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environment and quality of life

REPORTS
of the Scientific Committee on Cosmetology
(Third series)

Report

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INTRODUCTION

The Scientific Committee on Cosmetology was set up by Commission Decision 78/45/EEC of 19 December 1977 (OJ N° L 13 of 17 January 1978, p. 24) in order to provide the Commission with informed opinions on any scientific and technical problems arising in connection with cosmetic products, and in particular on the substances used in their manufacture, on their composition and on the conditions for their use.

The members of the Committee are independent scientists highly qualified in the fields of medicine, toxicology, biology, chemistry or other similar disciplines.

The Committee is serviced by the Directorate-General for the Environment, Consumer protection and Nuclear safety.

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SCIENTIFIC COMMITTEE ON COSMETOLOGY

Notes of guidance for the toxicity testing of cosmetic ingredients

(opinion expressed 28 June 1982)

Definition

"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).

Ingredients are defined as "any substances used in cosmetic products".

Introduction

Cosmetic products have a history covering many thousands of years with the use of many ingredients from plant, animal and mineral sources. Present-day use, particularly as toiletries, is extensive and affects most population groups, but the degree and nature of this use varies widely within different countries of the European Community.

The purpose of this document is to give guidance to national and international authorities within the European Communities and to the person(s) responsible for putting cosmetics on the market (manufacturers or importers within the European Community).

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 then their past record in use and the relevant toxicity data already in existence.

They are drawn up in general terms and will require amendments in future as scientific knowledge advances. It is strongly advisable therefore that, whenever possible, the test proposals and procedures should be discussed in advance with official experts.

In practice, cosmetic products have seldom been associated with serious hazards 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 the human life span, has created a need to insure, so far as possible, their safety-in-use by controlling the ingredient content and toxicity.

The question of safety-in-use cannot be resolved by the restriction of ingredients to those used without known problems in the past, for the following reasons: first, previously used ingredients may become difficult to obtain for economic or legislative reasons; second, consumers now demand products with certain properties and this may require the use of new ingredients. The toxicological data on such ingredients are often scanty, or absent, and the possible long-term effects from absorption unkown. This is not to say established products should necessarily present a hazard to health, or that knowledge gained from extensive usage by man should be ignored in the assessment of the safety of such ingredients. The important point is that safety assessment of all ingredients should be on an appropriate basis. The use of natural as opposed to man-made ingredients does not confer any degree of safety. Indeed some of the most toxic substances known are "natural" in origin and many plant derivatives may be potent allergenic substances. In addition the purity of "natural" ingredients is often difficult to establish or control.

Testing of ingredients and products

Following Article 2 of the Council Directive 76/768/EEC 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 conditions of use.

However, the large number of products compared with the number of ingredients creates severe problems for considering the safety of the former. Hence, it is more realistic to perform toxicity studies, particularly for long-term hazards, on ingredients rather than on products, as this avoids unnecessary and costly duplication of studies, particularly with those ingredients used in a wide range of products. However, the assessment of the safety of an ingredient will greatly depend on the types of products in which it is intended to be used. For example, a combination of ingredients may alter the safety-in-use of the products.

Another problem is that a product can undergo chemical modification during use, as for example with the oxidizing hair dyes, or that the degree of absorption of the ingredient of cosmetic products may be altered by the solvents and oils used. For these reasons, therefore, the testing programme may have to be designed to take these factors into account.

Positive lists

In article 11 of the Council Directive 76/768/EEC it is stated that "without prejudice to Article 5 and not later than one year after expiry of the period laid down in Article 14 (1) for implementation of this Directive by the Member States, the Commission shall, on the basis of the results of the latest scientific and technical research, submit to the Council appropriate proposals for establishing lists of permitted substances".

Categories of cosmetics

The assessment of the safety of ingredients depends greatly on the manner in which the cosmetic products containing them are used. The type of product will determine the proposed and foreseeable sites of the body which the ingredients may reach, and the duration of contact. These factors are important as they in turn will determine the amount of substance which may be absorbed through the skin or mucous membranes; they can also affect the quantity of ingredient applied to the contact surface. Soaps, for example, are applied in diluted form and, although the area of application may be

extensive, the product is rapidly washed off. Sun-tanning products may be applied also over large surfaces of the body and the ingredients can remain in contact with the skin over several hours. Products used on the lips and in the mouth will be ingested in to some extent, so that gastro-intestinal absorption may occur. Cosmetics used around the eyes and genital regions may come into contact with the conjunctiva or mucosa respectively, resulting in reactions due to the thin epithelial lining of these areas.

Based on the type of product in which the ingredient is to be used, the intended sites of application or contact of the final product, other possible sites of contact, the area of the body exposed to the final product, the expected time of contact and other factors, it may be convenient to devide cosmetics into the 8 following categories.

1. Skin cosmetics - products rinsed off
2. Skin cosmetics - products not rinsed off
3. Eye cosmetics
4. Hair cosmetics - products rinsed off
5. Hair cosmetics - products not rinsed off
6. Nail cosmetics
7. Cosmetics applied in or around the mouth
8. Intimate cosmetics.

Important considerations which determine the nature of the toxicity studies required and the interpretation of the results are not only the product category but also the presentation of the product, in particular whether it is formulated in solid, liquid, powder or aerosol form.

Solid and liquid preparations intended for direct application will sometimes spread beyond their intended area of application. Hair preparations may enter the eyes, lipstick materials may be ingested; powders and aerosols may reach the atmosphere and may be inhaled. In choosing testing procedures therefore, one should have in mind not only the intended use, but also other foreseeable sites that the final product may reach under normal conditions of use.

Physical and chemical specifications

The precise chemical nature of the ingredient and its structural formula, if it is known, should be identified. With regard to ingredients which cannot be defined in terms of their structural formula, but only by their method of preparation, the latter should be sufficiently detailed to enable judgement to be made of the probable structure and activity of the compound.

The degree of purity of each ingredient should be defined, as well as an indication of the nature of any impurities that may be present, and their concentration.

Wherever possible, the substances tested in toxicity studies should be of the same specification as the substances used in the commercial products. Small changes in the nature of quantities of contaminants can considerably alter the toxicity of the substances. In general therefore the results of toxicity studies are relevant only when they are referable to the ingredient (or product) as marketed, or to even purer batches as incorporated into commercial products.

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

Toxicity studies

Some *in vitro* systems have been developed so that they can be used as screening tests to indicate the possibility of a long-term risk, but the results still have to be confirmed in mammals. Most of the adverse effects associated with cosmetics (for example erythema, oedema, allergic effects, or systemic toxicity) are such that they can only be demonstrated in mammals. It remains desirable that such testing requirements should be restricted to those studies which are necessary and appropriate in order to avoid unnecessary use of animals. As and when alternatives to animal studies become validated these should be used. Where possible, human observations can contribute to safety evaluation.

Toxicity studies in animals, especially with the higher doses employed, invariably invoke some reactions, many of them adverse.That is not to say that the same adverse effects will necessarly arise when the substance is a component of a cosmetic, applied topically to the skin or the mucosae. Consequently, it must be remembered that the interpretation of the results of toxicity tests in terms of the safety-in-use of the final product must be a matter for expert judgement.

Observations in man

Whilst it is recognized that for ethical reasons deliberate studies in man cannot be made compulsory, observations in man are nevertheless of importance in the extrapolation from animal data. It is desirable that information, particularly on irritancy and potential sensitization, be obtained in man. Observations on persons occupationally exposed to the ingredients may assist in assessing any potential hazard.

Pharmacological activity

Ingredients should not demonstrate such a degree of pharmacological activity that cosmetics in which they occur could be classified as pharmaceutical preparations (see recital of the directive 76/768) (1).

Studies required

As ingredients and final products vary widely in their nature and mode of use, it is not possible to set out a single system of testing which will apply to all ingredients. The type of product in which an ingredient is to be used will also affect the possible risk for man. Hence different sets of toxicity studies may have to be carried out with the different categories of cosmetic products. Annex I indicates the appropriate toxicity studies for an ingredient, according to proposed use in different product categories.

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(1) OJ L 262, 27.9.1976, p. 169

Irritancy

a) Skin irritation studies

These studies should be performed on all ingredients, with the exeption of oral preparations, and should be designed to show the degree of irritancy at least at proposed levels of use in cosmetic products. Studies on the ingredient will indicate whether or not that ingredient will be suitable for use in a cosmetic, whilst testing of the final product is necessary to ensure that irritancy is not increased by the vehicle or by other ingredients. Both the ingredient and the final product should be tested with at least one application to intact and abraded skin. In animals the rabbit remains the species of choice. Testing in human volunteers may provide valuable supplementary evidence and confirmation.

b) Eye irritation studies

These are basically an extension of skin irritancy studies for ingredients intended for use in products which may be applied in or around the eye, or which may enter the eye during normal application (for example shampoos). Hence these studies are not necessary when the ingredient has been shown to be a skin irritant. A suitable animal species (such as the rabbit) should be used, and the results of instillation in the eye of the ingredients in a suitable vehicle, and the final product, followed over a number of days. For ingredients or final products used irregularly (for example insect repellents and hair dyes) a single application is sufficient. Local anaesthetic properties should also be looked for where preparations may enter the eye.

As soon as acceptable *in vitro* tests for eye irritation have been devised and validated these should be substituted for those in the intact animal.

c) Specific membranes irritation

Where products are intended to come into contact with mucous membranes more specific studies are required, because of the greater permeability and sensitivity of these areas. These studies are not necessary when the ingredient or product has been shown to be a skin irritant.

Sensitisation studies

These studies are essential for ingredients. Careful animal studies should virtually exclude the possibility that a powerfully allergenic substance might find its way into cosmetic products. The studies should involve the administration of the test substance to guinea pigs over a number of days followed by a further single administration after a non treatment period to assess if sensitisation has occured. Observations in man are also of great value in the evaluation of the allergic potential of cosmetics.

Phototoxicity and photosensitisation

Studies of phototoxicity and photosensitisation are required for certain ingredients where knowledge of the chemical structure indicates a possible hazard. In some instances (as with sunscreening agents) such studies should be performed where the risk could be greater in view of the mode of use.

The techniques to be followed should be agreed beforehand with the appropriate authorities.

Absorption, kinetics and metabolism

Adequate absorption studies after dermal application and estimation of the amount of the ingredient absorbed and excreted are in most cases essential, supplemented where possible with adequate information of the metabolic changes undergone by the ingredient in the body. A knowledge of the degree of tissue storage of the ingredient and its metobolites might also be necessary. Acute and subacute dermal toxicity studies may also be useful to give an indication of the level of absorption from dermal application.

If there is evidence of significant absorption via the skin, studies for systemic toxicity should be performed. The main route of administration in their toxicity studies should mimic human exposure. With most cosmetic products this will be dermal application.

When considering dermal absorption studies, it should be borne in mind that the solvent and other ingredients used may affect the amount of absorption so that it should be related to the vehicle ultimately to be used. The degree of absorption in man will depend upon the part of the body exposed to the product as well as to the potential total surface of the body which the product may reach. This will be relevant to the evaluation of the results of the absorption studies. Especially with products which are not rinsed off, information on the rate of absorption is essential.

When products are applied to the lips or used in the mouth small quantities of the products are ingested. Hence the ingredients used in such products need to be investigated as other ingested chemicals. Special attention has to be given also to intimate cosmetics. Due to the thin epithelial lining of the mucosa the absorption rate of such cosmetics may be relatively high.

Ingredients used in aerosols or powders may be inhaled. Particles of less than 10 microns in size may well be absorbed through the alveolar lining whilst a proportion of the particles trapped in bronchi or the upper respiratory tract will subsequently be swallowed and may be absorbed from the gastro-intestinal tract. Hence absorption studies are required with this type of products.

Mutagenicity

Mutagenesis refers to those changes in the genetic material of cells brought about by chemicals, whereby succeeding cells differs in a permanent and heritable way from their predecessors. Apart from the implications of exposure to chemical substances for future generations if genetic diseases are induced there is evidence that somatic cell mutations (as opposed to germ cell mutations) may be associated with the production of cancer. It is therefore required that, if no long-term study is available, any ingredient for cosmetic products should be investigated for mutagenic potential by testing procedures which cover both gene and chromosome damage, both *in vitro* and *in vivo*. A battery of tests *in vitro* is suggested, such as the Ames-test, with and without microsomal activation, evidence for DNA repair of unsche-

duled DNA synthesis, evidence for covalent binding to DNA protein and *in vitro* cell transformation and sister chromatid exchange, *in vivo* tests such as the micro nucleus test and the sex-linked recessive lethal test in *Drosophila melanogaster*.

Oral studies

a) Acute

The acute toxicity is used for the classification and labelling of ingredients. Besides the quantitative expressure of acute toxicity (as LD_{50}) the ill-effects that are noticed are of importance. The results of acute toxicity studies following oral administration of the ingredients are valuable for the design of further studies.

b) Short-term 28 days

In short-term toxicity experiments the effects of the administration of multiple doses over short periods of time are studied. They provide basic information on the systemic toxicity of ingredients.

Where ingredients are used in products which are applied to the skin or the hair and then rinsed off after a short time, the opportunities for absorption of individual ingredients are minimal and therefore systemic toxicity does not play a major role. The absorption rate may be also slight from nail-cosmetics. Short-term studies alone may therefore be adequate for such products. The results of this study are also valuable for the design of further studies.

c) 90-day study

The primary objective of the 90-day study is the characterization of the toxicological effect of an ingredient following repeated exposure over a significant fraction of the life span. Such studies provide information on the toxic effects of the test compound, on dose-response relationships and on the effect- and no-effect level.
These studies are necessary where there is a possibility of regular ingestion and in certain cases when absorption takes place. Such studies should be carried out in at least one species.

d) Chronic toxicity and carcinogenicity studies

When there is a possibility of continuous and prolonged absorption of the ingredient, the short-term toxicity studies should be completed by long-term feeding studies to investigate possible long-term effects. Such testing in animals requires exposure to the test substance at appropriate dosages for the major part of lifespan of the test animals. The objective is to assess potential toxicity in animals as the results of long-term low-level exposure, which would not be detected in short-term studies. It is generally acknowledged that, with the exception of cancer and certain other irreversible forms of toxicity, adequate short-term testing will detect most of the toxic effects. Generally, the aim is to establish a no adverse effect level which may be useful for setting acceptable daily exposure. It is unrealistic to require long-term toxicity studies for the majority of the ingredients at the present time. However, substances found positive in mutagenicity studies require lifetime studies, with special emphasis on carcinogenicity. Other relevant factors are: the chemical structure, the duration of exposure, the area exposed, absorption and type of ingredient and in exceptional cases the cosmetic products. Especially when cosmetic products are applied in or around the mouth long-term oral studies may be required.

Dermal Toxicity studies

These studies are particularly applicable to cosmetic products. In general, acute dermal studies should be performed on all cosmetic ingredients. These studies may indicate whether significant absorption takes place at high concentrations. They may also provide evidence of the hazard to man of excessive exposure, whether occupationally, accidentally or through misuse. They also furnish preliminary information for choosing the dosage ranges for short- and long-term tests in order to determine the lowest dose which induces an adverse toxic response and the highest dose at which no effect is observed.

When no data exist on absorption, short-term dermal toxicity studies are required for all cosmetics applied on the skin and hair. The primary aim is to study the systemic toxicity after dermal application. These studies are

intended to detect functional and/or histopathological changes in organs and tissue of the animal exposed to an ingredient for periods up to 90 days. In terms of human experience these studies have to predict the adverse effects produced by repeated exposure at dose levels below those which cause toxic effects.

To mimic human exposure dermal toxicity and carcinogenicity studies have to be carried out in animals by continuous and prolonged exposure. When long-term effects on the skin can be expected, these studies are particularly necessary. However, when systemic toxicity due to absorption from the skin is suspected, these dermal studies may (in exceptional cases) be replaced, for practical purposes, by long-term oral studies.

Inhalation studies

Studies are required whenever the ingredient could be inhaled, as for instance when it is to be delivered from aerosols or when in powder form. As a minimum, short-term studies (28 days) should be available for all ingredienst which may be inhaled. Depending on the chemical structure and results of preliminary experiments, even long-term inhalation studies may be required in some circumstances.

Appropriate measurements of particle size distribution, concentration and total dose are needed. These will indicate the likelihood of absorption through the lungs, but it should be remembered that even with the larger particle size considerable nasal deposition with subsequent swallowing occurs. Consultation on the design of the experiment with the authorities is desirable.

Teratology and reproduction

Studies on teratogenesis and reproduction are necessary for those ingredients or cosmetic products which are absorbed or ingested to study the probability that a substance possesses teratogenic potential.

When an ingredient is ingested or absorbed, it is also necessary to obtain an indication of the potential effects on reproductive performance. A reproduction study is designed to provide information on fertility and general reproduction performance, particularly on gonadal function, oestrous cycles, mating behaviour, conception rates and the early stages of gestation. The reproduction studies can be carried out in parallel with the long-term toxicity studies.

Special studies

If the results of the acute, short-term or long-term toxicity tests or the chemical structure or properties of an ingredient suggest particular hazards, it may be necessary to carry out special investigations, to exclude neurotoxicity, hormonal activity, behavioural effects and immunosuppression. In such cases there should be consultation with the authorities.

Testing procedures

Protocols of the toxicological studies mentioned in these guidelines and in Annex I and II will be provided at a later stage. Toxicological testing should be performed according to internationally accepted procedures. Further guidance shall be given in a supplementary annex.

Annex I

Progression of safety testing

The animal studies and observations in man mentioned below are meant to be only an inventory of the several types of tests which should be carried out in the assessment of the safety of ingredients or of final cosmetic products. The scheme has to be used as flexible as possible. Each ingredient or final product must be considered on its merits. It is impossible to lay down a scheme of investigation which is applicable to all. The precise pattern of tests required in a particular case is always a matter of discussion between the manufacturer or importer and the national or international agency concerned. No booklet or scheme can replace this essential dialogue.

The following investigations at least should be carried out with ingredients:

1. Acute oral and dermal toxicity
2. Dermal or mucous membrane irritation
3. Sensitization
4. Short-term oral toxicity (28 days)
5. Mutagenicity.

Special emphasis should also be given to absorption by the skin or mucous membranes.

The concentration of the ingredient in the end product, the intended and potential sites of application, the level of exposure, the presentation of the product (solid, liquid, powder or aerosol) and the expected duration of contact, should define the appropriate tests. For example, data on percutaneous absorption may eliminate the need for some of the tests.

Interaction of ingredients in the final product is also possible and so it is advisable to study dermal or mucous membrane irritation and sensitization with the final products.

Annex II

Animal studies for ingredients related to their proposed use. (x)

Category of cosmetic product	dermal/mucous membrane irritation	eye irritation	sensitization	phototoxicity/sensitization	absorption/pharmacokinetics	oral - acute	oral - short-term (28 days)	oral - short-term (90 days)	dermal - acute	dermal - short-term	inhalation - short-term	mutagenicity	chronic toxicity/carcinogenicity	teratology/reproduction
1. Skin - rinsed off products	+	±	+	±	±	+	+	±	+	+*	±	+	±	-
2. Skin - not rinsed off products	+	±	+	+	+	+	+	±	+	-	±	+	±	±
3. Eye cosmetics	+	+	+	±	±	+	+	±	+	+*	-	+	±	-
4. Hair - rinsed off products	+	+	+	±	±	+	+	±	+	+*	±	+	±	-
5. Hair - not rinsed off products	+	+	+	±	+	+	+	±	+	-	±	+	±	±
6. Nail cosmetics	+	-	+	-	-	+	+	±	+	-	±	+	±	-
7. Mouth cosmetics	+	±	+	-	+	+	+	±	+	-	±	+	±	±
8. Intimate cosmetics	+	-	+	-	+	+	+	±	+	+*	±	+	±	±

\+ : wanted

\- : not necessary

± : depending on some circumstances

* : only when no data on absorption are available

(x)
In addition it is desirable that information on skin/mucous membrane and eye irritation, sensitization and absorption should be obtained from observations in man, especially for the final products.

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