This document presents the general consensus of the SCCNFP regarding one aspect of human testing, however stating again that, at present, human testing of cosmetic ingredients should not be preferred to animal testing and that the safety testing of cosmetics on humans may not be considered to be an alternative method to the use of animals.

The present opinion also stresses the concept that confirmatory skin tolerance tests of cosmetics in humans are subject to ethical concern. According to the Declaration of Helsinki "safety studies of cosmetics in human must be subjected to National Regulations and Good Clinical Practice for Trials on Medicinal Products in the European Union".

Test protocols to be applied in the safety evaluation of cosmetic ingredients or their mixtures with human studies have not been validated yet. SCCNFP's opinion is that a set of specific guidelines concerning the most applied protocols can be prepared in the near future and presented to the European Commission. The SCNFP has been requested by the responsible Commission Service to offer guidance on:

- **The ethical and safety considerations of the testing of cosmetic finished products on human volunteers to assess skin compatibility;**
- **The end-points for which such testing is appropriate and the most robust protocols for such studies (22.07.98).**

A draft proposal of "Guidelines on the Testing of Cosmetic Finished Products on Human Volunteers" is currently under preparation and is being discussed by the SCCNFP. An opinion should soon be available.

4.2. Revision of Annex 7 of Notes of Guidance. Microbiological Quality of Finished Cosmetic Products (XXIV/1878/97)

As stated several times by the former SCC, the "Notes of Guidance..." will require future amendments as scientific knowledge advances. A second reason for revising the document will depend on the improvement of cosmetic technologies in the industrial sector.

On September 23rd 1998 the SCCNFP has adopted the Revision of Annex 7. "Microbiological Quality of the Finished Products", as amendment to the previous document (SCCNFP/0004/98 Final). Annex 5.

5. Work Programme for 1999

The work planned for 1999 in fulfillment of the Commission's request is schematically represented by the following list:

1. **Present development and validation of adequate alternative methodologies to the use of animals in the safety testing in cosmetics.**
2. **Eye irritation: possible strategies for using *in vitro* validated methods for selected classes of cosmetic ingredients.**
3. **Minimal Criteria of the *in vitro* test protocols for assessing percutaneous absorption of cosmetic ingredients;**
4. **Minimal Criteria of the protocols for the testing of potentially cutaneous irritant cosmetic ingredients or mixtures of ingredients on human volunteers;**
5. **Levels of exposure of consumers to cosmetic ingredients and finished cosmetic products. Revision of Annex 4 of document XXIV/1878/97 (XXIV/1481/97);**
6. **Guidelines on the use of human volunteers in the testing of finished cosmetic products (SCCNFP/0068/98);**
7. **Guidelines on the use of human volunteers in the testing of potentially cutaneous sensitizing cosmetic ingredients or mixtures of ingredients;**

ANNEX 1

SCCNFP/0070/98 Final - November 1998

The Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers

OPINION ON *IN VITRO* METHODS TO ASSESS SKIN CORROSIVITY IN THE SAFETY EVALUATION OF COSMETIC INGREDIENTS OR MIXTURES OF INGREDIENTS

Adopted by the plenary session of the SCCNFP of 25 November 1998

Terms of Reference

Two *in vitro* methods developed to assess skin corrosivity of chemicals, the "Rat skin Trancutaneous Electrical Resistance (TER) test" and the "EPISKIN test" have been validated by ESAC (ECVAM Scientific Advisory Committee).

The Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) has been requested by DG III to advise the Commission on the applicability of the methods to the safety assessment of chemicals used as cosmetic ingredients.

1- *Background*

The European Centre for the Validation of Alternative Methods (ECVAM) has conducted in 1996-1997 a validation study of *in vitro* tests developed to assess skin corrosivity of chemicals. This study was a follow-up to a pre-validation study of tests developed for

replacing the *in vivo* Draize skin corrosivity test in rabbits.

The main objectives of the validation study, as defined by the sponsors and the management team before the study began, were :

(a) to identify tests capable of discriminating corrosives (C) from non corrosive (NC) for selected groups of chemicals (e.g. organic acids, phenols) and/or all chemicals (single chemical entities only);

(b) to determine whether the tests could identify correctly known R35 (UN packing group I) and R34 (UN packing groups II & III) chemicals.

2- *Organisation of the study*

The study was coordinated from ECVAM. A Management Team (MT) was constituted by four representatives of « lead laboratories », each of them being responsible for one of the four tests being evaluated.

The tests selected for inclusion in the validation study were the rat transcutaneous electrical resistance (TER) test, Corrositex^{TM}, the Skin^{2TM} ZK1350 corrosivity test, and Episkin^{TM}. Each test was conducted in three different laboratories, according to principles, criteria and procedures previously defined by ECVAM. Prediction models for each of the four tests were defined in the test protocols.

Coordination /MT /Laboratories

Sixty chemicals were selected by an independent Chemicals Selection Sub-Committee, and distributed coded to the participating laboratories. These included organic acids (6C/5NC), organic bases (7C/3NC), neutral organics (9NC), phenols (2C/3NC), inorganic acids (6C/1NC), inorganic bases (2C/2NC), inorganic salts (1C/2NC), electrophiles (3C/5NC), and soaps/surfactants (3NC). The selection is fully described in a publication (Ref. 1); the main criterion for including chemicals in the test set was that the corrosivity classifications were based on unequivocal animal data.

The results obtained were analysed by statistician experts. The classifications of the corrosivity potential of the test chemicals, as derived from the *in vitro* data obtained in the three laboratories conducting the test, were compared to the *in vivo* classifications independently assigned to the chemicals before the blind trial, to yield sensitivity, specificity, predictivity and accuracy of the test.

3- *Main results*

The full details of the validation study have been published (Ref. 2). Two tests, with a good reproductibility within and between test laboratories, proved applicable to the testing of a diverse group of chemicals : the TER test and Episkin.

In the TER test, test materials are applied for 2 to 24 hours to the epidermal surface of skin discs taken from the pelts of humanely killed young rats, and corrosive chemicals are identified by their ability to produce a loss of normal stratum corneum integrity, which is measured as a reduction of the inherent transcutaneous electrical resistance (below a predetermined threshold level).

Episkin is a tri-dimensional human skin model with a reconstructed epidermis and a functional stratum corneum. When utilised in corrosivity testing, application of test chemicals to the surface of the skin for 3, 60 and 240 min, is followed by an assessment of cell viability.

Sensitivity, specificity, predictivity and accuracy in distinguishing corrosive from non corrosive chemicals were very high for both tests: 88, 72, 72, 79 and 83, 80, 77, 81 % respectively for the TER test and Episkin. In addition, Episkin was also able to distinguish between known R35 (UN packing group I) and R34 (UN packing groups II & III) chemicals

4- *Opinion of the SCCNFP*

ECVAM Scientific Advisory Committee (ESAC), which had been fully informed of the progression of the validation procedure, reviewed the final results and unanimously endorsed a statement that the rat skin TER test is scientifically validated for use as a replacement for the animal test for distinguishing between corrosive and non corrosive chemicals, and that Episkin is scientifically validated as a replacement for the animal test, and that these tests are ready for regulatory acceptance.

Sixty chemicals were used for the validation of these two methodologies; twenty of them are used as cosmetic ingredients, according to the "European inventory and common nomenclature of ingredients employed in cosmetic products" (Ref. 3).

SCCNFP reviewed publications from the validation study and ESAC statements, and propose that these two methods could be applied to the safety assessment of chemicals used as cosmetic ingredients.

A cosmetic ingredient or mixture of ingredients can be corrosive per se. When corrosivity cannot be excluded, testing for irritancy on animals or humans should be preceeded by a corrosivity test using one of these two validated *in vitro* methodologies.

5- *References*

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ANNEXE 2

SCCNFP/0069/98 Final - November 1998

OPINION ON *IN VITRO* METHODS TO ASSESS PHOTOTOXICITY IN THE SAFETY EVALUATION OF COSMETIC INGREDIENTS OR MIXTURES OF INGREDIENTS

Adopted by the plenary session of the SCCNFP of 25 November 1998

Terms of reference

DG III requests the opinion of the Scientific Committee on Cosmetic and Non-Food Products (SCCNFP) as to the status of alternative methods for the safety assessment of cosmetic ingredients according to the current state of the art. Specifically DG III requests that the SCCNFP assesses the possibility of replacing data obtained on the basis of animal tests by data obtained making use of alternative methods in the safety evaluation of cosmetic ingredients (XXIV/1890/98)

1- *Background*

UV-absorbing chemicals are employed as ingredients of various cosmetic products. Guidelines for the safety testing of cosmetics require a test for photo-irritation potential of this type of compounds. Testing usually is done on animals, although an accepted protocol to test *in vivo* for photo-irritation potential does not exist.

2- *Different phases in the study*

2-1. In a first phase in 1992-1993, a joint EU/COLIPA prevalidation study was designed to identify *in vitro* test procedures for a validation trial under blind conditions. Twenty chemicals with known phototoxicity properties were selected according to scientific criteria by an independent COLIPA task force of experts. The chemicals underwent different tests e.g. photohaemolysis test, histidine oxidation test, Candida albicans test, SOLATEX PI®, Skin^{2}®, Testskin® and the 3T3 mouse fibroblast test. It came out that the 3T3 Neutral Red Uptake Phototoxicity Test (3T3 NRU PT) with mouse fibroblasts using a sun simulator UV source (UVA 5J / cm^2) was giving better overall correlation to *in vivo* data than results from any of the other tests.

2-2. At ZEBET a prediction model for the 3T3 NRU PT test was developed, which took the IC-50 values from cytotoxicity dose-concentration curves in the presence and absence of exposure to

UV-light into account. A photo-irritation factor (PIF) was calculated which is the ratio of IC_{50} (-UV) / IC_{50} (+UV).

Discriminant analysis showed that a PIF of 5.0 provided the best prediction to discriminate between phototoxic and non-phototoxic chemicals.

(Spielmann et al.1994b, 1995).

2-3. In the second phase in 1994-1995, the formal validation trial, the most promising *in vitro* phototoxicity tests were validated using 30 carefully selected chemicals. 11 Laboratories were involved in a bind trial. This study was conducted jointly by ECVAM and COLIPA. The test chemicals were selected according to the recommendations of an ECVAM workshop on phototoxicity testing (Spielmann et al. 1994a). The test chemicals were selected according to their phototoxic properties in humans. The aim of the study was to correctly predict the phototoxic potential of chemicals applied systematically or topically in humans. Besides the assessment of the phototoxic potential by PIF using a cut-off value of 5.0, the mean photo effect (MPE), which takes into account the slope of the concentration response curves for cytotoxicity, with a cut-off value of 0.1 was also used. The latter model was published independently from the validation study (Holzhütter 1997).

2-4. The results of the 3T3 NRU PT test were reproducible and correlated well with the *in vivo* data. Therefore, in 1997, the ECVAM Scientific Advisory Committee (ESAC) and in 1998 DG III and DG XI of the European Commission concluded from the formal validation study under blind conditions "that the 3T3 NRU PT is a well validated test and ready to be considered for regulatory acceptance" (Anon. 1998).

2-5. In 1996, the former Scientific Committee on Cosmetology (SCC) asked ECVAM to test the UV chemicals from Annex VII of the Directive 76/768/EEC in a blind trial using the 3T3 NRU PT test (XXIV/1878/97). The selection of the filters out of this list was done according to scientific criteria based on reliable *in vivo* data. (Guillot et al. 1985; Kaidbey and Kligman 1980). 8 UV filters were tested which were shown *in vivo* to be non phototoxic. To balance the study, 10 phototoxic and 10 non-phototoxic chemicals were tested under blind conditions in 4 laboratories; a correlation between 95 and 100 % was obtained when PIF or MPE, respectively, were used to predict the phototoxic potential and when concentrations between 0.1 and 10.0 µg/ml were tested. The management and the participants of this study concluded in 1998 (Spielmann et al. 1998 b) that the phototoxic potential of UV filters can be correctly assessed by the 3T3 NRU PT test.

2-6. In 1998, the SCCNFP reviewed carefully the publications from the validation studies, the ESAC statement and the application study of the UV filters. Critical questions were posed to the management team. These were all answered using appropriate scientific criteria.

3- *Opinion of the SCCNFP*

Taking the results obtained in the prevalidation and formal validation study of the 3T3 NRU PT test and the results of the application study of this test to the UV filters of Annex VII of the Directive 76/768/EEC into account, the SCCNFP proposes the use of the 3T3 NRU PT test as the standard method for testing the UV light absorbing cosmetic ingredients or mixtures of ingredients for phototoxic potential.

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ANNEXE 3

SCCNFP/0088/98 Final - January 1999

OPINION ON IN VITRO METHODS TO ASSESS PERCUTANEOUS ABSORPTION OF COSMETIC INGREDIENTS

Adopted by the SCCNFP at the plenary meeting of 20 January 1999

1. *Background*

In 1995, COLIPA (European Cosmetic, Toiletry and Perfumery Association) presented to the former SCC (Scientific Committee on Cosmetics) Sub-Committee "Alternatives" an industrial view on the *in vitro* assessment of percutaneous absorption / penetration of cosmetic ingredients.

Guidelines for the testing of *in vitro* percutaneous absorption and some different protocols related to the use of excised skin (human, pig and rat) were proposed. Also, a general view on percutaneous absorption / penetration *in vitro / in vivo* correlation was presented based on a set of papers published in the scientific literature. The *in vitro* tests conducted by the cosmetic companies were developed to evaluate the safety of their cosmetic ingredients. They had not been intended for regulatory purposes and they were not subjected to the official validation processes.

The main conclusion of that Sub-Committee was the following (DGXXIV/1874/95): "The most important problem deduced from the documentation submitted is the absence of results and correlation data (in the protocols not in the references attached). The documentation should be implemented with intra- and inter-laboratory results obtained on percutaneous absorption of several strategic compounds (wide spectrum) as well as on correlation of *in vitro / in vivo* data. A more uniform presentation of *in vitro* percutaneous absorption methodology should be considered, taking into account the different protocols presented".

In 1996, a report and recommendations of ECVAM Workshop 13 about Methods for assessing percutaneous absorption was published (ATLA 24, 81-106, 1996).

In the last few years, two OECD Proposals to evaluate percutaneous absorption by *in vivo / in vitro* methods have been presented. COLIPA members have upgraded their initial data submission as requested by the Extended Steering Committee of the OECD but to our knowledge the document has not been finalised by the organisation.

2. *Position of the Scientific Committee on Cosmetics (SCC)/Scientific Committee on Cosmetic and Non-Food products (SCCNFP)*

In the Notes of Guidance for Testing of Cosmetic Ingredients for their Safety Evaluation (XXIV/1878/97) the former SCC emphasised that the test protocols used by industry were not subjected to a

formal validation test and it recommended that the existing documentation must be supplemented, as regards intra- and inter-laboratory reproducibility, the influence of the vehicle on the release of the cosmetic ingredients and other technical and experimental details. However, the SCCNFP is convinced of the relevance of *in vitro* methods and has since recent years agreed to consider *in vitro* percutaneous absorption data in the evaluation of the safety of several cosmetic ingredients.

3. *Submission of COLIPA data on in vitro/in vivo dermal absorption/percutaneous penetration (SCCNFP/0073/98)*

In November 1998, COLIPA submitted a new document on *in vitro / in vivo* dermal absorption / percutaneous penetration including data and protocols used by several cosmetic companies.

These data refer to the dermal absorption / percutaneous absorption of chemical UV-filters, hair dyes (with rinsing or without rinsing) and several other ingredients.

In the methodologies used, the penetration cell design, the composition of the receptor fluid, the membrane integrity checking and the preparation of the dose of a given substance are described.

Experimental details concerning the application of test substance, reference chemicals, the fluid dynamics, temperature, exposure time, duration of the study, sampling and analytical techniques are also indicated.

Porcine back and flank skin, rat dorsal skin, guinea pig skin and human split-thickness skin have been used for the *in vitro* tests.

Some reference chemicals with a broad range of partition coefficient octanol/water (log P) and with different percutaneous absorption profiles have been evaluated. Benzoic acid, caffeine, estradiol. hydrocortisone, inulin, pentadecanoic acid, salicylic acid, sucrose, thiourea, tritiated water have been tested.

Among others these comparisons have been made:

Pig skin *in vitro* / Human skin *in vivo* (SC stripping)

Pig skin *in vitro* / Rat skin *in vivo*

Human skin *in vitro* / Pig skin *in vitro*

Some intra-assay reproducibility and inter-laboratory comparisons are included in the documentation. Additionally, in this document, information is included about the self- evaluation of each methodology according to the Canadian/US proposal for the Data Submission Form (OECD).

4. *Opinion of the SCCNFP*

The SCCNFP has reviewed the documentation submitted by COLIPA and agrees with the rationale for using *in vitro* methods to evaluate the dermal absorption / percutaneous penetration of cosmetic ingredients. The data reported in this document indicates the possible usefulness of the *in vitro* methodologies.

However the data provided at the moment are not sufficient to formulate a scientific opinion on how to conduct *in vitro* percutaneous absorption studies and assess the results.

The minimal requirements needed for the acceptance of *in vitro* percutaneous absorption studies to be evaluated, will be formulated by the SCCNFP, based on the scientific literature and on the experience of the Committee in evaluating the dossiers submitted for inclusion of cosmetic ingredients in the annexes of the Cosmetics Directive 76/768/EEC.

Studies to standardise methodologies for *in vitro* percutaneous absorption for cosmetic ingredients are necessary and the methods should be shown to give reproducible and relevant results. It is recommended that independent research institutes should perform or co-ordinate this work.

ANNEXE 4

SCCNFP/0003/98 Final - November 1998

OPINION - GUIDELINES ON THE USE OF HUMAN VOLUNTEERS IN THE TESTING OF POTENTIALLY CUTANEOUS IRRITANT COSMETIC INGREDIENTS OR MIXTURES OF INGREDIENTS

Adopted by the plenary session of the SCCNFP of 25 November 1998

1 Background

1.1 Emphasis on consumer safety

According to the Council Directive "a cosmetic product put on the market within the Community must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use" (76/768/EEC). In order to achieve this goal of product safety, toxicological data on cosmetic ingredients are needed as outlined in the SCCNFP Notes of Guidance for Testing of Cosmetic Ingredients for their Safety Evaluation 2nd Rev. (XXIV/1878/97). Among the data mentioned, also «human data» are cited. However, the document does not specify these in detail. Regarding skin irritation, the SCCNFP considers that at present human testing of cosmetic ingredients or mixtures of ingredients should not be preferred to animal testing.

1.2 Animal tests for assessment of safety to be replaced by

alternative methods

In the past, most of the toxicological data mentioned above have been generated by testing on animals. However, according to Council Directive 76/768/EEC, the marketing of cosmetic products containing ingredients or combinations of ingredients tested on animals after 30 June 2000 in order to meet the requirements of this Directive shall be prohibited. The Commission's general policy regarding research on animals supports the development of alternative methods to reduce or replace animal testing when possible.

1.3 Testing of cosmetic ingredients in humans

In this context, the scientific and ethical considerations for testing cosmetic ingredients or mixtures of ingredients in human subjects need to be defined more clearly. The skin irritancy reaction in humans is not an absolute measure and must be related to appropriate controls defining the range of response.

The SCCNFP stresses three points:

1. Since tests in animals or validated alternative methods may be limited regarding their predictive value for exposure of a human population, confirmatory safety tests in humans may be necessary scientifically and ethically, provided that the toxicological profile of an ingredient or a mixture of ingredients based on animal or alternative methods is available and that a high degree of safety is to be expected.

2. Confirmatory tests of ingredients or mixtures of ingredients in humans must be limited to situations where no irreversible damaging effects are to be expected for the volunteers and where the study goal is reasonably achievable with a study population of limited size.

3. The recruitment of human volunteers should be in line with the "World Medical Doctors Association Declaration of Helsinki" and "the Good Clinical Practice for trials on Medicinal Products in the European Community."

2 Procedure of irritancy assessment

The following text outlines the steps of an assessment of the irritancy of an ingredient or mixture of ingredients. While this text focuses on irritancy, it is understood that other aspects of toxicity have to be considered in parallel before performing tests in humans.

2.1 Initial considerations

Available chemical and physico-chemical data and structure-activity relationships making use of computer programs and databases for the prediction of skin irritation potential should be used.

2.2 Evaluation of irritation

Ingredients or mixtures of ingredients should be tested on animals and humans only at non-corrosive concentrations. This decision may be based on pH and acid/alkaline reserve measurements and on in vitro tests for skin corrosivity. At the present, in vitro methods for the assessment of irritancy have not yet been validated.

2.3 Confirmation by human volunteer testing

On the basis of a low irritation potential as proven by animal or future validated in vitro methods, the skin tolerability of an ingredient or a mixture of ingredient can be confirmed by testing in human volunteers. A number of test protocols are available such as open and closed patch-tests, single and repeated-exposure-tests. They should be chosen on the basis of the relevant use pattern of the ingredient or mixture of ingredients (1).

- In the open test, the tested ingredient or mixture of ingredients is applied on the skin without occlusion for time periods between 15 min and 24 h.
- In closed patch tests, diluted or undiluted products are applied under occlusive chambers over 24 or 48 hours.
- Cumulative or repetitive closed patch tests involve applications on the same test site between 1 and 7 times per week over a period of 1 to 5 weeks. These repetitive tests allow the assessment of cumulative irritation that is missed by single application tests.
- Controlled use or repeated open application tests (ROAT) imply the repeated application of an ingredient or a mixture of ingredients closely modelled to the use-situation.

While these tests historically have been assessed by clinical methods, non-invasive bioengineering technology such as measurement of transepidermal water loss or of blood flow may provide higher sensitivity and objectivity of these tests and thereby reduce the exposure and risk to volunteers.

However, neither the above confirmatory tests nor the use of bioengineering methods have been validated according to modern scientific criteria. The SCCNFP recommends the Commission to support further research in this area.

2.4 Consumer market surveillance

The evaluation of irritation of an ingredient or mixture of ingredients is not finished with the introduction of respective cosmetic products on the market, but it should continue by making use of data generated by consumer market surveillance and other sources.

3 Ethical considerations

Confirmatory skin tolerance tests of cosmetic ingredients in humans are subject to ethical concerns. In order to take account of these concerns, to minimise the risk to volunteers and to safeguard their rights, test protocols should be submitted to an acknowledged ethical committee and be in compliance with the followings :

- World Medical Doctors Association Declaration of Helsinki in its current revision (2).
  Human testing is to be conducted and monitored under the direction of relevantly trained personnel to ensure the health and well being of volunteer subjects involved in the testing. The health and welfare of the subject has first priority and must be highly protected. Importantly, the human testing that is conducted for chemicals and consumer products is associated with minimal risk as it is conducted:

i) to supplement non-clinical information,

ii) to confirm that exposure will not cause significant harm, and/or,

iii) in a controlled fashion that minimises subject risk (4).

- National regulations regarding human studies
- Good Clinical Practice for Trials on Medicinal Products in the European Community (3).

The investigator(s) in skin tolerability tests of cosmetic ingredients should fulfil the qualifications as mentioned in the CPMP Working Party on Efficacy of Medicinal Products Note for Guidance on Good Clinical Practice (3).

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ANNEXE 5

SCCNFP/0004/98

Notes of Guidance for testing of Cosmetic Ingredients for their Safety Evaluation

Revision of Annex 7 : Microbiological Quality of the Finished Cosmetic Product

adopted by the plenary session of the SCCNFP of 23 September 1998

1. Preamble.

Skin and mucous membranes are normally protected from microbial attack by a natural mechanical barrier and defence mechanisms. However, protective integuments may be damaged and slight trauma may be caused by the action of some cosmetics that may enhance microbial infection. These situations may be of particular concern when cosmetics are used in the eye area or on mucous membranes or on damaged skin and when used by children under 3 years, elderly people and people showing compromised immune responses. These are the reasons to define two separate categories of cosmetic products in the microbiological quality control limits.

Although a very low number of cases of contamination in cosmetics leading to microbial infections have been reported, it is likely that under-reported clinical microbiological problems (for instance infectious folliculites) associated to the use of contaminated cosmetics are recognised by several dermatologists (to be reported in a separate document). On the other hand microbial contamination may spoil cosmetic products or reduce the intended quality. These statements make it necessary to carry out routine microbiological control of cosmetics, in order to ensure their quality and the safety for customers to use.

2. Categories of cosmetics in microbiological quality control.

In relation with the microbiological quality control, two categories of cosmetics are defined.

Category 1: Products specifically intended for children under 3 years, eye area and

mucous membranes.

Category 2: Other products.

3. Quantitative limits.

The limit for cosmetics classified in ***Category 1*** is: total viable count for aerobic mesophyllic micro-organisms not more than 10^2 cfu/g or ml in 0.5 g or ml of the product.

The limit for cosmetics classified in ***Category 2*** is: total viable count for aerobic mesophyllic micro-organisms not more than 10^3 cfu/g or ml in 0.1 g or ml of the product.

4. Qualitative limits.

Pseudomonas aeruginosa, *Staphylococcus aureus* and *Candida albicans* are considered the main potential pathogens in cosmetic products. These specified potential pathogens must not be detectable in 0.5 g or ml of the cosmetic product in cosmetics of Category 1 and in 0.1 g or ml in cosmetics of Category 2.

5. Product preservation.

Microbial contaminants have two origins: during production and filling, and during the use of the cosmetic by the customer. From the moment in which the cosmetic unit is opened until the consumer finishes the product, there is a permanent, variable and additive microbial contamination of the cosmetic caused by the domestic environment and the consumer's body (hands and body skin). The reasons for the need of microbial preservation in cosmetics are the following:

5.1. ***To ensure the microbial safety of cosmetics for customers to use.***

5.2. ***To maintain the quality and specifications intended for the product.***

5.3. ***To confirm hygienic and high-quality handling.***

6. The challenge testing

The efficacy of the preservation has to be assessed experimentally during the development process to ensure microbial stability and preservation by challenge testing. Challenge testing is mandatory for all those products that in normal conditions of storage and use, a risk of infection for the consumer or a deterioration of the product exist. The challenge test consists of an artificial contamination of the finished product and a posterior evaluation of the decrease of this contamination to levels ensuring the microbial limits established in products of Category 1 and 2.

The micro-organisms used in the challenge test will be issued from official collection strains from any state in the EU to ensure reproducibility of the test and will be: *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida albicans.* Additional bacteria and fungi might be used for additional specific purposes of the challenge testing. The microcidal activity of preservatives or any other compound in the finished cosmetic must be ruled out in the challenge test by dilution, filtration, neutralisers or any other means. The experimental performance of the microbial controls and the

challenge tests must be laid down and validated by a microbiologist.

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7. Good Manufacturing Practice.

In order to accomplish with the Good Manufacturing Practices and Microbial Quality Management, manufacturers of cosmetics have to define and follow specific cleaning, sanitation and control procedures to keep appropriately clean and free of micro-organisms that could be harmful for the consumers or adverse for the quality of the cosmetics. These proceedings will include procedures to microbiology control raw materials, bulk and finished products, packaging components, personnel, equipment and locals.

[©] - [CONSUMER HEALTH PROTECTION] - [SCIENTIFIC COMMITTEES] - [SCIENTIFIC COMMITTEE FOR COSMETIC PRODUCTS, AND NON-FOOD PRODUCTS INTENDED FOR CONSUMERS] - [OUTCOME OF DISCUSSIONS]

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

NOTES OF GUIDANCE FOR TESTING OF COSMETIC INGREDIENTS FOR THEIR SAFETY EVALUATION

(THIRD REVISION)

Adopted by the SCCNFP during the plenary meeting
of 23 June 1999

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