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 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).

4- References

1 Patrick E, Maibach HI: Predictive assays: Animal and man, and in vitro and in vivo. In: Rycroft R.J.G., Menne T., Frosch P.J., (1995) Textbook of Contact Dermatitis. Springer Heidelberg New York.

2 World Medical Association Declaration of Helsinki, (1997) JAMA 227: 925-926

3 CPMP Working Party on Efficacy of Medicinal Products Note for Guidance: Good Clinical Practice for Trials on Medicinal Products in the European Community (1990) CB-55-89-706-EN-C.

4 Organisation for Economic Co-operation and Development: Development of OECD Test Guidelines for Use in Tests with Human Volunteers. 27th Joint Meeting of the Chemicals Group and Management Committee, 11th-13th February 1998 (ENV/MC/CHEM/RD (98))

ANNEX 12 – GUIDELINES ON THE USE OF HUMAN VOLUNTEERS IN COMPATIBILITY TESTING OF FINISHED COSMETIC PRODUCTS*

Ethical considerations with respect to human testing of cosmetic products have to include the problem of the first topical contact of a human volunteer with the product to be tested. Guidelines have therefore to be based on the principle that no fortuitous e.g. badly defined contact can be allowed. Strict rules have to be defined.

The following guidelines take into consideration the ethical and practical aspects when human volunteers are involved in studies organised to assess skin and mucous membrane compatibility of cosmetic finished products.

1. Background

1.1 Legal requirements for consumer safety

According to the Council Directive (76/768/EEC), "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". According to the 6th Amendment of the Cosmetics Directive (93/35/EEC), a European dossier must be kept readily accessible for inspection by the competent authorities, containing a toxicological file based on safety assessment of the ingredients and the finished products. However, there is no legal requirement that finished products have to be tested on animals nor on human beings before marketing.

1.2 Side effects caused by cosmetic products

Cosmetic products are developed to be applied to the skin and external mucosa and to be used by the normal population. It must, however, be considered that people suffering from skin disorders or sensitive skin also use cosmetics. Occasionally undesirable side effects, both local and systemic, may occur. Local reactions may be, among others, irritation, contact allergy, allergic contact dermatitis, contact urticaria and sunlight, especially UV light, induced reactions. Skin and mucous membrane irritation are the most frequently observed reactions.

1.3. Description of terms

For the purpose of the document, the following terms are described as indicated:
- Compatibility test: corresponds to a test intended to confirm that there are no harmful effects when applying a cosmetic product for the first time to the human skin or mucous membrane.
- Acceptability test: corresponds to a test intended to confirm the fulfilment of the expectations for a cosmetic product in-use.

* Adopted by SCCNFP in its Plenary Meeting of 23 June 1999 (SCCNFP/0068/98 Final)

1.4. General statement

Since tests in animals and alternative methods are of predictive limited value with respect to human exposure, confirmatory compatibility tests of cosmetic finished products in humans may be needed scientifically and ethically, provided that the toxicological profile of their ingredients, based on animal testing and/or the use of alternative methods, is available. A high degree of safety has to be expected. Finished cosmetic products are usually tested in small populations

- to confirm the skin and mucous membrane compatibility of the finished products;
- to assess their cosmetic acceptability.

2. Ethical considerations

2.1 Basic Principles

The basic principles for testing in humans are provided by the following documents :

* World Medical Association Declaration of Helsinki in its current revisions (1964-1975-1983-1989-1996)

* Recommendation N° R(90)3, of the Committee of Ministeries/Council of Europe adopted on 4th February 1990

* Draft Directive on Good Clinical Practice for Trials on Medicinal Products in the European Community

* National Regulations regarding human studies.

2.2. SCCNFP recommendations

According to these basic principles, the SCCNFP recommends the following ones which apply directly to the compatibility testing of cosmetic products:

- Cosmetic compatibility tests on human volunteers cannot be considered as a replacement for animal testing.

- Cosmetic compatibility tests on human volunteers can only be performed to confirm, in a limited number of subjects, that products do not damage skin and mucous membrane, as already expected from other sources.

- The study supervisor must have at his disposal, prior starting any test, the full quantitative formula of the product to be tested, its preclinical safety assessment, its conditions of use and possible warnings.

- Studies should conform to generally accepted scientific principles. They should be based on an adequate knowledge of the potential risks incurred, resulting from laboratory experimentation and/or appropriate knowledge of the scientific literature.

- Research involving human volunteers should not be carried out unless the importance of the objective is in proportion to the inherent risk for the subject.

- Tests involving human volunteers which do not conform to scientific criteria and which are unable to provide exploitable results, are unacceptable even if they do not present any risk for the consenting subjects.

- The interest of the human subject should always prevail over the interest of science and society. Therefore the Investigator should cease as soon as risk is found to outweigh the potential benefit of the study.

- Skin compatibility testing involving human volunteers should be conducted only by technically qualified persons and under the supervision of a clinically competent medical doctor/physician.

- Acceptability tests in consumers do not require review by an ethical committee.

- Compatibility test protocols of cosmetic products possibly posing a risk to volunteers ought to be submitted for consideration and comments to an ethical committee provided that this committee conforms with the laws and regulations of the country in which the study is performed.

- Human volunteers should be adequately informed of the aims, methods used and potential risks of the study and the discomfort they may entail. Free informed written consent is mandatory prior to entering the study.

- Volunteers with any current dermatitis or known past allergic contact dermatitis related to the ingredients of the cosmetic product concerned should be excluded from the panel participating in safety tests.

- Except for specific cosmetic products, especially intended to be used by pregnant women and whose safety has been specially assessed for such employment, pregnant or lactating females should never be included in safety confirmatory tests.

- Children should not be involved with the testing of the compatibility of cosmetic products.

- In selected cases when the inclusion of adolescents (10-16 years) is warranted, they should be fully informed of the aims, methods used and potential risks of the study in order to obtain their free personal co-operation. They should personally give a free informed consent in written form. Parents or guardians should also give their consent.

- Study reports have to provide all experimental information in order to allow to understand the rationale of the study and to preserve the accuracy of the results.

3. Test methods in human volunteers for the skin compatibility assessment of finished cosmetic products

- Possible adverse reactions include skin irritation, contact allergy, photomediated reactions, acne, contact urticaria, pigment changes, hair and nail changes, subjective symptoms and various end-points measured by non-invasive techniques (elasticity, skin thickness, wrinkling, roughness etc.). Therefore it is not possible to make a complete list of current testing methods. The design of the test protocol depends on the specific question asked. In each case the reasoning and the scientific background of the test should be given.

- Among the most frequently used tests for finished cosmetic products are skin irritation tests as human repeated insult patch tests, chamber scarification tests, repeated open application tests, and soap chamber tests for detergents, and various other occlusive or open test methods developed to stimulate intended use situations. Irritancy reaction in humans is not an absolute measure and should be related to appropriate controls defining the range of response.

- In some test methods the skin of the volunteers may be preconditioned by various physical and chemical factors before exposure to the cosmetic product occurs. The design of tests may vary considerably with respect to the selection of volunteers, exposure time, patch test technique and reading.

- Often visual assessment is applied. Although this type of assessment is subjective, good results can be obtained with trained experimenters.

- Non-invasive bioengineering techniques can be applied in safety assessment to quantify and objectivate the results, to measure even sub-clinical symptoms and, generally speaking, to obtain additional information ; this has not been a common practice so far and further validation of these methods is encouraged by the SCCNFP.

- An important aspect in all human testing with finished cosmetic products is that the result obtained should be regarded as relative to the result of control substances, giving the range of reactivity within the test group. At the basis lays the considerable inter-individual variation between skin responses from different volunteers.

- For specific products, confirmatory safety tests may be performed in the surrounding area of the eye. In such a case, extreme attention should be given with respect to possible local irritations. Such tests should be stopped as soon as a significant adverse effect is observed in anyone of the subjects involved in the study. In such tests only one eye should be investigated per volunteers. The study can only be carried out under the strict supervision of an ophthalmologist.

ANNEX 13 - CLASSIFICATION OF SUBSTANCES

Classification of substances as ingredients of cosmetic products is recommended by the Scientific Committee on Cosmetology on the basis of evaluations of data provided pursuant to the Guidelines on the Safety Assessment of Cosmetic Ingredients. The overriding consideration is that the substances should be safe for consumer use under conditions of intended exposure at the relevant concentrations.

Candidate substances for the positive lists must not be used until a final classification in Group 1 has been made. For substances already in use, the classification may be reconsidered if necessary.

For substances in provisional lists for which there are insufficient data for a final safety assessment, additional information must be adequate and provided within a specified time limit. Otherwise it is concluded that no further use of the substance in cosmetic products should be allowed for the specified purpose.

Group 1:

Substances for which data at the time of assessment support the conclusion that they do not pose a health hazard. They may be used in cosmetic products for the designated purposes and in concentrations not exceeding the limits indicated.

Group 2:

Substances which must not be used in cosmetic products. Substances may be included in this group because either

a) the available data support the conclusion that they constitute a health hazard or

b) the available data do not justify the assumption that their use in cosmetic products can be considered safe.

ANNEX 14 - STANDARD FORMAT OF THE OPINIONS

Executive Summary

1. General data

1.1 Identity of the ingredient
1.2 CAS n°
1.3 Use

2. Terms of reference

3. Toxicological Evaluation & Characterisation (max. two lines per endpoint, no figures)

3.1 Acute toxicity (dermal, oral, i.v., i.p.)
3.2 Chronic/sub-chronic toxicity
3.3 Reproductive toxicity
3.4. Percutaneous absorption
3.5 Irritation and corrosivity
3.6 Allergenicity and sensitisation
3.7 Genotoxicity/carcinogenicity
3.8 .....

4. Opinion

5. Statement on the toxicological evaluation

The SCCNFP is the scientific advisory body to the European Commission in matters of consumer protection with respect to cosmetics and non-food products intended for consumers.

The Commission's general policy regarding research on animals supports the development of alternative methods to replace or to reduce animal testing when possible. In this context, the SCCNFP has a specific working group on alternatives to animal testing which, in co-operation with other Commission services such as ECVAM (European Centre for Validation of Alternative Methods), evaluates these methods.

SCCNFP opinions include evaluations of experiments using laboratory animals; such tests are conducted in accordance with all legal provisions and preferably under chemical law regulations. Only in cases where no alternative method is available will such tests be evaluated and the resulting data accepted, in order to meet the fundamental requirements of the protection of consumer health.

Full Opinion

1. Terms of Reference

1.1 Context of the question

The adaptation to technical progress of the Annexes to Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products.

Request for inclusion of ..... in Annex ..., part 1 – List of ..... which Cosmetic Products may contain – to Council Directive 76/768/EEC.

1.2 Request to the SCCNFP

The SCCNFP is requested to answer the following questions :

* Is ..... safe for use in cosmetic products?

* Does the SCCNFP propose any restrictions or conditions for its use in cosmetic products?

1.3 Definitions of terms where appropriate

2. Toxicological Evaluation and Characterisation

2.1.	General

2.1.1.	Primary name

Ref. :

2.1.2.	Chemical names

Ref. :

2.1.3.	Trade names and abbreviations

Ref. :

2.1.4.	CAS no.

Ref. :

2.1.5. Structural formula

Ref. :

2.1.6. Empirical formula

Emp. Formula :
Mol weight :

Ref. :

2.1.7. Purity, composition and substance codes

Ref. :

2.1.8. Physical properties

Subst. Code :
Appearance :
Melting point :
Boiling point :
Density :
Rel. vap. dens. :
Vapour Press. :
Log P_{ow} :

Ref. :

2.1.9. Solubility

Ref. :

2.2. Function and uses

Ref. :

TOXICOLOGICAL CHARACTERISATION

2.3. Toxicity

2.3.1. Acute oral toxicity

Ref. :

2.3.2.	Acute dermal toxicity

Ref. :

2.3.3.	Acute inhalation toxicity

Ref. :

2.3.4.	Repeated dose oral toxicity

Ref. :

2.3.5.	Repeated dose dermal toxicity

Ref. :

2.3.6.	Repeated dose inhalation toxicity

Ref. :

2.3.7.	Sub-chronic oral toxicity

Ref. :

2.3.8.	Sub-chronic dermal toxicity

Ref. :

2.3.9.	Sub-chronic inhalation toxicity

Ref. :

2.3.10. Chronic toxicity

Ref. :

2.4.	Irritation & corrosivity

2.4.1.	Irritation (skin)

Ref. :

2.4.2.	Irritation (mucous membranes)

Ref. :

2.5.	Sensitisation

Ref. :

2.6.	Teratogenicity

Ref. :

2.6.1.	One-generation reproduction toxicity

Ref. :

2.6.2.	Two-generation reproduction toxicity

Ref. :

2.7.	Toxicokinetics (incl. Percutaneous Absorption)

Ref. :

2.8.	Mutagenicity/Genotoxicity

Ref. :

2.9.	Carcinogenicity

Ref. :

2.10.	Special investigations

Ref. :

2.11.	Safety evaluation

Ref. :

CALCULATION OF THE MARGIN OF SAFETY

(Name of substance)

(Class / Group)

Based on a usage volume of X ml, containing at maximum X %

Maximum amount of ingredient applied: I (mg)=
Typical body weight of human: 60 kg
Maximum absorption through the skin: A (%)=
Dermal absorption per treatment: I (mg) x A (%)=
Systemic exposure dose (SED): SED (mg)= I (mg) x A (%) / 60 kg
No observed adverse effect level (mg/kg): NOAEL =
(species, route of application)

Margin of Safety: NOAEL / SED =

2.12.	Conclusions

Classification:

Ref. :

2.13.	References

3. Opinion of the SCCNFP

4. Other considerations (if any)

5. Minority opinions (if any)

添付資料-2

Europa

The European Commission

Health and Consumer Protection

Health and Consumer Protection

Consumer Health Protection ▭ Scientific Committees ▭ Scientific Committee for Cosmetic Products, and Non-food Products intended for Consumers ▭ ***Outcome of discussions***

Opinion concerning present development and validation of adequate alternative methodologies to the use of animals in safety testing of cosmetics - adopted by the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers during the plenary of 23 June 1999

1. *PREAMBLE*

One of the main objectives of Council Directive 76/768/CE of 27 July 1976 on the approximation of the laws of the member states relating to cosmetic products, as stated in its recitals is "the safeguarding of public health". Moreover "cosmetic products must not be harmful under normal or foreseeable conditions of use... taking into account the possibility of danger to zones of the body which are contiguous to the area of application".

These positions have been maintained by means of a set of Commission Directives, and reiterated in a series of Amendments to the Council Directive.

In 1977 the Commission Decision 78/45/EEC of 19 December established a Scientific Committee on Cosmetology (SCC) to assist the Commission in the process of drafting and amending the Community cosmetic laws. The SCC is formed by scientists highly qualified in the fields of medicine, toxicology, biology, chemistry and other similar disciplines.

In 1997 Commission Decision 97/18/EEC of 23 July 1997 reorganized such precious technical assistance to the Commission by establishing a "Scientific Committee on Cosmetic and Non-Food Products intended for Consumers" (SCCNFP) to be consulted in the case laid down by Community legislation, and on questions of particular relevance to consumers' health. The SCCNFP has been requested to produce "scientific advice concerning matters relating to consumers' health in its strict sense".

Art. 4 of Council Directive 76/768/ECC, amended by Council Directive 93/35/EEC, affirms a prohibition of the marketing of cosmetic products containing "ingredients or combinations of ingredients tested on animals after 1 January 1998". The date was later postponed to 30 June 2000 by Commission Directive

97/18/EEC of 17 April 1997.

The Commission shall submit draft measures to postpone the date of implementation of this provision by 1 January 2000. A justification of a possible postponement of the deadline of 30 June 2000, could be an insufficient progress in developing alternative methods to replace animal testing or, also, other cases where alternative methods would not have been scientifically validated as offering an equivalent level of protection to consumers. Before submitting such measures, the Commission shall consult the SCCNFP.

In particular, the Commission has requested the SCCNFP as regards the status of alternative methods for the safety assessment of cosmetic ingredients according to the current state-of-the-art. Specifically, the Commission has requested the SCCNFP to assess the possibility to replace the data obtained on the basis of animal tests with data obtained making use of alternative methods in the safety evaluation of cosmetic ingredients, and to indicate those end-points for which alternative methods to animal testing are not available yet (Doc. no. 16831 of 11 August 1998).

2. *SAFETY EVALUATION OF COSMETIC INGREDIENTS*

The SCCNFP and previously to it, the SCC, has illustrated in a set of documents the concepts and the criteria of the present procedure of safety evaluation of cosmetic ingredients, based on the experience developed during more than 20 years, by regulating ca. 800 individual cosmetic ingredients of which over 400 have been proposed for a ban, due to their toxic and harmful effects to consumers' health (Report EUR 8794; SPC/803-5/90; XXIV/1878/97; SCCNFP/0119/99 Rev.1 draft).

As stressed several times by the SCCNFP, the primary goal of the safety testing of all cosmetic ingredients presented to the European Commission for their possible inclusion in the technical Annexes of the Cosmetic Directive, is to determine the potential of these ingredients for their harmful effects in an experimental model, so that it makes possible, by extrapolation, to predict the same effect or the absence of harmful effects for consumers.

According to medical science, the safety studies should permit a quantitative determination of the potential for a cosmetic ingredient, or a mixture of cosmetic ingredients to produce local and systemic adverse effects and allow a determination of factors which may influence the nature, severity and possible reversibility of effects (Ref. 1).

Information necessary to the above purposes can be obtained only from carefully designed and well conducted studies. Toxicology testing programmes generally begin with single exposure *in vivo* or *in vitro* studies and progress to evaluate the effects of long-term repeated exposures.

The most used and recognized adequate models for safety testing

are those represented by living laboratory animals (mice, rats, rabbits, guinea pigs etc.) which have been the object of millions of experimental studies developed by the toxicological research. In the last twenty years new toxicological systems no longer based on animal models, have been employed by scientists and accepted by national, continental (EU, Ref. 2, 3) and international (OECD, Ref. 4) regulations.

These new test systems are represented by mutagenicity/genotoxicity *in vitro* tests which make use of individual cellular organisms (bacteria, yeast, mammalian cells) or insects. This development has enabled, in many cases, to avoid the use of a large number of animals, as requested by the very expensive and laborious long-term carcinogenicity bioassays (Ref. 1).

After the approval of Sixth Amendment, the SCC and later the SCCNFP have been monitoring the several actions developed by scientific groups, including academics, industrial research and public institutions, to stimulate the progress in the development and validation of alternative methods to the use of animal models in the safety testing of cosmetics. In particular, the SCCNFP has been discussing and evaluating together with ECVAM (European Centre for the Validation of Alternative Methods) and COLIPA (European Cosmetic, Toiletry and Perfumery Association) scientists, the results of the pre-validation and validation studies and the applicability of these results to the safety evaluation of cosmetic ingredients and cosmetic products. An opinion has been adopted by the SCCNFP on 20 January 1999 during its Plenary Meeting on the use of some alternative methods to animal testing in the safety evaluation of cosmetic ingredients (Ref. 5).

3. *PRESENTLY VALIDATED ALTERNATIVE METHODS*

The following notes are representing the opinion on some alternative methods which could be of some relevant use in the safety evaluation of cosmetic ingredients, and on the state-of-the-art of some *in vitro* methods which could be validated in the near future.

3.1. SKIN IRRITATION

The present scientific knowledge on the mechanistic basis of skin irritation *in vivo* is still limited, due to the complex set of reactions involved , and in the impossibility to define the key specific and relevant end points which could be evaluated by an *in vitro* system (Ref. 6).

However, a pre-validation study is in progress by using human skin models and a pig ear test, under the sponsorship of ECVAM.

In the evaluation of a potential skin irritant effect by a cosmetic ingredient, it is still possible by using a combination of different criteria of evaluation, to identify the corrosivity/non-corrosivity potential of chemical ingredients.

Recently, two alternative *in vitro* methods for skin corrosivity have been validated and demonstrated to be applicable to the procedure for safety testing also in the sector of cosmetic ingredients. A draft new guideline on skin corrosivity testing has been submitted to OECD and to the European Commission (EC) for its inclusion in the Annex V of Council Directive 67/548/EEC. The new *in vitro* methods are represented by the Transcutaneous Electrical Resistance (TER) Test and by the Episkin Test. The SCCNFP has proposed the use of these two methods when corrosivity of cosmetic ingredients must be tested on animals, or when humans cannot be excluded. (Ref. 5)

3.2. PHOTOTOXICITY

OECD guidelines or EC guidelines on phototoxicity testing have not been adopted yet for the testing of UV light absorbing substances on animal models. Pre-validation, validation and applicability on cosmetic ingredients, such as the UV filters have been the object of a series of studies and different projects. An *in vitro* model, the 3T3 NEUTRAL RED UPTAKE Phototoxicity Test has been developed and demonstrated to be valid for the identification of phototoxic UV absorbing chemicals, including cosmetic ingredients (Ref. 7). This method is based on a cell phototoxicity process, observed in a mammalian cell population *in vitro*.

A draft protocol for testing phototoxicity, by employing this new alternative method has been presented to the OECD and to the European Commission for its inclusion in Annex V of Council Directive 67/548/EEC.

The SCCNFP in its Plenary Meeting of 20 January 1999 has adopted an opinion which proposes to the European Commission the use of the "3T3 NRU Phototoxicity Test" as the standard method for testing the UV light absorbing cosmetic ingredients or mixtures of ingredients for phototoxic potential.(Ref. 5)

3.3. PERCUTANEOUS ABSORPTION

OECD guidelines or EC guidelines on safety testing for percutaneous absorption have not been adopted yet. However, some draft measures have been presented to OECD.

The assessment of percutaneous absorption of cosmetic ingredients has primary relevance in the procedure for evaluating the safety of cosmetics for consumers. The SCCNFP has recently reviewed the available scientific literature and data developed by cosmetic industry in this sector of testing and has agreed with the rationale for using *in vitro* methods to evaluate the percutaneous absorption. An opinion has been adopted by SCCNFP during its Plenary Meeting of 20 January 1999 proposing the use of *in vitro* methodologies for the safety testing of cosmetic ingredients. Moreover, due to the lack of a guideline approved by OECD or by the European Commission, the SCCNFP has defined a set of basic criteria for the *in vitro*

assessment of percutaneous absorption of cosmetic ingredients, which have been adopted during the Plenary Meeting of 23 June 1999. These basic criteria represent the recommendation put forward by the SCCNFP for all cosmetic industries, in their assessment of the percutaneous absorption (Doc. SCCNFP/0167/99 Final)

3.4. OCULAR IRRITATION

Ocular irritation testing is needed for many cosmetic ingredients applied in particular zones of the consumers' body, especially those which may come into contact with the eye.

Since the approval of the Sixth Amendment, several collaborative studies have been developed within the European Union on chemicals of different use or cosmetic ingredients; similar studies have been developed in the USA (finished cosmetic products) and Japan (cosmetic ingredients) (Ref. 8.1-8.6).

The results of such extensive studies have revealed that no single test can fully replace the Draize rabbit test; that some *in vitro* tests have a certain level of predictivity and some are promising; that the level of predictivity is improved when combining several and different test systems (batteries) (Ref. 9). Some of these *in vitro* tests combined with Structure Activity Relationships and Physicochemical data could be used to identify potentially non-ocular irritant chemicals, but the need to use *in vivo* tests is still requested.

A document prepared by ECVAM and COLIPA on the current status of the alternatives to eye irritation (Doc. SCCNFP/0174/99) indicates the utility of *a short-time approach optimising the current strategies and methods, and a long-term approach allowing gaps in knowledge to be filled, so as to increase the current predictivity of the alternative methods, and as a basis for the development of new methods, are being developed and conducted.*

Attempts are currently being carried out by COLIPA: (1) to review the validation studies concluded so far, as to extract the maximum bulk of information to help refine the currently available prediction models; (2) to optimise the tier testing strategies as a "reduction alternative" proposed by ECVAM; (3) to propose a research programme to increase the knowledge on the mechanisms of chemically induced eye irritation so as to develop complementary test methods to the current alternative or to modify these in view of improving their predictive capacity (Ref. 9).

3.5. SKIN SENSITIZATION

Skin sensitization is a complex phenomenon which implies a series of biological reactions; skin permeation by the allergen; reaction of the hapten with a skin protein; processing haptenated proteins by epidermal Langerhans cells; migration of Langerhans cells to draining lymph nodes and interaction with T cells; recognition of

hapten by specific T cells; etc (Ref. 10).

It should be possible by combining computerized expert systems with appropriate biological *in vitro* systems to identify chemicals able to perform the initial reactions. At present the elucidation of the critical stages of the phenomenon is still under study and considerable research is being undertaken. Recently, a substantial opportunity to refine and reduce animal use in the hazard identification of skin sensitizing cosmetic ingredients has been achieved with the Murine Local Lymph Node Assay (LLNA) (Ref. 11). This aspect is being considered by the SCCNFP.

3.6. OTHER TOXICOLOGICAL END-POINTS

Besides, apart carcinogenicity, the other fields of toxicology do not seem at present to offer the possibility to substitute animal models with alternative methods not using animals. Due to the same essential basic mechanisms between certain types of carcinogenic substances (genotoxic carcinogens) and mutagenic substances, chemicals that induce mutations in somatic cells *in vitro* should be regarded to as potential carcinogens and hence mutagenicity screens are of value in identifying potential "genotoxic" carcinogens. This is not the case for other fields of toxicology, such as reproductive toxicology, neurotoxicity, teratogenicity, sub-chronic toxicology, etc. The scientific knowledge of the basic mechanisms of the different types of toxic events still requires development of long-term planning or research into basic and cellular events underlying toxicity.

3.7. THE USE OF HUMAN VOLUNTEERS IN THE SAFETY EVALUATION OF COSMETIC INGREDIENTS AND FINISHED COSMETIC PRODUCTS

In a recent opinion, the SCCNFP has stressed the concept that the tests on animals for skin irritation or (not yet) validated alternative methods may be limited regarding their predictive value for exposure of human population. The SCCNFP states that confirmatory tests on humans may be needed scientifically and ethically, provided that the toxicological profile of an ingredient, or a mixture of ingredients, or a finished cosmetic product, based on animal or alternative methods is available and that a degree of safety is to be expected (SCCNFP/0003/98). This opinion also stresses the concept that confirmatory skin tolerance tests of cosmetics in human should not be preferred to animal testing; that the safety testing of cosmetics on humans may not be considered an alternative method to the use of animals; and that the use of human volunteers in the safety evaluation of cosmetics is subjected to ethical concern.

The SCCNFP has recently approved Guidelines on the use of human volunteers in the testing of potentially cutaneous irritant cosmetic ingredients or mixtures of ingredients (SCCNFP/0003/98) and Guidelines on the use of human volunteers in compatibility testing of finished cosmetic products (SCCNFP/0068/98 Final).

4. *OPINION OF THE SCCNFP*

On the basis of the scientific literature, after the evaluation of different research programmes conducted by cosmetic industries, the European Commission (ECVAM) and other Institutions, and considering the results obtained during the period 1993-1999 on the development and validation of alternative methodologies to the use of animals in the safety testing of cosmetic ingredients, the SCCNFP expresses the following opinion to the European Commission.

1. There has been a considerable effort in the technical and scientific fields of the safety testing of chemicals in general and cosmetics in particular, to develop and validate alternative methodologies to the use of animal models which could offer to the consumers an adequate and acceptable level of protection;

2. Due to the complexity of biological mechanisms that represent the basis for the occurrence of toxic events in human organism, a significant effort of scientific research is needed to understand all different steps of the aforementioned mechanisms and their molecular events. A set of research programs have been planned in the sectors of ocular irritation, skin irritation, skin sensitization, neurotoxicity, etc. The results of such researches will considerably influence scientific knowledge on several toxic events which, on turn, will allow the identification of more rigorous and rational criteria and systems to be applied in the safety evaluation of cosmetics, by possibly reducing the need of laboratory animals (Ref. 12);

3. At present, the SCCNFP has identified with the help of the contribution made by ECVAM in this field of activity, the following alternative methods that can be used for the safety testing of cosmetics:

a. In Vitro Methods to assess skin corrosivity in the safety evaluation of cosmetic ingredients or mixtures of ingredients (SCCNFP/0070/98 Final);

b. In Vitro Methods to assess phototoxicity in the safety evaluation of cosmetic ingredients or mixtures of ingredients (SCCNFP/0069/98 Final);

c. In Vitro Methods to assess percutaneous absorption of cosmetic ingredients (SCCNFP/0088/98 Final).

4. Moreover, the SCCNFP has defined the "Basic criteria for the *in vitro* assessment of percutaneous absorption of cosmetic ingredients" (SCCNFP/0167/99 Final) in order to provide the cosmetic industry with a set of recommendations for an adequate protocol for applying the *in vitro* methods in the studies of percutaneous absorption.

5. The SCCNFP has also produced a set of guidelines on the use of