SAFETY EVALUATION OF COSMETIC INGREDIENTS IN THE EUROPEAN COMMUNITY AND IN OTHER COUNTRIES

N. Loprieno Chairman of the Scientific Committee for Cosmetology, EEC Commission University of Pisa, Italy.


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Synopsis

The control of potentially harmless cosmetic ingredients has been defined by the 78/768/EEC Directive by Authorizing:
1-Lists of substances which could include colouring agents, antioxidants, hair dye, preservatives and sunscreens (tenth recitals);
2-Taking into account in particular the problem of sensitization.
For the regulator, cosmetic products should be produced in a way that they could not cause damage to human health.
The situation in Europe, where the absolute number of cosmetic ingredients employed in the finished products has never been defined, is such that we cannot state that the consumers are fully protected in the use of presently marketed cosmetics. The situation in USA, where a different regulation exists, is not too different from that in Europe. The further development of toxicological data for cosmetic ingredients therefore seems to be a need for health and regulatory agencies.

Riassunto

Il contratto sull’innocuità degli ingredienti di uso cosmetico è stato definito dalla direttiva 78/768 ECC che ha autorizzato le liste delle sostanze positive dei coloranti, degli antiossidanti, dei conservanti e dei filtri solari, tenendo in dovuto conto soprattutto il problema della sensibilizzazione.
Per il legislatore i cosmetici devono essere prodotti sempre in modo tale da non arrecare danni alla salute dell’uomo. Ciò nonostante sia in Europa che negli Stati Uniti d’America il consumatore non è ancora completamente protetto, dato che non sono state ancora ben definite tutte le sostanze utilizzabili nel settore cosmetico, soprattutto sotto l’aspetto tossicologico.
È necessario quindi, sviluppare e verificare in modo più approfondito la reale innocuità di tutti gli ingredienti utilizzati analizzandoli più attentamente soprattutto sotto l’aspetto tossicologico.
The 76/768/EEC Directive (1) regulates the quality of the cosmetic products put on the market in the Countries of the European Community: the main objective of the Directive is the protection of the consumer's health from the use of cosmetic products which could be dangerous due to the presence of toxic chemical ingredients in the finished products*. This objective is mainly expressed by the Article 2 of the Directive. For the regulator, cosmetic products should be produced in a way that they could not cause damage to human health, and they should be developed taking into account economic and technological requirements, i.e. the procedures should be able to put on the market cosmetic products based on an adequate technology capable of preserving the consumer's health.

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On December 19th, 1977, the Commission of the European Communities decided to establish a Scientific Committee for Cosmetology (SCC) to advise the Commission on scientific and technical problems related to cosmetic products and, particularly, on the ingredients employed in the finished products (2). The Committee at the moment consist of 18 members coming from 11 member Countries.

Most of the work prepared by the SCC since 1977 has involved the:
1- revision of all annexes present in the original 76/768/EEC Directive;
2- identification of those cosmetic ingredients that, due to their toxicological potential, have to be banned from the preparation of cosmetic products (Annex II);
3- evaluation of the limits of usage for those cosmetic ingredients which represent a hazard to the public health (Annex III).

Up to now the SCC has published 7 reports giving its opinion on cosmetic ingredients employed as colouring agents, hair dyes, preservatives, etc.

The 76/768/EEC Directive has been amended 13 times up to 1990 for the content of the technical Annexes.

At the present it includes:
- a list of 400 cosmetic ingredients which must not be employed in the production of finished products, due to their toxicological properties (Annex II);
- a list of 54 cosmetic ingredients which may be included in cosmetic products under certain restriction (Annex III-1);
- a list of 159 permitted colouring agents (Annex III-2);
- a list of 39 permitted and 25 temporarily admitted preservatives in the cosmetic products (Annex VI);
- a list of 6 permitted and 31 temporarily admitted sunscreens (Annex VII).

The actual knowledge about the safety of cosmetic ingredients is therefore represented by a collection of toxicological data, still inadequate for evaluation of every synthetic chemical ingredient so far used in the cosmetic products.

The situation in Europe, where the absolute number of cosmetic ingredients employed in the finished products has never been defined, is such that we cannot state that the consumers are fully protected in the use of presently marketed cosmetics. The situation in the USA, where a different regulation exists, is not too different from that in Europe.

A document issued by the National Academy of Sciences of the USA, in 1984, (3), indicated that

*Toxicity is expressed not only by cutaneous toxic effects, such as irritation, sensitization, etc; but also by systemic toxic effects such as carcinogenicity, mutagenicity and teratogenicity.
in USA only the 25% of all the cosmetic ingredients, employed by the industry (852 out of 3,410) had been analyzed for their toxicological potential, which would have permitted, to some extent, the assessment of their safety. We may therefore assume that cosmetic industries do not currently possess enough toxicological data for 2 - 3,000 cosmetic ingredients to make their complete hazard assessment possible.

The further development of toxicological data for cosmetic ingredients therefore seems to be a need for health and regulatory agencies.

The discussion in progress in the Commission of the European Communities on a possible evolution of the 76/768/EEC Directive on cosmetics has been defined some new lines of action, by means of which it would be possible to improve the regulation on the safety of the cosmetic products.

The possible actions to be taken are:

- the establishment of a European inventory of existing cosmetic ingredients: as the task of evaluating and testing all these cosmetic ingredients puts severe constraint on public resources, the establishment of priorities became almost indispensable. Several criteria for setting up priorities among cosmetic ingredients for their testing and evaluation are possible.

Starting from the concept that the consumer’s health is not protected if cosmetic products contain chemical ingredients for which no toxicological data are available, a high priority criterion for selecting cosmetic ingredients to be submitted to a toxicological screening program applies to those ingredients for which toxicological data are necessary such as hair dyes, preservatives, sunscreens, colouring agents, etc. In this case a minimum set of toxicological studies to be employed in the evaluation of these chemicals should be defined. This criterion also meets the requirements indicated by the EEC Consumer Consultative Committee (4). For these cosmetic ingredients the following minimum tests could be proposed: acute toxicity (oral and dermal); dermal irritation; eye irritation; skin sensitization; sub-chronic toxicity (90 days; oral); mutagenicity (bacterial test for gene mutations and in vitro mammalian cells culture test for chromosome aberration); phototoxicity (for light absorbing substances, including photoirritancy, photosensitization and photomutagenicity); dermal absorption; inhalation acute toxicity (for volatile substances); human data (if available).

- New cosmetic ingredients, belonging to colouring agents, preservatives, sunscreens, hair dyes, independently of their natural or synthetic chemical origin, therefore must be tested for their toxicological potential in a complete set of toxicological tests, according to international defined guidelines, as reported in the 84/499/EEC and 87/302/EEC Commission Directives (5, 6) before their inclusion in the European Inventory. Guidelines for toxicological testing of cosmetic ingredients have been defined by the Scientific Committee for Cosmetology of the EEC (9).

All available information on each cosmetic product on the market in each of the 12 Member States of the European Community, must be organized in a working document or dossier with a standard format, content and method. These dossiers of the cosmetic products must be the focal point for the operating policies of health authorities, all document control efforts, and all evaluation of data.


Each finished cosmetic product is an individual
and unique combination of ingredients. The number of finished products is extremely large when compared to the number of ingredients. The SCC is therefore of the opinion that the dossier of a finished product or of a group of finished products should contain adequate information to make possible a safety evaluation. In general this would be obtained by the knowledge of the toxicity of the cosmetic ingredients. Toxicity studies on the ingredients should include the evaluation of the most relevant toxicological end points.

In some cases, however, as for instance, when the formulations used in the finished product are different from the solvents employed in the toxicity studies of the ingredients and it is likely to improve penetration or irritancy of some of the ingredients, there will be a need for additional studies on finished products to allow a better safety evaluation.

If potentiation of the toxic effects of the ingredients, or if its toxic effects resulting from chemical interaction between individual ingredients, are likely to occur, specific toxicological studies on the finished products are required.

When the combination of the ingredients present in the finished product make highly probable the formation of new substances of toxicological concern, additional toxicological studies on finished products, are needed. The dossier should be deposited at the place of production where national inspectors could make an evaluation of the available data. National Health Authorities could have access to the dossier for its evaluation for those cosmetic products present in their national market (7,8). The assessment of the toxicological potential is the first step in the hazard evaluation of a chemical agent and consists in distinct toxicity studies, specific for toxicological end points; phototoxicity studies need to be performed in some particular cases.

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 area other than screening for mutagenicity/genotoxicity and for pre-screening for severe irritancy. Moreover the in vitro methodologies so far available have yet not been adequately validated in other areas to be included in regulatory guidelines at this time.

At 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 toxicologic 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 (12) 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 biochemical 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 toxicologic 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”.

An immediate consequence of the principles expresses in Directive 86/609/EEC took form in
Seminar "LD 50 and classification schemes - the possibilities for change" held in Brussels from 19th to 21st September 1989. In the course of it, the foundations were laid for the general revision of the rules provided for in Directive 79/831/EEC, concerning regulations of chemical substances.

Further, a proposal from the EEC Council has been approved; it concerns the institution of a European Center for the finalization of toxicologic research procedures as alternatives to methods of experimentation based on live animals. The Central Laboratory will be located in ISPRA, in the EEC Research Center. That is partly in consequence of art. 23, Directive 86/609/EEC, which contemplates the necessity that the Commission "encourage research aimed at developing and making alternative techniques more effective, geared to provide the same level of information as the experimentation on animals". Scientific toxicology research has developed and tackled such issues as the identification of the toxicologic processes, induced by variously used chemical substances, through the study of cellular, in vitro populations. The essential goal is to identify, on an analytic base, the mechanisms of the process. The use of cell cultures in toxicologic studies has increased, along with the development of knowledge and molecular biology techniques, which have enables us to conduct research, in an analytic way, into internal processes of cellular metabolisms: protein synthesis, macromolecular synthesis, DNA molecule repair, cytoplasmatic structures and membrane alterations, cellular enzymology, etc.

In recent years, because of the necessity of reducing the number of animals used in toxicologic experimentation, many of these in vitro methodologies have been directed towards the identification of some types of toxicologic effects induced by chemical substances. In brief, here are indicated the areas of research, in which there are programmes being carried out with the aim of finalizing alternative, in vitro methodologies of toxicologic research.

1. Inflammation and irritation

As an alternative to the Draize test (ocular irritation) or to the Cutaneous Irritation test: 34 potential, in vitro tests have been singled out, which may contribute to the identification and classification of eye-irritating substances.

2. Genotoxicity and Carcinogenicity

These represent areas of research in which the employment of in vitro methodologies has brilliantly succeeded from the start (Ames test, chromosomal aberration of in vitro grown cells, DNA repair test, etc.). Current research is trying to identify improvements in existing methodologies in order to increase their predictivity in comparison with animal studies, even in respect of carcinogenicity.

3. Teratogenicity

In vitro methods for studying normal processes of development have long existed; they have recently been used to analyse abnormal development. Embryo-cultures of rodents and other species have successfully been realized: there is some reason to believe they will fruitfully be used as alternative in vitro methodologies for studies of teratological factors.

4. Toxicity of specific organs

The branch covers all areas of acute toxicity: valid research exists at present, on cellular cultures obtained from specific organs for the study and assessment of specific toxic effects regarding particular tissues and organs; this research is especially delving into action mechanisms.
5. Toxicokinetics and Metabolism

The understanding of metabolism of exogenous chemical factors in the various types of tissues and organs constitutes the base for assessing and quantifying the hazard. The study of the distribution of toxic substances in various tissues allows us to tell exactly the nature of the hazard. Several studies are currently aimed at establishing a correspondence between metabolic effects in vitro and in vivo.

6. Structure-activity relationship

The type of analysis which does without any kind of experimental biological material, whether in vitro or in vivo, has always been utilized in pharmacology and in identification of the chemical substances to be employed as active principles.

The use of this method in toxicology is quite recent; it tries to utilize every type of existent toxicologic data for the construction of predictive models; these, in turn, need rigorous in vitro verification in order to improve the models. There are now computerized models for the prediction of acute toxic effects, as well as genotoxic, irritating, carcinogenic, teratogenic eco-toxicologic effects. These are the six areas of toxicologic studies, that do not use animals, which are at present being carried out by many laboratories throughout the world. We must point out that these studies are not definitive at the moment; we cannot affirm that the methodologies so far studied are conclusive. However, it seems fair to say that, in the near future, it will not be possible to supply a piece of toxicologic information based on the application of a single in vitro methodology.

During a recent workshop organized by FDA in Washington on September 26-27, 1991 on updating Eye Irritation Test Methods: Proposal for regulatory consensus, the US Agencies (FDA, EPA and CPSC) have made the following statements which reflect the present status of in vitro methodologies:

1. In vitro are inherently an over-simplification of the physiology and response of the whole-animal test. In vitro tests should not be considered at this time as total replacements for the rabbit eye irritancy test.

2. In vitro tests, despite their inability to detect all eye irritants, can be used early in the development phase of a product to screen and eliminate chemicals which are potential irritants before they would need to be tested in animals.

3. When data are available, it is conceivable that in vitro tests, based in part on prior standardization with animal tests, could also be used as final safety tests. These tests might be used in those situations where there are changes in the concentration of ingredients in a mixture or where there has been the substitution of structurally similar components. When an in vitro test is to be used for the assessment of safety in these circumstances, previously established data (in vivo and in vitro) on components and formulations related to the unknown product should be used to assure the capability of the in vitro system to detect possible changes in eye irritancy potential.

4. The use of in vitro methods can become established tools for testing certain chemical classes, or types of products. One need not demonstrate the universal applicability of in vitro methods among all chemical classes and product line.

5. In vitro test need to be standardized against the in vivo scoring/classification system used by regulatory agencies and not just the maximum average Draize score.
As in vitro tests become validated, combining one or more of these tests with other screening tools such as pH and dermal irritation in making assessments for eye irritation, should be considered.

Batteries in vitro tests probably hold the greatest promise for effectively screening products and replacing animal testing.

These statements may be of value also for other toxicological tests as it will be demonstrated in the final report (9, 10).

References


