Cosmetics Europe
the personal care association

COSMETICS EUROPE:

GUIDELINES FOR THE SAFETY ASSESSMENT OF A COSMETIC PRODUCT

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GUIDELINES FOR THE SAFETY ASSESSMENT OF A COSMETIC PRODUCT

CONTENTS

1. INTRODUCTION

The 6th Amendment (93/35/EEC) to the Cosmetics Directive (1;2) (76/768/EEC) has introduced major changes into the European Union (EU) legislation on cosmetic products.

The new provisions of Article 7a introduce the obligation to have available for every product marketed in the EU a set of product information. The key part of the product information package is a safety evaluation of the finished product to be performed by a qualified professional, defined in the legislation as the "safety assessor".

Another new aspect of the 6th Amendment is the introduction of a potential ban on animal testing for purposes related to the Cosmetics Directive.

These two new provisions represent contradictory challenges for industry. On the one hand, industry is required to provide a safety evaluation as part of detailed product information for each product marketed in the EU in order to assure consumer safety. On the other hand, animal testing is to be considerably reduced.

Most of the safety data needed will be related to the testing of ingredients (3). In some cases, however, it will be necessary to have available or to generate some safety data on the finished product.

These guidelines have been prepared by the Colipa Steering Committee on Alternatives to Animal Testing (SCAAT). Their main purpose is to show how finished products can be assessed for their safety whilst avoiding new product testing making use of animals.

In almost all cases, it should be possible to obtain sufficient information on finished products without testing them on animals. However, the application of these guidelines requires a new way of thinking in that the traditional approach is abandoned. It should also be emphasised that this new approach requires the development of an important amount of relevant information which largely depends on acquired expertise in order to come to an acceptable safety assessment. This approach may therefore require more investment, especially in terms of personnel, data collection and cost.

The Cosmetics Directive stipulates that a "safety assessor" must make the safety evaluation on the finished product (1;2). Anybody marketing cosmetic products must therefore use such a safety assessor. The assessor may be a consultant or all employee, provided the qualifications laid down in Article 7a (1) (e) of the Cosmetics Directive are met. This person may also form part of the staff of a contract laboratory which may be handling the safety evaluation of the finished product. The importance of making use of a properly qualified safety assessor cannot be overemphasised.

2. GENERAL APPROACH

The 6th Amendment to the Cosmetics Directive(1) stipulates under Article 2 that :

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, taking account, in particular, of the product's presentation, its labelling, any instructions for its use and disposal as well as any other indication or information provided by the manufacturer or his authorised agent or by any other person responsible for placing the product on the Community market.

Hence cosmetic products have to be safe both for consumers and, if relevant, for involved professionals (e.g. hairdressers, beauticians, etc.).

As far as skin is concerned, the two main untoward reactions to be avoided are skin irritation and skin sensitisation (4). Cosmetic products are often applied on areas exposed to environmental factors. Thus, care has also to be taken to avoid photon-induced reactions such as photoirritation and photosensitisation (see Appendix 1, Annex 1) (4).

Products applied on the scalp or the face may come in contact with the eye. Consequently, eye tolerance has to be addressed with optimal attention as a major component of the safety assessment for a cosmetic product.

Systemic toxicity that may result from percutaneous absorption or from accidental (children) or reasonably foreseeable (e.g. oral hygiene products, lipsticks) oral intake should also be considered.

Ensuring the safety of a cosmetic product requires a global approach throughout the life of the product from the choice of raw materials to the marketing follow-up. A number of issues have to be taken into account, including:

- careful selection of cosmetic ingredients, making sure that they will be safe at a given concentration in a given finished product;
- checking local tolerance of the finished product;
- selection of adequate packaging to maintain the quality of the product and to avoid, as far as possible, risks of misuse or accident;
- applying Cosmetic Good Manufacturing Practice Guidelines (published by Colipa);
- quality control, mainly microbiological, also chemical contaminants;

- appropriate labelling - presentation of the product, instructions for use and disposal, warnings (if relevant) and appropriate action to take in case of accident;

- adequate procedures in case of side effects with the marketed product - case-by-case treatment, appropriate medical, dermatological, ophthalmologic etc. - advice as necessary, follow-up of the product on the market and consumer comments, information storing etc.

The aim of this guideline is to cover the safety aspects in the light of the 6th Amendment to the Cosmetics Directive (1) which requires an "*assessment of the safety for human health of the finished product. To that end, the manufacturer should take into consideration the general profile of the ingredients, chemical structure and level of exposure"*.

Although it is not possible to attain zero risk or to obtain absolute safety in any kind of human activity, including cosmetology, reasonable efforts have to be made to reduce the risk from cosmetic products to the minimum, according to the state of the art at the time.

There is no formalistic approach to the safety evaluation process. The actual process will vary from product to product according to the novelty of the product composition and to the relevance and adequacy of information available. However, as a general rule, the major basis for safety evaluation is provided by considering the toxicological profile of ingredients (3).

From a scientific point of view, in almost all cases finished product testing does not require the use of toxicological tests in animals. In general, all questions which are posed at this stage can be answered by utilising other information sources, including skin compatibility tests ethically performed on the skin of human volunteers(5).

3. INGREDIENTS

Cosmetic ingredients are mostly chemicals and often mixtures of chemicals of synthetic origin or natural extracts. The careful selection of ingredients is the key issue for ensuring the safety of the finished product.

The structure of the chemical determines its chemical and biological reactivity e.g., Barratt, 1995 (6). This has to be considered from two points of view: cosmetic interest and safety. Other considerations are the degree of chemical purity, the possible interactions with other ingredients in the formulation and potentiation of skin penetration. In general, the presence of impurities is technically unavoidable. But these impurities have to be of no significant toxicological relevance in the finished product.

Based on the state of knowledge, possible interactions between ingredients with a potential safety relevance have to be considered. Influence on skin penetration may also be of importance, especially for sensitisation and systemic risks (7). Skin penetration can be assessed using *in vitro* methods (7). Determination of allergic potential may also require testing of ingredients formulated with suitable vehicles.

On the other hand, the safety-in-use of an ingredient largely depends on the exposure conditions (type of formulation, concentration, frequency and duration of contact, body area involved, effect of the sun, etc.) taking into account normal conditions of use and foreseeable misuse.

3.1 INGREDIENTS T0 BE AVOIDED

For each raw material, it is necessary to check whether it is covered by current legislation and, if so, whether the proposed usage is within the prescribed parameters. The following ingredients must be excluded:

- ingredients prohibited under the Cosmetics Directive (Annex II) (2);
- ingredients restricted under the Cosmetics Directive when used beyond the allowed conditions (Annex III) (2);
- ingredients with toxicological data incompatible with the intended concentration and use;
- ingredients which have neither sufficient toxicological data nor safety in use experience;
- ingredients which are not properly characterised.

Data to be taken into consideration, besides those directly relating to toxicity, include positive identification of the ingredient, potential impurities of relevance, physicochemical properties and analytical chemistry, potential interaction with other ingredients of the formulation and possible role in skin penetration.

The toxicological profile of a raw material is obtained by analysing available data, published or not, concerning the raw material. These data may include results of *in vitro*, *in vivo* and clinical testing, as well as results of epidemiological studies where available.

It is clear that new ingredients or ingredients used in a novel application require particular attention.

3.2 SOURCES OF TOXICOLOGICAL DATA

The main sources of toxicological data on ingredients are the suppliers. These companies have to comply with national and EU legislation on chemicals/dangerous substances (occupational safety, transport, packaging and labelling), for example, EU Dangerous Substances Directive (9) and thus are obliged to characterise their chemicals in toxicological terms. Most effort should be made to collect toxicological data and other relevant information from the suppliers. It may be necessary to encourage the supplier to conduct additional studies. Because these data are needed for regulatory purposes other than the Cosmetics Directive, the use of alternative (non-animal) test methods is restricted to those which are generally accepted (e.g. OECD guidelines).

Other sources of toxicological data may be obtained from:

- scientific literature, databases (e.g. Toxline, Medline), reports issued by the US Cosmetic Ingredient Review (CIR) program, Research Institute for Fragrance Materials (RIFM) monographs, reports by ECETOC, NTP, BIBRA., etc.;

- Safety Data Sheets;

- in-house experience with the particular ingredient and cosmetic products containing it;

- expert judgement based on similarities with chemically related substances.

Ingredients listed in Annexes III to VII of the Cosmetics Directive do not need supporting evidence provided that they are used as specified in the Annexes. In the case of substances in Annex VI in which concentrations higher than those specified may be used for other functions, supporting information is likely to be necessary.

The composition of fragrances and flavours is generally not available to the cosmetic manufacturer and use should be made of the safety evaluation which has to be provided by the supplier. A guideline has been prepared by EFFA (the European Fragrance and Flavour Association) and Colipa on how this should be handled (8). Information on any changes in composition and changes in the regulatory status of ingredients should be notified by the supplier so that appropriate action can be agreed and implemented.

It should be noted that the EU Scientific Committee on Cosmetology (SCC) has produced Notes of Guidance for Testing of cosmetic Ingredients for their Safety Evaluation (see Appendix 1).

3.3 CONDITIONS OF USE AND EXPOSURE

Evaluation of the safety of ingredients is certainly not adequate as a stand-alone procedure but has to include considerations of exposure (magnitude, route, duration, frequency, etc.) (3).

The following parameters have to be considered:

- class of cosmetic product(s) in which the ingredient is used;
- method of application (e.g. rubbed-in, sprayed, applied and washed off, etc.);
- concentration of ingredient in product;
- quantity of product used for each application;
- frequency of application;
- total area of skin contact;
- site of contact (e.g. mucous membrane, sunburnt skin);
- duration of contact (e.g. rinse-off products, leave-on products);
- reasonably foreseeable misuse which may increase exposure;
- type of consumers (e.g. children, people with sensitive skin);
- projected number of consumers;
- application to skin areas exposed to sunlight;
- quantity likely to enter the body.

This last point, which relates to systemic availability, is a critical issue in safety evaluation - the information is mainly provided by percutaneous absorption data.

4. SAFETY EVALUATION OF FINISHED PRODUCTS

The assessment of the safety of any cosmetic product clearly relates to the manner of use. This factor is most important since it determines the amount of substance which may be absorbed through the skin or mucous membranes, or ingested or inhaled.

As mentioned above, the main sources of information are the toxicological characteristics of ingredients and the available human experience (including market experience, beauticians, factory workers, etc.) with similarly composed products. Each ingredient has to be considered carefully. Particular attention should be paid to new and novel ingredients. Open questions of safety assessment are defined by expert judgement in each individual case after careful review of all available information.

In general, the potential of a cosmetic product for sensitisation, genotoxicity and all other types of systemic (toxic) effects will be evaluated on the basis of the properties of the ingredients. Adequate consideration of human exposure is, however, of paramount importance for the interpretation of available data. This involves an examination of the potential role of the vehicle. This holds particularly true for percutaneous absorption or quantitative data concerning any other route of entry into the systemic circulation. The question of possible interaction between different ingredients will usually be evaluated on the basis of experience (similarities, published data on related compounds/mixtures, theoretical considerations, etc.) and may be controlled using *in vitro* testing and/or skin compatibility tests.

For assessing the safety-in-use of a finished product, especially the local tolerance, it can be very useful to compare it with other formulae successfully marketed by the company.

lf the new product is a simple variant of an existing product, or if the formulation only consists of raw materials or ingredients previously used in similar products at common use levels, then it is likely that no additional safety data will be needed.

lf raw materials are used in new ways, then additional safety data may be required by the safety assessor.

If novel raw materials or raw materials new to the company are to be used, then more detailed information will be necessary.

Local tolerance largely depends on the whole formulation. Consequently, even with known and safe-in-use ingredients, it may be necessary, in exceptional cases, to check the skin compatibility of a new formulation by appropriate testing.

When exhaustive analysis of toxicological data on ingredients appears insufficient to define with certainty the local tolerance of the finished product, additional experiments can be performed *in vitro* and/or in human volunteers.

In vitro testing may be carried out to complement available information with the necessary use of appropriate benchmarks. For ocular safety, methods such as those listed below are available:

- BCOP - Bovine Cornea Opacity and Permeability Test;
- FLT - Fluorescein Leakage Test;
- HET-CAM - Hen's Egg Test - Chorioallantoic Membrane;
- RBC - Red Blood Cell Test;
- TEA - Tissue Equivalent Assay.

Skin compatibility or tolerance may be checked using reconstructed skin models and/or ethically conducted trials on human volunteers.

Clinical trials in man should be based on the principles of Good Clinical Practice (GCP) of the EU (10). The following type of tests may be performed:

- Open epicutaneous application (single or repeated);
- Closed epicutaneous application (single or repeated);

- Controlled application tests;
- Further testing may involve in-use tests and /or market tests.

5. SAFETY CLAIMS

If a safety claim is to be made, e.g., "dermatologically tested" or "hypoallergenic" it has to be supported by adequate evidence. In most cases, appropriate human testing on the finished product will be necessary rather than animal testing. The testing must meet all necessary ethical requirements for a clinical trial (11; 12). One important prerogative in this respect is the safety assessment by a suitably qualified and experienced person before the trial starts (5).

6. RESPONSIBILITIES OF THE SAFETY ASSESSOR

A modern approach to safety assessment is based on a thorough analysis of available data and conditions of exposure. Ideally, the development of the formulation should take into account these elements from the start by a close collaboration between toxicologist and formulator.

A proper choice of ingredient at an adequate concentration level is sufficient to avoid the major risks (e.g. genotoxicity, carcinogenicity, systemic toxicity) and, also to avoid to a large degree, sensitisation. Testing on finished products is unnecessary in most cases to assess these risks, provided potential interactions between ingredients and role of vehicle are considered.

In most cases, the knowledge of all information available is sufficient to assess the safety of finished products. In the case of totally new ingredients, new combinations of ingredients or new formulation processes without safety-in-use experience, additional testing may be needed.

However, in all cases, all information on ingredients and formulations should be made accessible by the suppliers and formulator to the safety assessor to ensure an adequate safety assessment.

The person in charge of assessing the safety of the product is called the safety assessor.

This person has to be qualified as defined in Article 7a of the Cosmetics Directive (1):

That person must hold a diploma as defined in Article 1 of Directive 89/48/EEC in the field of pharmacy, toxicology, dermatology, medicine or a similar discipline.

The role and responsibility of the safety assessor have to be emphasised. It is in the interest of the company to select a person knowledgeable in the field of toxicology applied to cosmetics and who is responsible and ethical.

The safety assessor is responsible for determining:

- whether or not the ingredients present in the formula meet the requirements of the legislation in respect of the concentration for authorised substances, absence of substances prohibited by the law and, more generally, in respect of all legal requirements;

- whether or not particular endpoint(s) have to be considered for a given ingredient;

- whether the data available are relevant and sufficient;

- whether or not interactions of toxicological relevance and/or modifications to penetration are likely to occur;

- whether or not complementary data are needed either on ingredients or on the finished product.

The safety assessor must;

- have recognised competence and ethics in the field;

- have access both to the toxicological and to the analytical information pertinent from a safety view point. Some questions are likely to be raised by the safety assessor concerning, e.g., purity of raw materials, impurity profile - if available, and control procedures applied, detailed information on a test mentioned or referred to by supplier, quantitative analysis of an impurity with a potential toxicological relevance etc;

- not be involved with the commercial aspects related to the product.

Safety assessment may require human testing to check skin compatibility of both cosmetic ingredients and finished products. Any such trials have to be carried out following the appropriate ethical requirements (5; 11 ; 12).

The judgement of the safety assessor relies on:

- the knowledge and experience of toxicological properties and safety-in-use of the known ingredients;

- the history of safety-in-use of products containing the same or similar ingredients;

- the expert judgement of the set of data available on an unknown, new or novel ingredient;

- if necessary, the results of additional data obtained either on one or more ingredients or on the finished product.

The safety assessor may conclude:

- the product is safe as such without special warnings or precautions;

- the product is safe provided a given type of packaging is used or provided a warning is added or the mode of use and usage instructions are defined more precisely or provided a complementary test with favourable results is performed;

- the product is not safe for the proposed use;

- that available data are not sufficient to determine whether or not the product will be safe and that further studies need to be carried out to obtain the required information;

- specific safety claim(s) may or may not be used.

A product cannot be marketed if the conclusion of the safety assessor is that the product may not be marketed safely under the normal or reasonably foreseeable conditions of use. Recommendations by the safety assessor which are relevant for the safety-in-use of the product have to be followed. They are part of the safety statement the assessor signs which should be presented to the authorities (inspectors) when required.

Selecting the safety assessor thus appears to be a key issue for the manufacturer of cosmetic products. It is not only a legal issue: it may also have importance for other aspects such as, for example, the image of the company as well as product liability implications.

7. REFERENCES

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APPENDIX

COMMISSION OF THE EUROPEAN COMMUNITIES SCIENTIFIC COMMITTEE FOR COSMETOLOGY. NOTES OF GUIDANCE FOR TESTING OF COSMETIC INGREDIENTS FOR THEIR SAFETY EVALUATION (FIRST REVISION*)

1. INTRODUCTION

"Cosmetic products put on the market within the Community must not be liable to cause damage to human health when they are applied under normal condition of use'" (Council Directive 76/768/EEC of 27 July 1976, art.2).

"A cosmetic product means any substance or preparation intended for placing in contact with the various parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and mucous membranes of the oral cavity with a view exclusively or principally to cleaning them, perfuming them or protecting them, in order to keep them in good condition, change their appearance or correct body odours", (Council Directive 76/768/EEC of 27 July 1976, art.1).

Ingredients are defined as any substances used in cosmetic products. Examples of ingredients are provided by Annexes III, IV, VI, VII of the Council Directive 76/768/EEC of 27 July 1976 and its amendments.

Cosmetic products have a history covering many thousands of years with the use of many ingredients from plants, animals and mineral sources. Present technology has resulted in the use of many synthetic chemicals as ingredients in cosmetic products. Present day use, particularly as toiletries, is extensive and affects most population groups, although the degree and nature of the use may vary within different countries of the European Community.

In practice, cosmetic products have seldom been associated with serious hazard to health. However, this does not mean that cosmetics are safe in use, especially with regard to possible long-term effects, and this, together with the fact that the products may be used extensively over a large part of human life span, has created a need to ensure, as far as possible, their safety-in-use by controlling the ingredient content and its toxicity.

The purpose of this document is to give guidance for testing of cosmetic ingredients to authorities within the European Communities responsible for their safety evaluation and to the person(s) responsible for putting cosmetics on the market (manufacturers or importers within the European Community).

(*) Approved by SCC during the 45th meeting (Oct. 2, 1990)

A first document on "guidelines for the toxicity testing of cosmetic ingredients" was prepared by the Scientific Committee on Cosmetology on June 1982 (Report EUR 8794).

The present document represents a first revision which has taken into account both the experience developed by the SCC during its past activity on the evaluation of toxicological profiles of many cosmetic ingredients and the development of scientific knowledge in the field of particular or specific areas of toxicology.

These guidelines will apply mainly to new cosmetic ingredients and will also be adopted for other ingredients over which concern about safety-in-use has been brought to notice, bearing in mind their relevant toxicity data already in existence. They are drawn up in general terms and will require amendments in future as scientific knowledge advances.

The relevance of the present document derives also from the need to give a scientist support to the evolution of the Council directive 76/768/EEC.

2. TESTING OF INGREDIENTS OR OF THE FINISHED PRODUCTS

Although there are many thousands of different cosmetic products on the market within the EEC, these are based on a much smaller number of ingredients. This is the rationale for concentrating toxicity testing on ingredients, and particularly those of most concern. This is the basis of the lists of authorised ingredients in the preamble to Council Directive 76/768/EEC at this moment covering colouring agents, preservatives and UV filters. This approach avoids the costly duplication of studies and the unjustifiable use of animals that would result from the routine testing of products.

Article 2 of Council Directive 76/768/EEC requires that cosmetic products put on the market within the community must not be liable to cause damage to human health when they are applied under normal and reasonable anticipated conditions of use. Adequate information should therefore be provided in order to evaluate the safety of the final product. In general, this would be provided by a knowledge of the toxicity of the ingredients, with no need to test the final product. However, in few cases, testing of the final product may be necessary (see Annex 2). Examples are when the vehicle used resulted in markedly enhanced skin penetration from that observed in the toxicity studies on the ingredients; or if interaction between ingredients was likely to result in the formation of a new substance of toxicological concern, or when there is a claim of reduced skin penetration or toxicity resulting from the formulation. It is the responsibility of the suppliers of new products placed on the market within the Community to ensure that adequate information call be provided for a safety assessment of the finished product to be made.

3. LISTS OF INGREDIENTS

By progressive amendments to the Council Directive 76/768/EEC, several lists of ingredients have been established on the basis of the results of the latest scientific and technical researches.

These lists contain cosmetic ingredients for which already existing and new toxicological data are evaluated and for which conclusions about a risk for human health by their use in cosmetic products has been expressed.

For some ingredients, only concentrations below certain limits are allowed and field of application is limited, for safety reasons.

All cosmetic ingredients so far analysed by the SCC have been included in a series of Annexes to the 76/768/EEC Directive, they represent the actual “positive lists”.

In the 76/768/EFC Directive, Annex II lists all the cosmetic ingredients which have been banned for their use in the cosmetic products, due to their toxicological properties.

4. CATEGORIES OF COSMETIC PRODUCTS AND EXPOSURE LEVELS IN USE

The assessment of the safety of any cosmetic product clearly relates to the manner of use. This factor is important since it determines the amount of substance which may be ingested, inhaled or absorbed through the skin or mucous membranes. Consideration of the quantity of ingredients applied in the different products is also important as the following examples may illustrate.

For example, soaps are applied in dilute form and although the area of application may be extensive, the product is rapidly washed off.

Product used on the lips and mouth will be ingested to some extent.

Cosmetics used around the eyes and genital regions may come into contact with the conjunctiva or mucosa respectively, resulting in reaction due to the thin epithelial lining of these areas.

Sun-tanning products, body lotions or body creams may be applied over a large surface of the body, and the ingredients, often at appreciable concentrations, may remain in contact with the skin over several hours. Sun-tanning products, due to their extensive skin contact, combined with direct exposure to UV radiation for prolonged periods, require a distinct type of safety evaluation (see Annex 1).

Thus before any safety evaluation and risk assessment of a smashed product is made, the degree and route of consumer exposure must be known. This needs to be carried out on a case-by-case basis but the following may provide guidance.

In calculating the exposure, at least the following factors must be considered:

1. Class of cosmetic product(s) where the ingredient may be used;
2. Method of application - rubbed-in, sprayed applied and washed off, etc;
3. Concentration of ingredients in product;
4. Quantity of product used at each application;
5. Frequency of application;
6. Total area of skin contact;
7. Site of contact (e.g., mucous membrane, sunburnt skin);
8. Duration of contact (e.g., rinse-off products);
9. Foreseeable misuse which may increase exposure;
10. Nature of consumers (e.g., children, people with sensitive skin);
11. Quantity likely to enter the body, resulting from bioavailability studies;
12. Projected number of consumers;
13. Application on skin areas exposed to sunlight.

The relevant exposure depends upon the toxicological effects under consideration. For example, for skin irritation or phototoxicity the exposure per unit area of skin is important, while for systemic toxicity the exposure per unit of body weight is of more significance.

The route or routes of exposure (skin, mucosa membranes, ingestion, inhalation, skin exposed to sunlight) must be considered in designing any test programme and in risk analysis. The possibility of secondary exposure by routes other than those resulting from the direct application should be considered, e.g. inhalation of hairsprays, ingestion of lip products.

Use level of cosmetic products are subjected to several factors, some of which will vary with time, such as age group, seasonal variation, local habits, fashion trends, disposable income, product innovation.

Because of these changing conditions, it is not possible to include in this document specific use levels of cosmetics. They should be defined in a case-by-case approach in the safety evaluation, once the results of testing, as advised in the guidelines, have become available.

5. PHYSICAL AND CHEMICAL SPECIFICATIONS

The precise chemical nature of the ingredient and its structural formula, if it is known, should be identified. When available EINECS or CAS number should be provided. With regard to ingredients which cannot be identified in terms of their structural formula, sufficient information should be made available on the method of preparation and the material used in their preparation which will enable a judgement to be made on the probable structure and activity of the compound.

The degree of purity should be defined, as well as an identification of the nature of any toxicologically significant impurities that may be present and their concentration.

The substances used in toxicity studies should be of the similar specifications as the substances used in commercial products. Small changes in the nature of impurities can considerably alter the toxicity of substances. In general, therefore, the results of safety studies are relevant only when they are referable, to the ingredient used or to the product marketed.

It is the responsibility of the manufacturer to ensure that no other and no higher amounts of impurities than those chemically defused or technologically unavoidable, which could influence the safety of the finished products, are present in the commercially used material.

Due to the frequent unavailability of chemically pure ingredients, it will be required to define a purity level, and, in the case of the presence of a toxicologically relevant impurity, to define the maximum admitted concentration of the impurity. The maximum admitted concentration must be based on toxicological values.

With a view to checking the chemical nature of the ingredient and its degree of purity, its physical, chemical and physicochemical properties should be known and methods should be devised for identification, qualitative and quantitative control.

6. TOXICITY STUDIES

The assessment of the toxicological potential is the first step in the hazard evaluation of a chemical agent and consists in a series of distinct toxicity studies, specific for distinct toxicological end points; also phototoxicity studies have to be performed for some specific cases (See Annex l and Annex 2).

6. 1. *IN VITRO* STUDIES

The *in vitro* methodologies for evaluating the toxicological potential of chemical substances which have been reported in the literature have not yet been sufficiently validated for use in areas other than screening for mutagenicity/genotoxicity, and for pre-screening for severe irritancy.

Moreover, the *in vitro* methodologies so far available have not yet been adequately validated in other areas to be included in regulatory guidelines at this time.

At the present, therefore, there is no alternative, but to use *in vivo* studies in most areas. (*)

(*) Within the scope of the European Community Directive 86/609/EEC affirms a few general principles which must regulate the use of animals in toxicity experiments on chemicals. These principles although at variance with those of previous regulations, have stimulated the layout of strategies of research and development of methodologies for the knowledge of the toxic effects of chemical substances in agreement with alternative scientifically valid principles.

Directive 86/609/EEC affirms that all experiments on animals are forbidden unless they are carried out with the object of:

- research aimed at preserving the species at issue, or
- essential biomedical purposes, provided that the species employed in experiments represent the only specific ones for attaining the purpose.

This means in principle a restriction on animal experimentation in the very scope of toxicity studies and, above all, in those cases where the predictive significance of studies of similar effects on humans is rather scant.

The above mentioned rule firmly maintains (art. 7.2.) that "An experiment shall not be performed if another scientifically satisfactory method of obtaining the result sought, not entailing the use of an animal is reasonably and practically available"

6.2. *IN VIVO* STUDIES

The *in vivo* studies allow the possibility to investigate the toxicological potential of a cosmetic ingredient when applied to an animal by a route of exposure (topical, oral or inhalation route) similar to that of human exposure. They provide for the determination of the no effect level (NOEL) or the non observed adverse effect (NOAEL) and also the likely effects after the exposure to higher level.

6.3. OBSERVATION ON HUMAN SUBJECTS

For an adequate analysis of potential adverse effects of a chemical ingredient or of a cosmetic product (e.g. skin irritation, sensitisations non-invasive penetration studies) observations on human subjects may be available.

6.4. TOXICOKINETIC STUDIES

Data on dermal absorption of a cosmetic ingredient are requested for the evaluation of test results from other toxicity studies and for the extrapolation of data from animals to man. In addition the toxicokinetic studies may be required for ingredients bearing some toxicity, absorbed at high rate, and over an extended period of time.

6.5. LONG-TERM STUDIES

The objective of long-term studies is to determine the effects of a chemical ingredient in a mammalian species following prolonged and repeated exposure. In these tests, effects which require a long latency period or which are cumulative become manifested (e.g. carcinogenicity, impairment of fertility, reproductive disorders, etc.).

6.6 TESTING FOR UV-LIGHT ABSORBING COSMETIC INGREDIENTS

Tests are available in the scientific literature. The scientific community is urged to evaluate appropriate tests.

7. TEST PROCEDURES (METHODOLOGIES)

Test procedures (guidelines) for the performance of toxicity studies evaluating different toxicological endpoints are those reported in the Commission Directive 84/449/EEC of 25 April 1984 (Annex: Part B: Methods for the Determination of Toxicity) and in the Commission Directive 87/302/EEC of 18 November 1987. Tests for the assessing of photomutagenicity, photoirritancy, photosensitisation and skin absorption are not yet included in these Directives.

ANNEX 1

GUIDELINES FOR ASSESSING THE POTENTIAL FOR TOXICITY OF COMPOUNDS USED AS SUNSCREEN AGENTS IN COSMETICS

SPECIFIC REQUIREMENTS FOR TESTING "PHOTOTOXIC" EFFECTS

INTRODUCTION

All compounds used as sunscreen filter are, by their nature, chemicals that are able to absorb UVA and/or UVB light. The range of wavelengths which are absorbed by a given compound is termed its absorption spectrum.

As a consequence of a such light absorption, a chemical may change its molecular configuration, or may be transformed into a different chemical molecule. The resulting molecule may undergo biological reaction of toxicological relevance different from those displayed by the original molecule, hence the need to investigate specific phototoxic effects. These relate particularly to photoirritancy, photosensitisation and photomutagenicity.

Testing for photoirritancy and photosensitisation will routinely be required on all such compounds.

The following draft guidelines consider the need for testing of sunscreen agents for photomutagenic potential, that is screening for mutagenic properties under the influence of solar simulated radiation; guidance on the methodology to use is given.

TESTING FOR PHOTOMUTAGENICITY

INTRODUCTION

Sunscreen agents should routinely be tested for their potential to induce gene mutation in bacteria and chromosome aberrations in mammalian cells *in vitro* both in the presence and absence of a metabolic activation system. In addition, studies to investigate the potential of such agents to exhibit photomutagenic properties will normally be required. However, if evidence can be provided using adequate methods to demonstrate that the compound exhibits complete stability after 10 hours exposure to solar simulated radiation, such photomutagenicity testing may not be required.

OUTLINE OF TEST METHOD

Test substance

The sunscreen agent must be characterised by its absorption spectrum in an appropriate solvent.

Test systems to be used

Both a bacterial test for gene mutation and an *in vitro* test for chromosome aberrations in mammalian cells should be performed in the presence of UV radiation. Further testing may be required depending on the results obtained.

Test conditions

Light source

The test system should be exposed to radiation produced by a solar simulator lamp. The wavelength spectrum of the lamp must be indicated; it should cover both UVA and UVB radiation.

Doses of radiation

The doses of the solar simulated radiation and the concentration of the sunscreen agent used should be defined in such a way that they permit an adequate evaluation of the potential of the agent to induce mutagenic effects in the presence of light. The rationale for the selection of doses should be given in the test report.

Metabolic activation

Although there exists some information on the possible synergistic effect between metabolic activation and light, the present scientific knowledge does not allow the definition of standard conditions for testing the effect of light on a chemical in the presence of a metabolic activation system. The evaluation of the effect of radiation in the presence of an exogenous metabolic activation system is thus not recommended at present.

Positive control

It is suggested that 8-methoxypsoralen be used as positive control, with effects investigate in both the presence and absence of solar simulated radiation.

Protocol

Regarding general aspect of these mutagenicity studies, these should possibly conform to the guidelines given in Directives 84/449/EEC and 87/302/EEC.

ANNEX 2

GENERAL TOXICOLOGICAL REQUIREMENTS FOR COSMETIC INGREDIENTS AND FINISHED PRODUCTS

A. When requested, the manufacturer shall provide the Commission with the information set out below:

1. Acute toxicity (oral or by inhalation in case of volatile substances);
2. Dermal absorption;
3. Dermal irritation;
4. Mucous membrane irritation;
5. Skin sensitisation;
6. Sub-chronic toxicity (oral or by inhalation in case of volatile substances);
7. Mutagenicity (bacterial test for gene mutations and *in vitro* mammalian cell culture for chromosome aberrations);
8. Phototoxicity (in case of UV-light absorbing substances);
9. Human data (if available).

When considerable oral intake can be expected or when the data on dermal absorption indicate a considerable penetration of the ingredients through the skin. Taking into account the toxicological profile of the substance and its chemical structure, the following further information may be necessary:

10. Toxicokinetics
11. Teratogenicity, reproduction toxicity, carcinogenesis and additional genotoxicity.

There may be instances in which it does not appear to be necessary, or it is not technically possible to provide the information: in such cases, scientific justification needs to be given.

According to Art. 7 of Council Directive 86/609/EEC, "regarding the protection of animals used for experimental and other scientific purposes" an animal study shall not be performed if another scientifically satisfactory method of obtaining the result sought, not entailing the use of an animal, is reasonable and practically available.

Tests must be conducted according to the guidelines reported in the 84/449/EEC and in the 87/302/EEC Directives. Deviation from these procedures shall be justified by scientific reasons. The bodies carrying out the tests shall comply with the principles of good laboratory practice.

When complete studies and the results obtained are submitted, it shall be stated that the tests were conducted using the substance of the same physical and chemical characteristics of that to be included in the finished cosmetic product.

The dossier of the information must include data on the identity of the substance and its physicochemical properties, as specified in the Annex VII of the 79/831/EEC Directive.

B. Each cosmetic finished product is an individual and unique combination of ingredients. The number of the finished products is extremely large when compared to the number of cosmetic ingredients

The dossier of a finished product or of a group of finished products should contain adequate information to make possible a safety evaluation of the finished product.

In general, this would be obtained by the knowledge of the toxicity of the cosmetic ingredients. Toxicity information on the ingredients should include the evaluation of the most relevant toxicological end points.

In few cases, however, as, for instance, when the formulations used in the finished product were different from the solvents employed in the toxicity studies of the ingredients and they were likely to increase considerably the penetration or the irritancy of some of the ingredients, additional information on finished products to allow a better safety evaluation would be needed.

If a potentiation of the toxic effects of the ingredients, or if toxic effects resulting from chemical interaction between individual ingredients, would be likely to occur, specific toxicological information on the finished products would be required. Conversely, as indicated previously, any claim of decreased absorption or potential hazard of some ingredient, due to the formulation, should be supported by adequate information.

When the combination of the ingredients present in the finished product makes highly probably the formation of new substance of toxicological concern, additional toxicological information on finished product would be needed.

COLIPA

Colipa, the European Cosmetic, Toiletry and Perfumery Association, was established in 1962. Its objectives are:

- To provide expertise and support to a range of working groups dealing in scientific, economic, fiscal, legal, consumer and environmental issues.

- To assist members in complying with European Union legislation affecting cosmetic industry products and operations.

- To act as an industry voice working with both international authorities and organisations. Additionally, Colipa provides a worldwide perspective to its members through its relationships with equivalent organisations in the USA and Japan.

- To serve as a communication and information centre for the European cosmetic industry, strengthening the industry's position through continuous interaction with its members.

The membership of Colipa comprises national associations from the fifteen EU Member States, six associate or corresponding member associations (Australia, Israel, Norway Poland, Switzerland, Turkey) and twenty-one major international companies. They are Avon Products, Beiersdorf, Benckiser Group, Bristol Myers Squibb, Chanel, Colgate-Palmolive, Estée Lauder, Gillette Industries, Hans Schwarzkopf, Henkel, Johnson & Johnson, L'Oréal, Parfums Christian Dior, Procter & Gamble, Yves Rocher, Sanofi beauté, Shiseido, SmithKline Beecham Consumer Healthcare, Stafford-Miller/Block Drug, Unilever and Wella.

THE COLIPA
Steering Committee on Alternatives to Animal Testing (SCAAT)

SCAAT was established in June 1992. All initiative of Colipa's International Companies' Council, its primary objective is to coordinate the efforts of the cosmetic industry in the research and development of alternative methodologies.
Currently, there are four SCAAT Task Forces focusing on Eye Irritation, *In-vitro* Photoirritation, Human Skin Compatibility and Percutaneous Absorption.

SCAAT has already taken a series of indicatives which will result in the execution of programmes and the generation of data to contribute to the validation of alternative methods. It is now recognised by the authorities as a credible and authoritative voice on this issue.

COSMETICS EUROPE IS THE EUROPEAN TRADE ASSOCIATION REPRESENTING THE INTEREST OF THE COSMETICS, TOILETRY AND PERFUMERY INDUSTRY

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