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We wish to dedicate this Journal of Applied Cosmetology,
to the memory of the well-known english scientist
Prof. Francis John Ebling.
At the time of his death in Sheffield on May 29, 1992,
Prof. Ebling held, among the other offices,
the Vice-President of International Society of Cosmetic Dermatology
and he was a friend of our review.

Cosmetic Dermatology

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Volume 2
Every day Problems in Dermatology: The Cosmetic Connection

Editors: P. Morganti, F.J.G. Ebling

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The **JOURNAL OF APPLIED COSMETOLOGY** is an international journal devoted to publisching original papers, reviews and other material which represent a useful contribution to research on the skin and on cosmetics.
It is aimed at cosmetic chemists, dermatologists, microbiologists, pharmacists, experimental biologists, toxicologists, plastic surgeons, and all other scientists working on products which will come into contact with the skin and its appendages.
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J. Appl. Cosmetol. **10**, 57-60 (July-September 1992)

QUALITY CONTROL FOR THE CONSUMER'S PROTECTION

L. Gagliardi, A. Amato
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Received: *October 30, 1991. Presented at the IV International Congress on Cosmetic Dermatology "Progress in Cosmetic Dermatology: Science and Safety" Roma (Italy) October 31 - November 2, 1991.*

Key words: *Quality Control; Raw Materials Control; Manufacturing Procedures; EEC Standard Protocols.*

Synopsis

The protection of consumer cannot based only on necessary controls of government laboratories, because only analysis of raw materials and finished products, performed routinely, can provide some kind of protection against potentially dangerous contaminants or mistakes. European legislation will increase the necessity to manufacture quality cosmetic products in the near future. Directive 85/374 which is not yet ratified by all EC-members stresses product liability, putting the manufacture of "dangerous" and inferior products at considerable risk. In addition, changes in Council Directive 76/768 are presently being discussed that aim to legally impose some form of Q.C. and G.M.P. Of course many cosmetic manufacturers already practice G.M.P., especially the larger companies can efford to run a Q.C. labo ratory for raw-material validation and the control of finished products. Standard protocols for the control of raw materials, abudantly available in many pharmacopeias for the pharmaceutical industry, are scarce for most cosmetic ingredient. Attempts to provide these have been made by CTFA, the French industry association and UNIPRO.
It seems that cosmetic industry will probably follow the lead of pharmaceutical industry. Both the increasing scale of production, which makes production mistakes costly, as well as pressure from governments will move G.M.P. eventually inevitable, even if it is not legally imposed.

Riassunto

La protezione del consumatore non può essere affidata solo ai controlli dei laboratori pubblici, poiché solo l'analisi routinaria, effettuata nell'industria, di prodotti finiti e di materie prime può fornire una qualche forma di protezione nei confronti di errori e di contaminanti potenzialmente pericolosi. La legislazione europea d'altro canto sottolinea la necessità di produrre cosmetici, sempre più di qualità: la Direttiva 85/374, per esempio, evidenzia tra l'altro la responsabilità del produttore. In aggiunta le proposte di modifica della Direttiva 76/768, attualmente in discussione, introdnrranno, nella produzione industriale, alcune forme di controllo di qualità e norme di buona fabbricazione.
Certamente la maggior parte delle industrie cosmetiche, specie quelle più grandi, già hanno impostato laboratori di controllo per la verifica della qualità di materie prime e prodotti finiti. È da tenere poi in conto la scarsezza di informazioni di materie prime di interesse cosmetico, specie se confron-

tate con quelle di campo farmaceutico, malgrado gli sforzi fatti dal CTFA, dall'associazione delle industrie francesi e dall'UNIPRO.
Sembra inevitabile comunque che il futuro dell'Industria cosmetica debba in qualche modo essere simile a quello dell'Industria farmaceutica.

Introduction

The explicit demand by consumers and industry for safe and guaranteed products is increasing the importance of quality control within companies. Such control, along with compliance control - carried out by competent State authorities - is the only form of protection for the consumer. In recent years, turnover for the cosmetic industry in the EC has considerably increased. Also further development is expected soon with the opening of other markets. This will imply, for example, an increase in the size of industrial operations. Therefore, production will need to be more thoroughly controlled to prevent low-quality cosmetic products from reaching the market.

The increasing attention focused on environmental problems by governments and public opinion has led many people to lose confidence in chemistry and its products (as indicated by the enormous demand for the so-called, natural cosmetic products). Furthermore, mass media have alarmed public opinion when traces of carcinogenic substances - or substances considered as such - are found in a cosmetic. To face such calamities, quality control is the only form of protection for industry. Besides, in the near future, EC laws will put even more pressure on industry in order to obtain an ever more rigourous production. Directive no. 85/374, - which has not yet been ratified by all member states - underlines the manufacturer liability, imposing heavy sanctions on low-quality production. Moreover, the changes presently proposed to Directive 76/768 will legally enforce several forms of quality control and good manufacturing procedures (GMP) by the cosmetic industry.

Analytical chemistry appears basic for maintenance of the quality of a product and its importance will increase.

It is, however, a double-edged weapon. On the one hand, it makes it possible to determine the presence of substances at levels which were unthinkable only ten years ago. On the other hand, it can also often create unjustified alarm. Only the analysis of raw materials and finished products can protect against undesired substances and it is in the common interest of producer and consumer to do everything possible to guarantee safety of the finished product.

We will now examine, in detail, some points which are particularly important in this context.

Legislative aspects

Laws on cosmetic products are based on Directive no. 76/768 which regulates safety through a system of positive and negative lists. Positive lists include preservatives, sun filters and dyes. In spite of many obstacles, a list for antioxiders and hair dyes is expected soon.

The changes currently proposed to the Directive contain many innovations such as an obligation for the manufacturer to keep complete documentation of the entire production. This must include a description of production processes according to GMPs, and information about and specification of every raw material and all available data on undesirable effects which have followed the use of finished products. This means that some aspects of GMP must be added to the Directive.

These proposals are not expected to be approved without changes. However, they show the trend that will affect future EC laws.

GMP

Good manufacturing procedures and quality control have already been applied in the pharmaceutical industry on a large scale. This industry deals with highly active compounds, where mistakes or low quality cause great damage.

In this field, both raw materials and finished products are routinely tested, according to validated specifications.

The cosmetic industry will probably follow the

path of pharmaceutical industry because production is increasing and because of health policies which will impose the introduction of good manufacturing procedures.
Many cosmetic companies, especially the large industries, are certainly already using such procedures.
They are investing resources in laboratory quality control to validate raw materials as well as finished products and eliminate wastage.
Smaller companies will have many difficulties in adopting there procedures, such as, for example, the cost of analytical equipment or specialized staff. Therefore, they will often find it more convenient to rely on other laboratories, which, in many cases do not bave any deep experience in this field.
Another problem concerns raw materials which in many pharmacopeias are only described if they have pharmaceutical value; information is lacking if they have only cosmetic value. Extremely useful efforts have been made by the CTFA of the association of French industrialists and recently by UNIPRO, which has listed over 6,000 ingredients in its dictionary.

The EC and the control of cosmetic products

The control of cosmetic products is assigned by the EC to the single national authorities by establishing official analytical methods. In this regard, in 1971 the EC Commission set up a working group - called "Methods for the analysis of cosmetic products" - made up of experts from each member state, COLIPA and laboratory researchers who assist the Commission Secretariat. The aim is to develop the official analytical methodologies for the control of cosmetic products, as provided by art. of the EC Directive n. 76/768.
Since its creation there have been 32 plenary sessions and many meetings of subgroups.
The present directive presents seven annexes classifying temporarily permitted cosmetic ingredients, with restrictions and prohibitions. About 200 permitted and 400 prohibited substances have been identified in all.
At present, 29 methods bave been published and have therefore become official, and about ten others are in process. it is obvious that much is still to be done, not only because many substances bave not yet been studied, but especially because the designing of a method by the group is complicated. The procedure can be described as follows:
- the design and analytical method;
- a series of feasability studies in the laboratory;
- discussion and approval of the method in plenary session, preparation of the appropriate samples and carrying out of a cooperative study;
- assessment of the results; either final approval or modification of the method requiring a second collaborative test;
- final approval of the method and publication.

The 29 published methods can be applied to the substances listed in annexes III and IV. The methods use traditional techniques, such as titrimetry, gravimetry, colorimetry; some use GLC and TLC/GLC techniques; only one uses atomic absorption spectroscopy; most recent methods use TLC/HPLC techniques.
Currently, there is great need for methods for application to preservatives, dyes, solar filters, oxidation dyes and other classes of compounds.
Today, chromatographic techniques provide the solution to a great number of problems, but more updated techniques are going to be applied in the near future to face specific problems. This could create a situation in which only specialized laboratories would be allowed to make highly sophisticated analyses.

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J. Appl. Cosmetol. **10**, 61-64 (July-September 1992)

LIPOSOMES IN DRUG DELIVERY: STRUCTURE, BEHAVIOUR IN VIVO AND APPLICATIONS

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Received: *October 30,1991. Presented at the IV International Congress on Cosmetic Dermatology "Progress in Cosmetic Dermatology: Science and Safety" Roma (Italy) October 31 - November 2, 1991.*

Key words: *Liposomes; Liposomal Fate; Liposomal Drugs; Liposomal Applications.*

Synopsis

Many phospholipids, alone or in combination with other lipids (including lipid extracts from membranes), will forms liposomes.
The successful evolution of liposomes from an experimental tool to industrially manufactured products for clinical and veterinari use depends on efficient drug entrapment in vesicles of a narrow size distribution using simple, reproducible and inert methods. Encouraging results with liposomal drug in the treatment or prevention of a wide spectrum of diseases in experimental animals and humans have reiforced the view that clinical applications may be forthcoming.

Riassunto

Molti fosfolipidi da soli o in combinazione con altri lipidi danno luogo a formazione di liposomi.
L'evoluzione della tecnica dei liposomi dall'uso di laboratorio all'utilizzazione industriale per prodotti adatti sia per l'animale che per l'uomo dipende dalla loro capacità di intrappolare farmaci in modo stabile ed uniforme e con metodiche facilmente riproducibili.
I recenti risultati ottenuti, sia sugli animali che sull'uomo con l'uso clinico di farmaci liposomiali per il trattamento di una vasta gamma di patologie fanno intravvedere un uso clinico sempre più diffuso di questo nuovo tipo di veicolo.

Liposomes: Structure and properties

Phospholipids and other polar amphiphiles form closed concentric bilayer membranes (liposomes or vesicles) when confronted with excess water with each bilayer representing an unbroken bimolecular sheet (lamellae) of lipids (1). In the process of their formation liposomes entrap water and solutes if present. Alternatively, lipid soluble agents and molecules coupled to lipids can be incorporated into the liposomal membrane. Thus, almost any substance, regardless of solubility, size, shape and electric charge can be accommodated in liposomes as long as there is no interference with their formation (1).

Many phospholipids, alone or in combination with other lipids (including lipid extracts from membranes), will form liposomes. Depending on their gel-liquid crystalline transition temperature (Tc - the temperature at which hydrocarbon regions change from a quasicrystalline to a more fluid state), phospholipids determine bilayer fluidity and stability in terms of permeability to solutes in vitro and in vivo. Bilayer fluidity and stability can also he influenced by the inclnsion of sterols (for example cholesterol). The incorporation of charged amphiphiles will not only render the liposomal surface positively or negatively charged but also increase the distance and hence aqueous volume (and solute entrapment) between bilayers (1).
The unusually versatile nature of liposomes, which was established by membrane biologists who used then as a model for cell membrane studies prompted the development of another, perhaps more exciting, concept (2): the use of the system in targeted drug delivery.
Progress in this area with a wide range of liposomal drugs (for example anti-tumour and anti-microbial agents, enzymes, hormones, vitamins, metal chelators, genetic material, immunomodulators and vaccines) has been rapid and a vast amount of information has been obtained, already (1).

Liposome technology

The successful evolution of liposomes from an experimental tool to industrially manufactured products for clinical and veterinary use depends on efficient drug entrapment in vesicles of a narrow size distribution using simple, reproducible and inert methods (3). In this respect, there has been considerable success and well defined formulations containing a variety of active agents can now be produced in a stable form. A number of these formulations are currently undergoing clinical trials (1,4) and a few are already licensed. However, several of the methods developed, although highly efficient, have the drawback of being uneconomical, of being applicable only to drugs of low molecular weight (thus excluding vaccines, enzymes and other proteins) or requiring the use of detergents, sonication or organic solvents (3). These may, in turn, be detrimental to the structure-activity relationship of certain drugs, especially macromolecular agents.
In a recently reported technique (5,6), which is both simple and easy to scale up, high yield entrapment of drugs in dehydration-rehydration vesicles (DRV) occurs under mild conditions. Entrapment values for a number of drugs, antigens and immunomodulators in DRV were substantial and reproducible. Protein-containing DRV can be freeze-dried in the presence of a cryoprotectant and most of the protein content is retained within intact vesicles on reconstitution with saline. Moreover, microflnidization of DRV leads to the formation of smaller (about 100nm in diameter) vesicles retaining much of the originally entrapped drugs (6). Because of the limited number of steps involved in most methods of liposome preparation, sterility of the starting materials can easily be maintained using aseptic techniques.

Behaviour of liposome in vivo

Many workers (1,3,4,7) with diverse research interests have admistered drug-containing liposomes to animals and humans, parenterally and enterally. As a result, much is now known of their behaviour. Of particular interest are (a) the effect of components of biological fluids, with which injected liposomes first come into contact, on the retention of liposomal structural integrity and (b) the rates at which liposomes are cleared from the site of administration and distributed among the tissues, mostly within macrophages of the reticuloendothelial system (RES). In both cases, the behaviour of liposomes is dictated by their structural characteristics. For instance, plasma high density lipoproteins (HDL) will remove phospholipid molecules from the bilayers of intravenously injected conventional liposomes, for example those made of egg phosphatidylcholine (PC). These will then disintegrate and release their drug contents. By substituting PC with 'high melting' phospholipids (for example distearoyl phosphatidylcholine (DSPC) Tc=54°C) or supplementing phospholipids with excess cholesterol bilayers become rigid at 37°C or have their phospholipid molecules packed and, therefore, resistant to HDL attack. Thus, liposomal integrity is preserved and entrapped drugs remain with the carrier en route to its destination.

It is now established that the more stable the liposomes, the lower their rate of clearance from the blood circulation (1). It is suggested that liver-specific opsonins, implicated in the removal of liposomes from the circulation by the RES (principally in the liver), do not adsorb as avidly on vesicles with rigid or packed bilayers. The relationship between liposomal stability and clearance is altered when a negative or (under certain conditions) a positive surface charge is imposed on the bilayer surface, with even the most long-lived liposomes assuming short half-lives. A similar reduction in half-life occurs as vesicle size increases; this may be partially reversed by coating liposomes with hydrophilic molecules. Not suprisingly, liposomes with extended half-lives are deposited in the RES at reduced rates, with a considerable proportion (about 30% for small unilamellar vesicles) favouring the macrophages of the bone marrow. When these liposomes are small enough they will also gain access to the hepatic parenchymal cells through the fenestrations. Regardless of whether uptake is mediated trough opsonins or other ligands, it occurs through endocytosis although fusion may a so be involved to some extent (1).

While such findings on stability, clearance and tissue distribution relate to liposomes injected intravenously, they also concern preparations given by alternative parenteral routes such as intraperitoneal, subcutaneous and intramuscular (1): a proportion of liposomes, determined by vesicle size, composition and route of injection, enters the lymphatic and eventually, the blood circulation where they behave as if given intravenously. However, whereas liver, spleen and bone marrow take up nearly all liposomes given by the intravenous route, they will account for a smaller proportion of the dose given by other routes. The remainder (up to about 80% of liposomes injected subcutaneously or intramuscularly) is retained at the site of injection and attacked by infiltrating macrophages or other factors, or intercepted by the lymph nodes draining the injected site. Relative to their mass, uptake by lymph nodes is much greater (over 100-fold) than that by any of the other RES tissues.

Substantial efforts to ascertain whether liposomes given enterally enhance absorption of agents which are either not absorbed by, or unstable in the gut, have given inconclusive results. In spite of indications that insulin, factor VIII, anticoagulants and vitamins administered via liposomes do reach the blood circulation, their absorption is unpredictable and only mini-

mal. It is nevertheless apparent that liposomes of a lipid composition (for example cholesterol-supplemented phospholipids with high Tcs) that renders them resistant to detergents or phospholipase attack, protect agents from gut enzymes. Such liposomes may survive the gut milieu to some extent and thus facilitate the absorption of their contents, probably through the lymphatics (1).

Targeting of liposomes

Delivery of liposomal drugs to cells that do not normally take up the carrier effectively has been achieved by antibodies and other cell-specific ligands covalently or hydrophobically linked to the outer bilayer of liposomes. In vitro studies (1) have repeatedly demonstrated that polyclonal or monoclonal antibodies raised against a repertoire of cell surface antigens mediate the association of the drug-containing liposomal moiety (to which such antibodies are linked) with, and its introduction into, the respective cells. However, in vivo targeting of liposomes has proved a much more challenging proposition (1), especially when mediated via antibodies, the Fc portion of which binds to its receptors on the macrophage, thus accelerating removal of the carrier by the RES. Circumvention of this problem has been achieved by the use of the antigen-recognizing Fab portion of the immunoglobulin molecule as a ligand or by taking advantage of the already long half-lives of small, stable vesicles. In the latter case, Fc-mediated shortening of the half-life of vesicles will still allow them to circulate long enough for targeting to occur. Such complications, however, do not occur when certain galactose-, mannose-, and fucose-terminating glycoprotein and glycolipid ligands are used, since these will associate exclusively with their receptors in vivo (1).

Implications in medicine

Encouraging results (1,4,7) with liposomal drugs in the treatment or prevention of a wide spectrum of diseases in experimental animals and in humans have reinforced the view that clinical applications may be forthcoming. These include treatment of skin diseases, skin care, antimicrobial therapy, metal chelation, enzyme and hormone replacement therapy, vaccines (7) and diagnostic imaging. To that end, the first and obvious consideration is that a liposomal drug preparation designed to treat a particular disease should have clear advantages over the conventional use of the therapeutic agent. Recently, progress toward clinical uses of liposomes has gained new momentum thanks to the efforts of related biotechnology companies.

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

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Key words: *Safety of Cosmetic Ingredients; Genotoxicity; Carcinogenicity; Teratogenicity; Acute Toxicity; Structure-Activity Relationship.*

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'inocuità 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 cosmentici 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 inoquità 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.

The control of potentially harmless cosmetic ingredients has been defined by the 78/768/ECC 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.

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 Consultive 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.

The dossier will contain: *1. Chemical formulation of the product; 2. Cosmetic category; 3. Use, application, procedure, precautions; 4. Production phase, responsible; 5. Human exposure potential; 6. Toxicological information: a. on cosmetic ingredients; b. on finished products; 7. Official methods for chemical analysis of the ingredients. 8. Cosmeto-surveillance data (if they exist); 9. Raw material (chemical specification batches); 10. Working and production procedures; 11. Quality control; 12. Storage of finished products, batch identification.*

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 finisbed 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, tec.). 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 I*n 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.

6.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.

7.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).

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CONTACT DERMATITIS DUE TO COSMETIC INGREDIENTS

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Synopsis

In a retrospective study among 310 patients with ordinary contact dermatitis, 115 were found to have allergic contact dermatitis caused by cosmetic products. The most commonly involved sites were hands (including fingers) and face. The most frequently identified sensitizers were fragrances, including lichen and compositae extracts, preservatives and balsam of Peru. About 28% of the cutaneous reactions occurred among patients 20-29 years of age.

Riassunto

In uno studio retrospettivo effettuato su 310 pazienti affetti da una normale dermatite da contatto, è stato verificato che la causa di questa dermatite era rappresentata al 50% circa dall'uso dei cosmetici. Le zone più comunemente affette erano le mani ed il volto. I sensibilizzanti più frequentemente identificati erano i profumi (composti ed estratti dal lichene), i conservanti ed il balsamo del Perù. Circa il 28% delle reazioni cutanee si sono verificate in pazienti di età compresa tra 20 e 29 anni.

It is commonly believed that allergy towards cosmetic products is unusual.
Lay people very frequently quote promotional phrases such as "allergytested" or "allergenfree" not knowing that this is nonsense since all products on the market are tested for allergenic potential and, in principle, any compounds can still give rise to allergy regardless of previous testing, though they may differ in their potentiality to do so (1).

The incidence of unwanted side effects from cosmetics per million units sold have varied from 2 to 680 in various reports (2,3). In the USA, for example, this would give an average of one reaction to a cosmetic per person every 13,3 years (4). Adverse reactions with subjective complaints of irritation such as burning, stinging and itching, are mostly non-allergic and not so frequently seen by dermatologists. Real allergic reactions are, in fact, rare and account for perhaps only 10% of all unwanted effects from cosmetic products (2,5). In one study from Stockholm only 141 cases of contact dermatitis from cosmetics were diagnosed during the years 1973-1979 in a catchment population of 250 000 people (3). In various studies the prevalence rates of sensitization to cosmetics were 2-4% among patients seen in dermatologic clinics (2,7,8,9), but this percentage is increasing.
During recent years many of the ingredients in cosmetic products have gradually been replaced by others, and it is therefore important that studies on the incidence of allergic reactions and the occurrance of specific allergens continue to be regularly performed.
The present retrospective uncontrolled survey was conducted to evaluate the importance of cosmetic reactions seen at the department of dermatology, Ullevaal hospital, which is the city hospital for Oslo with a catchment population of about 500 000 people.

MATERIALS AND METHODS

In total, 310 records from all patients registered in 1987 and 1988 as cases of contact dermatitis, were evaluated. In 115 the patients had positive patch tests to cosmetics or cosmetic ingredients. Patch tests were performed with the European standard test series, specially composed perfume series, hairdresser series and plant series (table 1). Thirtythree patients were also tested with their own cosmetic products.
The plant series consisted of purified extracts and isolated compounds obtained from various species of lichens and compositae by crystallization, filtration, steam destillation or high vacuum distillation (NLH, Norway).
The purity was controlled by various methods such as HPLC/HPGC/Mass spectrometry, IR-or UV-spectroscopy. (Y. Solberg).
The tests were carried out with Finn Chambers (Epitest, LtD., Hyryla, Finland) which were fixed to the upper portion of the back with Scanpore paper tape (Norgesplaster A/S, Oslo, Norway). The patch tests were removed at 48 hours and readings were made at 48 and 72 hours. Each positive reaction was assessed for its clinical relevance.

RESULTS

The results of patch testing the patients with cosmetic related contact allergy are shown in tables 1 and 2. One hundred and fifteen patients (91 females and 24 males) out of 310 cases (37%) were identified as having cosmetically related contact allergy and showed allergic reactions to one or more of the coumpounds contained in cosmetic products (table 1). The fragrance mix was the most important cause of cosmetic allergy n=32 (table 1), followed by the preservatives, n=29, which included the following ingredients: formaldehyde, n=12, Kathon CG (chloromethylisothiazofinone), n=8, parabens, n=7 and

quaternium, n=2. Next were balsam of Perù, n=19, Colophony, n=18, wool alcohols, n=11 and p-phenylenediamine dihydrochloride, n=4. Patch testing with various perfume ingredients showed that most of the reactions were caused by oak moss abs, n=8, and jasmine synthetic, n=7, followed by cinnamic aldehyde, n=7. Almost one third of the reactions to fragrance mix were interpreted as being irritant. Patch tests with hairdressing compounds revealed nine allergic reactions with glycerol monothioglycolate as the most important allergen, n=5, while ammonium persulphate caused only two. Patch testing wirh various other compounds showed 41 allergic and 11 irritant reactions to various lichen compounds in 34 patients to various compositae extracts. In all, 225 reactions were evaluated as being due to sensitization while 58 were considered as irritant.

Thirtytwo patients were tested with their own products (table 2). Twentysix of them showed allergic reactions while in six the reactions were interpreted as irritant (table 2). The majority of the allergic contact reactions were caused by skin care products.

The large majority of the patients were Norwegians (113), only two had other ethnic backgrounds. About 27,8% of the cutaneous reactions occurred among patients 20-29 years of age. At the same time, the frequency of skin reactions among the various other age groups, was surprisingly constant: 30-39 year (n=17), 40-49 years (n=17), 60-69 years (n=17), 70-79 years (n=13), while it was lower in the age group 50-59 years (n=10), below 19 years (n=2) and above 80 years (n=7).

In several of the patients more than one area was involved. The localizations of the dermatitis were as follows: the hands (including the fingers) 46%, face 45,2%, the forearms 23,5o the legs 21,7%. In 2I patients the dermatitis was caused exclusively by allergy to cosmetics while the rest of the patients also showed positive patch test reactions to other non-cosmetic ingredients.

Several of these patients had one or more skin diseases in addition to contact dermatitis: Atopic dermatitis n=32, leg eczema n=13, light dermatosis n=5 and various conditions such as psoriasis, urticaria, seborrhoic dermatitis - n=7. In six patients the contact dermatitis was occupationally related (hair-dressers or hairdresser apprentices).

DISCUSSION

Our purpose was to evaluate the cases of cosmetically induced contact dermatitis. About 37% (115/300) of our patients with contact dermatitis were allergic to cosmetics or cosmetic ingredients. As in other studies (2,6,8) fragrance mixtures and individual fragrance ingredients were the most important cosmetic allergens. But this was also the category with the highest number of irritant reactions. Preservatives were the second most frequent cause of reactions. Formaldehyde and Kathon CG were the preservative ingredients which caused the greatest number of reactions. This study confirms that Kathon CG is and important cause of cosmetic allergy (10,11,12,13), but this preservative does not seem to be our most important contact allergen.

In the Netherlands (8) Kathon CG caused cosmetic allergy in 27,7% of the patients. In other studies (11) the incidence of Kathon sensitivity ranged from 0,78% to 8,7%. The recommended test concentration of Kathon CG is 100 ppm active ingredients in water which is the concentration used at our department.

We found 11 patients who had positive reactions to Kathon. As in other studies we also noticed an increasing sensitivity rate to this preservative. Only two patients showed positive reactions in 1987, while nine reacted in 1988.

We observed that only women reacted to Kathon. This preponderance of women has been reported in other studies (12). Unfortunately,

Table II

COSMETIC PRODUCTS CAUSING CUTANEOUS REACTIONS IN 32 PATIENTS

	Sensitization	Irritation	Sum
Skin care products	10	0	10
Perfumes	3	0	3
Suntan or sunscreen products	1	0	1
Nail preparations	1	0	1
Eye makeupproducts	1	0	1
Hair preparations (incl. colors)	1	2	3
Oralhygieneproducts	1	0	2
Shampo	1	1	2
Deodorant	3	0	0
Soap	4	3	7
	26	6	32

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A new look at old skin: A challenge to cosmetology

1st International Meeting on Cosmetic Dermatology, Rome, Italy, March 7-9, 1985

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Third year undergraduates, research workers in the field of Cosmetic Chemistry, Biochemistry, Medicine, Pharmacy and Pharmacology, researchers and managers working in the cosmetic and pharmaceutical industries.

The proceedings contained in this volume provide comprehensive view of the different aspects of the skin aging with its cosmetological implications.

Contents (main chapters)

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