVES IN CONTROLLING MICROBIAL CONTAMINATION INTRODUCED IN THE MANUFACTURE OF COSMETICS

E.F. Warwick
Rohm and Haas Company Spring House, Pennsylavania, USA

Receveid: *October 30, 1991. Presented at the IV International Congress on Cosmetic Dermatology "Progress in Cosmetic Dermatology: Science and Safety" Roma (Italy) October 31 - November 2, 1991.*

Key Words: *Microbial Contamination; Preservatives; Microbiological Monitoring; Programs.*

Synopsis

The use of a preservative or a preservative mixture cannot be the only means by which cosmetics and toiletries are protected from microbial contamination introduced during the manufacturing process. The use of a preservative must be coupled with laboratory tests which demonstrate that the preservative system is effective and stable in the product. In addition, manufacturing practices must strictly control the levels of microorganisms which are introduced to products via routes such as raw materials and improper storage and handling practices. A microbial quality assurance program is essential in manufacturing cosmetics and toiletries. Such a program will ensure that use levels of preservatives are not consumed eradicating high levels of contaminants introduced during manufacturing so that an adequate level of the preservative will be present to protect the product throughout its life.

Riassunto

L'uso di un conservante o di una miscela di conservanti non può essere il solo mezzo per eliminare i contaminanti introdotti durante i processi di lavorazione. L'uso del conservante deve essere convalidato dai test di laboratorio che ne dimostrino l'efficacia e la stabilità nel prodotto finito. Inoltre tutto il processo di lavorazione deve essere eseguito in modo da ridurre il livello dei microrganismi introdotti sia attraverso le materie prime che attraverso l'ambiente. É, quindi, di fondamentale importanza seguire le norme di buona fabbricazione affinchè i preservanti introdotti nel cosmetico servano a conservarlo bene durante tutto l'arco della sua vita.

Preservatives are designed to protect clean products from occasional microbial challenges encountered through use. The addition of a preservative or preservative mixture to a product cannot be the only means by which cosmetics and toiletries are protected from microbial contamination in a manufacturing environment. To prevent contamination of cosmetics and toiletries, it is essential that each of the following items are addressed in developing and manufacturing such products:

- An adequate level of a preservative must be added to the product.
- The preservative must be stable in and compatible with the product for the timeframe over which protection is required.
- Precautions must be taken as to how the product is manufactured, stored and handled (i.e., good hygiene practices must be followed in manufacturing).

Why do contamination problems occur in preserved products ?

On-going emphasis on safety, regulatory and environmental issues continue to impact on the preservation of cosmetics and toiletries. As a result, preservative use is being driven towards lower use levels, lower toxicity active ingredients (including "natural" and even "preservative free" products), and less volatile active ingredients.

Unlike the forgiving high levels of preservatives such as formaldehyde used in the past, typical use levels of many of today's preservative systems are not able to withstand continual repeated challenges of high levels of microorganisms which occur in improperly maintained manufacturing facilities. In such situations, the preservative(s) can be consumed or overwhelmed, and the product will no longer be protected from subsequent microbial challenges. This can result in consumer exposure to contaminated or inadequately preserved products.In addition, on-going focus on water conservation and waste minimization and detoxification is forcing manufacturers to recycle process and wash water, and to treat wastes prior to discharge. When recycled water is not effectively monitored and treated with biocides, microbial contamination problems will arise and will provide yet another source of challenges to the preservative systems used in products which come into contact with recycled water. Tightening regulations on waste water discharges can also lead to greater reluctance to clean and sanitize equipment since it is more difficult to discharge large volumes of water containing cleaners and sanitizers such as bleach or quateraty ammonium salts. If cleaning and sanitization frequency is reduced to avoid discharge regulations, microbial contamination problems can occur more frequently.

Unlike older preservatives such as formaldehyde, the preservatives used today have very low vapour pressures. The use of low vapour pressure actives results in little or no preservative presence in the headspace and condensation in storage tanks. As a result, microorganisms introduced into the headspace of a storage tank by poor storage and handling practices will often proliferate in the condensate water on the product surface, on the walls and ceiling of the tank and on the agitator shaft. When new material is added to the tank, the microorganisms on the walls and surface of the product are introduced to the bulk preserved product. Over time, this process initiated by poor storage and handling practices can lead to microbial contamination in a preserved product because:

- Some or all of the preservatives in the product can be consumed each time large numbers of microorganisms introduced to the product are

eradicated. Eventually, the preservative can be depleted.

- Biofilms can form on unprotected surfaces in storage tanks. Biofilms provide protection for microorganisms making it more difficult for the preservative in a product to eradicate the microorganisms.

- As a greater number of microorganisms come into contact with a preservative system there is a greater likelihood of encountering microorganisms which are less susceptible to the preservative. Continued poor storage and handling conditions can lead to the development of a microbial population which is not controlled by the preservative system, particularly when an inadequate level of preservative is being used.

- The more often large microbial populations are exposed to inadeqnate levels of preservatives, the greater the chance that some microorganisms may respond to the preservatives and after their susceptibility to it. This can lead to the development of a microbial population which is resistant to the preservative system being used.

How do you prevent contamination problems?

The first step in preventing microbial contamination in products is a thorough laboratory evaluation of candidate preservative systems during product development. Such an evaluation should include rigorous multiple challenge testing and accelerated aging studies. It is critical to include accelerated aging studies in evaluating preservative systems to ensure that the preservative system chosen will be stable in and compatible with the formulation from the time the product is manufactured until it is used by the consumer. Accelerated aging can be incorporated into the challenge test by performing additional challenges after various periods of aging. In addition, following the preservative levels remaining in the product after various aging intervals provides valuable information for assessing the ability of the preservative to protect a product over an extended time period.

The next step in preventing microbial contamination in products is to ensure that the facilities manufacturing the product are following good hygiene practices. Good hygiene practices must encompass the following:

- Raw materials
- Process water
- Cleaning and sanitization practices
- Storage and handling practices.

Raw materials can be a troublesome source of microbial contaminants in manufacturing facilities. Aqueous raw materials often support microbial growth, and many non-aqueous raw materials can harbour bacterial and fungal spores. Natural raw materials are usually very susceptible to microbial contamination. Raw materials which are susceptible to contamination must be treated and/or preserved prior to entering the manufacturing area. Microbial limit specifications and preservative specifications should be put in place for these raw materials to ensure that contaminated materials do not enter the facility, and that raw materials which are readily contaminated are protected with a preservative. Specifications must also include formulations or dilutions of raw materials such as aqueous solution of dyes which are made in the facility and which are often more susceptible to contamination than the raw materials as received.

Water is probably the most common source of microbial contamination in manufacturing facilities. Mains water often contain low levels of microorganisms such as the ubiquitous *Pseudomonas* species as water authority standards do

not demand the absence of all microorganisms. Given that water supplies will bring this low level of microorganisms into a manufacturing facility, care must be taken to ensure that the microorganisms are not exposed to environments which will allow them to multiply.
Treatment units such as de-ionizing resin beds and reverse osmosis purifiers offer ideal sites for bacteria to collect and multiply. Such units must be cleaned and disinfected regularly to prevent accumulation of microorganisms. Stagnant water must be avoided in pipes, and, if present, must always be flushed to waste with copious quantities of microbially clean water prior to using the pipe. If water is stored in tanks prior to use it should be treated with a biocide or stored at >75°C to control microbial growth.

Cleaning and sanitization procedures are also important tools which will help prevent microbial contamination problems if they are use correctly. It is crucial that such procedures are validated first to ensure they are effective. In addition it is equally important that the procedures are documented so that the desired results (eradication of contaminants) are achieved by all workers every time they are used. It is not enough to state that equipment be sanitized with steam after each use. An effective procedure would specify in detail when it needs to be done, how to clean product residues out to the system prior to steaming, how and where to steam, how long to steam, and how to validate that the procedure was effective.

Storage and handling practices in manufacturing can have a tremendous impact on the microbial quality of products. from the start, a manufacturing facility needs to be designed with hygiene issues in mind. Design should include details such as:

- High quality, non-porous materials of construction
- Short pipe runs
- Minimum number of joints, valves, manifolds, gauges
- No dead end lines
- Sloped pipes for good drainage
- Storage tanks with hatches that seal and air vents which are protected with microbiological filters.

In addition, **worker training** which emphasizes the importance of good plant hygiene and how to practice good plant hygiene is invaluable. Workers need to gain a basic understanding and appreciation of the facts: microorganisms are very small, microorganisms are everywhere, microorganisms grow rapidly, and microorganisms cause raw materials and products to go bad. Worker training should also raise the level of awareness of the ways in which they might introduce microorganisms into raw materials and products if specified practices and procedures are not followed. Examples of actions workers who receive appropriate training can and will control include:

- Leaving tank hatches open
- Pumping air into storage tanks with new deliveries
- Leaving hoses and pipes filled with product or water
- Improper use of protective clothing in packaging areas
- Improper cleaning and sanitization practices.

Finally, **microbiological** monitoring programs are a very important component in any program designed to ensure that contamination problems in manufacturing are controlled and minimized. Raw materials, water, products and equipment must be sampled for microbiological analysis on a regular basis. The frequency for sampling should depend on issues such as:

- Susceptibility of raw materials or products to contamination
- How water is treated, stored and used in the

facility
• How often equipment is shut down or changed over

For microbiological monitoring programs to be effective, in addition to sampling and analysis, one needs to develop responses to the detection of contamination whether the level is low or high. For example, if a low level of contamination is detected in a raw material should it be treated, returned to the supplier, used in the next production run, etc.? If a piece of equipment is found to be harbouring a contaminant how should it be cleaned and sanitized, and how should you verify that the contaminant has been eradicated before you use the equipment again?

In conclusion, if the above practices are incorporated into the product development and manufacturing of cosmetics and toiletries, the incidence of microbial contamination problems should be greatly reduced.

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J. Appl. Cosmetol. **11**, 55-62 (April - June 1993)

ASPECTS ON BIOCIDE USE

K.H. DIEHL
Schülke & Mayr GmbH, R & D Special Additives International D-2000 Norderstedt

Receveid: *October 30, 1991. Presented at the IV International Congress on Cosmetic Dermatology "Progress in Cosmetic Dermatology: Science and Safety" Roma (Italy) October 31 - November 2, 1991.*

Key Words: *Cosmetic Preservation; Toxicolgy of Preservatives; Challenge Test; Biovalidation; Contact Dermatitis; Euxyl K 400.*

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 tbe 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 bave to sbow 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 hy-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 tbe 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 he 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 an 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 ethanol.
Or what about the increased risk of incompatibilities by the use of preserving substances of "natural origin" like benzoin tincture, 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 amouut 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.

Product	Conc. (%)	INOCULATION CYCLES 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

ctical 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 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

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-

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 x 10^9, in 1989 6 x 10^9, and in 1990 6 x 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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J. Appl. Cosmetol. 11, 65-68 (April - June1993)

CONTACT ALLERGY AND IRRITATION FROM PRESERVATIVES

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Receveid: *October 30, 1991. Presented at the IV International Congress on Cosmetic Dermatology "Progress in Cosmetic Dermatology: Science and Safety" Roma (Italy) October 31 - November 2, 1991.*

Key Words: *Cosmetic Preservatives; Patch Testing; Katon CG; Contact Allergy; Parabens; Quaternary Ammonium Compounds.*

Synopsis

The use concentration of preservatives in topical products is generally in the range of 0.01% to 1%. Owing to their inherent reactivity, many of these chemicals can induce allergic contact dermatitis and occasionally irritant contact dermatitis. An overwhelming number of preservative formulations are marketed under various trade names and synonyms. Unfortunately, there is no single source of information regarding the production, import and use of the different preservatives. The present paper focus on 5 topics related to contact allergy and skin irritation caused by preservatives:

1) The relationship between predictive test results in animals and man and the clinical experience.
2) Routine patch testing with preservatives - ingredient labelling.
3) Kathon CG.
4) Change in the industry's choice of preservatives. New preservatives bring along new reports on allergic contact dermatitis.
5) Quaternary ammonium compounds as irritants.

Riassunto

La concentrazione d'uso dei conservanti per i prodotti di uso topico varia in genere dallo 0,01 al 1%. A causa della loro elevata reattività questi composti chimici possono indurre dermatite da contatto e occasionalmente dermatite irritativa da contatto. Molti conservanti sono catalogati ed elencati con diversi nomi brevettati, presentati spesso anche con sinonimi. In questo lavoro si pongono a confronto cinque problematiche connesse con l'insorgenza di eritemi cutanei o con allergie da contatto provocate dall'uso di conservanti.

1) La relazione riscontrata tra i tests predittivi sull'animale e sull'uomo e l'esperienza clinica.
2) I patch-test con i conservanti in relazione agli ingredienti riportati in etichetta.
3) Kathon CG
4) Cambiamenti nell'uso dei preservanti. L'uso di nuovi conservanti comporta la comparsa di dermatiteallergica da coutatto.
5) Gli ammoni quaternari come irritanti.

Preservatives may be defined as chemicals added to cosmetics, toiletries, household products, topical drugs, and aqueous and emulsion systems in industry to prevent them from spoiling. Biocides are chemicals capable of destroying living organisms, they are often used as preservatives and some are used as antimicrobial drugs. Common to these chemicals is their ability to interfere with certain chemical reactions and/or with the growth of molds, fungi, hacteria or parasites. The concentration used for preservatives in the finished products is generally in the range of 0.01% to 1%.

These reactive chemicals can induce allergic contact dermatitis, hence they are often included when dermatitis patients are patch tested.

An overwhelming number of preservative formulations are marketed under various trade names and synonyms. Unfortunately, there is no single source of information regarding the production, import and use of the different preservatives.

Predictive tests with biocides related to the clinical experience:

There are examples of biocides with a strong sensitizing potential in predictive allergy test in animals - but giving a low incidence of allergic contact dermatitis during practical use. Chlorocresol was a strong sensitizer in the guinea pig maximization test with a frequency of positive reactions ranging from 15% to 84% of the animals tested, depending on the concentration used for induction. Interestingly, the use of chlorocresol as a preservative in topical corticosteroids is extensive, and in spite of that, clinical chlorocresol allergy occurs only sporadically (1).

Cytox 3522, containing 10% methylene-bisthiocyanate, and equivalent products are used as biocides in industrial water systems. Cytox 3522 sensitized all animals in the guinea pig maximization test. In spite of that, human sensitization has not yet been reported. These two chemicals represent examples of strong experimental allergens used in the environment but which cause only few cases of clinical contact allergy.

On the other hand, there are biocides with a lower sensitizing potential, which provoke a significant number of contact allergies, probably due to widespread use, often in higher concentrations.

The parabens are moderate to weak experimental sensitizers. They are widely used and about 6000 of 19000 cosmetic formulations in the United States are preserved with parabens. Paraben allergy occurs with a frequency around 1% in patch test materials, which justifies the inclusion of parabens in the standard series for patch testing. Among 8000 patients tested at Gentofte from 1971 to 1986 0.8% of females and 1.2% of males were paraben sensitive (2). Earlier, when parabens were used in higher concentrations as antifungal agents - paraben sensitivity was more frequent. Edman and Möeller (3) and Gollhausen and co-workers (4) both found an increasing frequency of paraben sensitivity over the years among their eczema patients subjected to patch testing. Animal data with the parabens show a low sensitization rate. Goodwin (5) failed to sensitize with ethyl-paraben using the guinea pig maximization test. Maurer (6) used the optimization test and sensitized 3-4 of 20 guinea pigs to methyl-paraben - and none of 20 to propyl-paraben using epicutaneous challenge, while 10 to 20 reacted following intradermal challenge.

The predictive test data cannot stand alone but must be evaluated in relation to diagnostic patch tests and the exposure situation.

Routine patch testing with preservatives - ingredient labelling.

The Danish contact dermatitis research group tested a number of biocides on consecutive eczema patients in 1983-1984 (7). Some positive reactions were found, but they were of limited clinical value, because the results were frequently inexplicable. In most cases it was not possible to determine if the reaction was a false positive patch test or if it was an allergic reaction, where exposure to the allergen was not traced. In a recent review on the recommended patch test concentration for preservatives it was striking that for 21 of 34 chemicals it was not possible - on the published data - to give a firm recommendation (8).
This is an argument for the demand for labelling the biocide content on all products, in order to make it easier to choose the appropriate biocides for testing of the patients.

Kathon CG (Cl+me-isothiazolinone) MCI/MI).

MCI/MI is, of course, very much in focus - due to its widespread use and the occurrence of contact allergy to the compound. The active ingredients in Kathon CG, chloromethylisothiazolinone and methylisothiazolinone are strong experimental sensitizers (9-10). The allergen is now included in the standard series and the patch test concentration is currently 100 ppm in aqueous solution. This is a compromise and 200 ppm may yield more relevant positive reactions (11). The MCI/MI story is still not complete and more details are to be expected. A recent European multicentre study revealed that 3% of routinely patch tested eczema patients were positive to MCI/MI with a great variation in the frequency between the 22 centres (12).

Change in the industry's choice of preservatives.

The choice of preservatives in the cosmetic industry is interesting to follow. Unfortunately, the figures are published with a considerable delay; the latest figures are from 1984 (13). besides Kathon CG, Germall 2 and DMDM hydantoin are used in increasing amounts and subsequently reports on contact allergy to these new preservatives have appeared in the literature (14-15). New preservatives are followed by new reports on allergic contact dermatitis (16).

Quarternary ammonium compounds as irritants.

Irritant dermatitis from preservatives is probably very rare as the use concentrations used are so low. However, some preservatives may be added in higher concentrations to the product to yield an antimicrobial effect. An udder ointment marketed in Denmark was significantly more irritating than alternative skin care products in a chamber-scarification test on volunteers, due to a high content of benzalkonium chloride (17).

In conclusion a better understanding of preservative contact allergy requires:

1) a balanced view about the results of the predictive allergy test and dose-response determinations, 2) information about biocide consumption and distribution, and 3) labelling of biocide content in the products. The quotation from Theophrastus Paracelsus is still pertinent:
"Alle Ding sind Gift
un nichts ohn' Gift.Allein die Dosis macht,
dass ein Ding kein Gift ist".

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Lorenzo il Magnifico in Salute e in Malattia

Emiliano Panconesi, Lorenzo Marri Malacrida
Editore: Ed. Alberto Bruschi, Firenze, 1992. Vol. pag. 65, Figg. 7, Bibliografia, £ 20.000.

The background is that fascinating, genial, frenetic scenery of the Italian Renaissance or, in other words, its heart, Florence. Yet, while the Italians dominated Literature and Art in the whole of Europe, the political mind was practically absent, thus making it possible for foreign invaders to raid the peninsular. In this exciting, historical period dominated the figure of Lorenzo dei Medici, called the Magnificent who, besides wishing to increase the prestige of phylosophy, literature and poetry in Florence and medicine in Pisà, managed to keep an intelligent peace policy with the nearby states, showing himself to be courageous, patient and an able weaver of alliances and political balance. A good poet himself, he was the inspirer and protector of scholars and genial artists.
Focusing their attention on the cultural, artistic and political environment of the second half of the IV century, Emiliano Panconesi, refined scholar of medical science (dermatology), literature and art, and Lorenzo Marri Malacrida have published Lorenzo il Magnifico in salute e in malattia, with an introduction by Eugenio Garin on the Florentine Renaissance.
Lorenzo the Magnificent died at the age of 43 in 1492 when, with the discovery of the New World by Christopher Columbus, The Modern Era was born. In Italy, The Florentine "Signoria survived for just two years after the death of the "master of city" and then followed the fall of Florence and Italy. Ugly to look at but strong, audacious and valorous, Lorenzo was fond of beauty in all its expressions He was born under the sign of Capricorn and was in the Saturnine circle, that is to say he had the "poetio melancholy" that was considered positive even if linked to negative influences (over - indulgence typical of that ambiguous and many-sided sign of the zodiac. The death of his beloved brother, Giuliano, in the "Congiura dei Pazzi (Madmen Plot) on April 26, 1478 when he had also been wounded in the neck, left its mark on Lorenzo. It seems that he suffered from constitutional eczema while we are sure that he was plagued by gout and that he visited various spas with some results. The illness and suffering worsened considerably and he was treated according to the zodiacal and magic astrology of the time. He was given a potion of powdered emeralds and pearls, a treatment reserved in extreme moments for kings and popes.
Lorenzo's complex personality has been the reason for the interest in calculating tbe weight of his brain, I,548 gr. in relation to his body weight The co-efficient is very high, 3.045. (Dante Alighieri's was calculated to be 3.268). However, even mediocre subjects and idiots have been known to have a brain of more than average weight.
The death of Lorenzo dei Medici was accompanied by prodigious, premonitory signs. A thunderbolt fell on the lantern of the dome of Santa Maria del Fiore one of the golden balls fell off the Medici coat of arms; ribbons of fire crossed the sky from Fiesole to the top of the churcb of San Lorenzo; two lions at the Lorenzo villa went wild and fought to death; and finally, the head doctor, Pierleoni di Spoleto, accused of having ".. given the wrong treatment" to Lorenzo "who needed cool things and had been given hot things .." was found dead in a well, giving rise to the mystery as to whether be had been thrown in or had committed suicide.
The book, written without the division of chapters, involves the reader in the events which are scientifically documented and linked by a delicate feeling of estime for Lorenzo dei Medici who really was Magnificent.

Salvatore Damiano Randazzo

Chiuso in tipografia: 30 July 1993

Journal of Applied Cosmetology published quarterly by INTERNATIONAL EDIEMME, Via Innocenzo XI, 41 00165 Roma Italy. Direttore responsabile P. Morganti. Direzione, Redazione ed Amministrazione Via Innocenzo XI, 41 - 00165 Roma Italy. Stampa Grafica Flaminia Roma. Progetto grafico ed impaginazione STYLOgrafica Roma. Spedizione in abbonamento postale gruppo IV/70. Aut. del Trib. di Roma n. 3173/83 del 8-7-83

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