Safety evaluation of cosmetics in Europe

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Abstract

Council Directive 76/768/EEC forms the basis of the actual legislation of cosmetics in the European Union (EU).

After a short introduction on the background and philosophy of this legislation, the key points will be discussed.

In particular, attention will be given to the basic principles for safety and in this context the effects of the implementation of the 6th Amendment (Council Directive 93/35/EC) will be analysed.

The major points for discussion will be: the safety requirements for cosmetics and the final responsibility for bringing these products on the EU market; the EU concept of safety of the finished product based on the safety of the individual ingredients; the existence of positive and negative lists of ingredients and the requirement for a European dossier for all finished products. Special attention will be given to the use of validated alternative methods and the consequences of the new proposal of a 7th Amendment.

Finally, the safety evaluation as it is done by the SCCNFP (Scientific Committee on Cosmetics and Non-Food Products) in the case of an ingredient present on the positive lists and the evaluation done by a safety assessor in the case of a technical information file for a finished product, both will be discussed in detail.

EDUCATION

1964 Latin-Mathematics, KA Lokeren.

1970 Pharmaceutical Sciences, University of Ghent (B).

1975 Doctoral Degree in Pharmaceutical Sciences, Vrije Universiteit Brussel (B).

1997 Master in Applied Toxicology, University of Guildford (UK), Industrial Pharmaceutical Chemist. Clinical Biology, certificate A.

PROFESSIONAL AND RESEARCH EXPERIENCE

Full-time professor, highest level.

Head of Department of Toxicology, Dermato-Cosmetology and Pharmacognosy, in the Faculty of Medicine and Pharmacy at the V.U.B.

Teaching duties in Toxicology and Galenics; Cosmetics; Medical Terminology; Safety of Cosmetics in EU; Intensive Course in Dermato-Cosmetic Sciences.
Head of IPAVUB, Institute of Postacademic Formation at the V.U.B.

PUBLICATIONS

Author or co-author of more than 200 publications in international peer reviewed journals.
Author and editor of several scientific books.
Author of more than 180 oral presentations.
Author of more than 80 poster presentations.
More than 90 times invited speaker.
Active participation in the organisation of 20 international congresses.

SCIENTIFIC AWARDS

1980 prize of the Belgian Association for Cystic Fibrosis.
1982 Laureate of the "Reisbeurzenwedstrijd België".
1987 FISEA prize (alternatives for animal experimentation) in Luxembourg.
2000 Doerenkamp-Zbinden Award 2000, Switzerland (for a whole carrier on the development on alternative methods for toxicology).

MEMBERSHIP

SCCNFP (Scientific Committee on Cosmetic Products and Non-food Products intended for Consumers).
ESAC (Scientific Advisory Committee of ECVAM, the European Center for the Validation of Alternative Methods).
EEMCO (European Group for the Efficacy Measurements on Cosmetics and other Topical Products).
Health Council in Belgium - Section on Cosmetics.
Chairperson of *ecopa* (European Consensus Platform on Alternatives).
Chairperson of BADECOS (Belgian Association of Dermato-Cosmetic Sciences).
Membership of various scientific international associations in biochemistry, toxicology and cosmetics.
Member of editorial board of Archives of Toxicology, Toxicology and Eco-toxicology News; Associate editor of Archives of Toxicology.
Reviewer for Biochemical Pharmacology, Cell Biology and Toxicity, Archives of Toxicology, Life Sciences, Toxicology in Vitro, TEN, European Journal of Biochemistry, ATLA, Journal of Cosmetic Dermatology, European Journal of Pharmacology.

국문요약

Council Directive 76/768/EEC는 EU에서 화장품에 대한 기본적인 규정에 대한 기초가 된다. 이 규정의 배경과 원리에 대한 간단한 소개 후에 주요안건에 대해 강연할 것이다. 특히, 안전성에 대한 기본적인 원칙에 대해 주로 다루었으며, 6차 개정 이행(Council Directive 93/35/EC)에 따른 영향에 대하여 분석하였다.

토론의 주요 주제는 화장품의 안전성에 대한 요건과 EU시장에서 화장품 출시시 최종적인 책임, 개개의 성분의 안전성을 기초로 한 최종제품의 안전성에 대한 EU의 개념, 모든 최종제품에 대한 유럽에서 요구하는 서류와 개개의 성분들의 positive list와 negative list의 존재여부에 대하여 다루어지며. 또한 주요관심인 7차 개정에 의해 새롭게 제안된 것과 동물대체시험법의 사용에 대해 강연할 것이다. 마지막으로, positive list에 존재하는 성분의 경우 SCCNFP에 의하여 이루어지는 안전성평가와 최종제품에 대한 기술적인 측면에서 안전성평가자로서 이루어지는 평가에 대해 상세하게 다루어 질 것이다.

SAFETY EVALUATION OF COSMETICS IN THE EU

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1. BACKGROUND AND PHILOSOPHY OF THE EU COSMETICS LEGISLATION

Today the European Union (EU) counts 15 Member States but within the coming months and years, an additional number of so-called previous East Block Countries will gradually join and enlarge the EU.
One of the basic principles of the EU is to function as a Single Market, meaning that there should be free movement of people, goods, capital and services within the Member States.
Thus, according to the EU philosophy, cosmetic products should be able to move freely within the EU with the same packaging, labelling ands safety requirements.
For that purpose, however, a similar cosmetic legislation must be in place in all Member States.

2. EU COSMETIC LEGISLATION

Council Directive 76/768/EEC (1) forms the basis of the cosmetic EU legislation today. It is a legally binding instrument on all EU Member States but leaving to national authorities the choice of form how to implement. Compulsory provisions, however, must be taken over by national legislation.
The principles laid down in Directive 76/768/EEC take into account the needs of the consumer, but commercial exchange and the elimination of barriers to trade are also key issues. The Cosmetic Directive aims to guarantee human safety of cosmetics but without pre-marketing authorisation, thus placing the full responsibility under the manufacturer, first importer into the EU or marketer. This safety relates to the composition of the product, its packaging and information for the consumer.

Council Directive 76/768/EEC consists of a text with Articles and Annexes.
The Annexes are changed regularly in order to take account of recent scientific and technological findings and the opinions on cosmetic ingredients, produced by the SCCNFP.(Scientific Committee on Cosmetics and Non-Food Products). They are called "ADAPTATIONS TO TECHNICAL PROGRESS". Within the last 26 years 26 updates have been carried out.

The Articles can also be modified, but that is done only occasionally when changes of the basic philosophy or introduction of new policies become necessary.
Changes to the Articles are called "AMENDMENTS". Until now 6 Amendments have been realised. A 7th Amendment is underway and will be officially available during January 2003, but the basic philosophy of the text is already known now.

The 6th Amendment [Council Directive 93/35/EC (2)] introduced a number of important modifications which can be summarised as follows:

- adjusted cosmetic definition;
- compilation of an inventory of ingredients;
- stricter safety requirements;
- additions in labelling requirements for ingredients and product function labelling;
- package of information on each cosmetic product (safety and efficacy);
- notification requirement, information to poison information centres;
- restrictions on animal testing.

The coming 7th Amendment Proposal will in particular deal with an animal testing and marketing ban on ingredients and finished cosmetic products.

3. KEY PRINCIPLES FOR SAFETY IN ACTUAL COSMETIC LEGISLATION

3.1. Strict safety requirements and placing of responsibility (art. 2)

In the actual legislation, the following safety clause is present: "A cosmetic put on the market within the Community must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use, taking account, in particular, of the product's presentation, its labelling, any instruction for its use and disposal as well as any other indication or information provided by the manufacturer or his authorised agent or by any other person responsible for placing the product on the Community market".
This article clearly outlines the basic requirement for safety of the finished product for human health and places the full **responsibility on the manufacturer, the first importer in the EU or marketer**.
With respect to labelling (art. 6) of the package and recipient of cosmetics, the following indications are necessary:

- name and address of the manufacturer or distributor;
- nominal content (weight or volume);
- date of minimal durability if less than 30 months;
- precautions for use;
- batch number enabling identification of manufacturing;
- product function, unless evident;
- ingredient labelling in INCI (International Nomenclature of Cosmetic Ingredients);
- symbol of Annex VIII for off-pack labelling (book plus hand).

The last three labelling obligations came in with the 6th Amendment and provide more information to the consumer. In particular, the appearance of an ingredients list on the finished product was in particular asked by medical persons in order to offer the possibility to

sensibilised or contact allergy-sensitive patients to avoid contact with certain cosmetic ingredients.
All ingredients (except impurities) are listed now, with the exception of individual perfume / aroma components, in descending order of weight.
For amounts equal or below 1% random listing is allowed. Certain ingredients can be omitted through a confidentiality provision, but experience has learned that this is only seldomly
done (6).
Colourants are given as CI (colour index) numbers and may be listed randomly at the end of the ingredients list. More colourants than present in the product may be indicated by the sentence "may contain" or "+/-", giving the opportunity of using only one type of packaging for a number of differently coloured products of the same series.

3.2. Safety of finished product based on safety of individual ingredients and existence of positive and negative lists (art. 7)

The ingredients, for which concerns exist for human health, have been taken up in so-called positive lists (meaning that only the substances present in the list may be used in cosmetics). Positive lists exist for colouring agents (Annex IV), preservatives (Annex VI) and UV-filters (Annex VII). A negative list (Annex II) contains those substances that are forbidden for use in cosmetics. Finally, Annex III lists the ingredients for which restrictions exist in concentration and/or application field.
In order to be taken up in these lists, dossiers of new substances have to be evaluated by the SSCNFP and the final responsibility lays with the Commission (DG Enterprise) (see further under point 4).

3.3. Safety of finished product based on safety of individual ingredients (chemical structure, toxicological profile, exposure) and requirement of a European dossier (art. 7).

A compilation of information on each cosmetic product (dossier) must be kept readily available for inspection by the competent authorities of the Member State concerned at the address specified on the cosmetic package. This information source usually is called **a TIF (technical information file)** or **PIF(R) (product information file/requirements)** and consists practically spoken out of the following 4 major parts (3, 4):

1. An administrative dossier:
    - Trade name of the product and responsible company, manufacturer or distributor;
    - Product category (Annex I);
    - Integral composition of the product;
    - Identification of persons with ultimate responsibility.
2. An ingredients dossier:
    - Identity(ies), supplier(s) and composition(s) of the ingredients;
    - Details on manufacturer(s) and supplier(s) of the ingredients;
    - Physicochemistry and microbiology of the ingredients including the physicochemical properties and the physicochemical and microbiological inspections;

- Toxicity data including acute oral, dermal and inhalation toxicity; local toxicity, including skin irritation, eye irritation, sensitisation, photo-allergy and photo-irritation when relevant; long-term toxicity data, additional relevant toxicological data and available ecotoxicological data (see table 1);
- First aid measures;
- Risk and safety instructions with EU labelling according to Directive 67/548/EEC and amendments and specific labelling according to directive 76/768/EEC and amendments and national legislation(s).

3. A finished product dossier:
   - Fabrication of the product with place(s) of manufacturing, methodology, identification of person responsible for manufacturing;
   - Stability of the product including physical and microbiological stability;
   - Physicochemical properties and microbiological data on the finished product including examinations;
   - Safety data concerning the finished product including an overview of the toxicological data of the ingredients; the communication done with the national competent authorities and the poison control centres; toxicological animal testing performed on the finished product; toxicological tests using alternative methods; human tests performed on the finished product; undesirable effects on human health reported during use of the product; the identification of the safety assessor and the appropriate credentials. An important part is **the risk assessment of the product by the safety assessor;**
   - Efficacy of the finished product: a summing up of the claims made, efficacy tests that have been carried out, additional information or argumentation;
   - Packaging and labelling: this part starts with an overview of the data on packaging and labelling of the ingredients, provides the labelling of the finished product, giving information on packaging materials and weight/volume, packaging procedures, identification of the batch number, checks on the end products and finally identifies the person responsible for packaging.

4. Follow-up dossier of the market: a good functioning post-market complaint system, where consumers can communicate eventual complaints must be installed. All complaints and their follow-up must be added to the dossier.

By giving all this information, the TIF has to demonstrate that the product meets the safety requirements of the actual cosmetic legislation (art. 7b) and guarantees its stability over time (art. 8) as well for the ingredients as for the finished product. The Directive does not give rules of procedure to be followed for the risk assessment of the finished product, but stipulates that the chemical structure and the toxicological profile of the ingredients, plus the level of exposure should be taken into consideration (art. 7a.1(d)). This means that the safety assessor has some freedom in evaluating the safety of the cosmetic product under consideration.
Usually an experienced assessor will take the points into consideration shown in table 2 (3 - 5).
Also in art. 7a.1(e) details are given that the person responsible for the safety evaluation (called the safety assessor), must have a diploma in the field of pharmacy, toxicology, dermatology, medicine or a similar discipline.
In art. 7.a.4. notification premises are given.

3.4. Use of validated alternative methods and postponement possibilities (art. 4)

In art. 4, it is stated that safety for human health must be guaranteed without animal tests of ingredients or mixtures of ingredients from 1 January 1998 on, on the condition that appropriate validated alternative methods are available. Postponement of the date is foreseen when there is insufficient progress in developing satisfactory methods to replace animal testing and particularly in those cases where alternative methods of testing have not been scientifically validated as offering an equivalent level of protection for the consumer. Validation of alternative methods is co-ordinated at the EU level in Ispra, Italy at ECVAM (European Centre for the Validation of Alternative Methods). Scientific advice is given by a group of experts from all Member States, called ESAC (ECVAM Scientific Advisory Committee). An alternative method must pass ESAC and get approval, before it can be taken up in the actual EU legislation and be advised for cosmetics.
Furthermore, the Commission has to present an annual report to the European Parliament and the Council on progress and legal acceptance of alternative methods.
However, the preparation of such a report has been neglected for some years, which has caused damage to the general confidence of the actual strategy to reduce animal testing in cosmetics. At present, the date of implementation of the provision made in art. 4.1(i) has been postponed to 30 June 2002 (7). A further extension of the testing and marketing ban of cosmetics will be present in the Seventh Amendment.

Although the final official text will only become available in January 2003, the Commission and the Parliament have reached a consensus on the ban of animal testing for finished cosmetic products: namely a testing ban will apply for all cosmetic products manufactured in the EU and a EU marketing ban for cosmetics for which animal tests have been performed, including those done outside the EU. A transition period is foreseen in which the bans apply only for those tests for which validated alternative methods already exist. In all other cases, a period of 6 years is allowed to develop new animal-free methods, meaning that animal testing for cosmetic ingredients will be finished in 2009.

4. SAFETY EVALUATION OF COSMETIC INGREDIENTS

As already briefly mentioned, according to the actual cosmetic legislation in the EU, two distinct channels are operative for safety evaluation of cosmetic ingredients:

1. The safety evaluation of cosmetic ingredients of relevance to Council Directive 76/768/EEC, namely the ingredients taken up in the so-called positive lists, such as those attached to annexes III (ingredients subjected to restrictions), IV (colouring agents), VI (preservatives) and VII (UV-filters). The safety evaluation is done by the SCCNFP and the responsibility for the ingredients on these lists lays with the Commission (DG Enterprise).
2. The safety evaluation of cosmetic ingredients present in finished products of relevance to the dossier of information required under article 7.a of the Sixth Amendment (TIF or PIR). The safety evaluation is done by a so-called safety assessor (art. 7.a.1.(e)) in the context of the safety assessment of a given finished product. The ultimate responsibility lays with the manufacturer, importer or marketer.

4.1. Safety assessment by the SCCNFP

The SCCNFP is part of the Commission, namely of DG Sanco and is composed of highly qualified scientists from different Member States (B, D, DK, E, F, H, I, IRL, N, NL, UK). The SCCNFP is an advisory body for DG Enterprise, that is responsible for the administration of Directive 76/768/EEC including the Sixth and the future Seventh Amendment.

The procedure for safety evaluation (= risk assessment) of cosmetic ingredients currently applied by the SCCNFP consists of three phases:

1. Hazard identification by analysis of the studies on a particular ingredient, developed by the cosmetic industry and presented to the Commission (by individual firm(s) and/or through Colipa,The European Toiletry and Perfumery Association).
1. Risk assessment by evaluation of the recent literature and all studies available with respect to the different toxicological aspects of a particular ingredient under consideration, thus allowing the evaluation of the safety levels for consumers potentially exposed to such chemicals as ingredients of finished cosmetic products.

- The requirement, in some cases, of additional toxicological tests in order to be able to make a reassessment of the safety profile of the ingredient under consideration.

The general toxicological requirements for cosmetic ingredients on the positive lists of the Cosmetic Directive 76/768/EEC are summarised in the SCCNFP Notes of Guidance (8, 9) and are shown in table 1.

1	Acute toxicity (oral or by inhalation in case of volatile substances)
2	Percutaneous absorption
3	Skin irritation
4	Mucous membrane irritation
5	Skin sensitisation
6	Sub-chronic toxicity (oral or by inhalation in case of volatile substances)
7	Mutagenicity (bacterial test for gene mutations and *in vitro* mammalian cell culture test for chromosome aberrations)
8	Phototoxicity and photomutagenicity in case of UV light absorbing substances
9	Human data
10	Toxicokinetics
11	Teratogenicity, reproduction toxicity, carcinogenicity
12	Metabolism studies

Table 1: General toxicological requirements for cosmetic ingredients as foreseen in Annex 1 of the 4th revision of the SCCNFP "Notes of Guidance".

4.2. Safety assessment by a safety assessor

The procedure for safety evaluation of cosmetic ingredients, present in a given cosmetic formulation, is carried out in the framework of the safety assessment of that particular finished cosmetic product.

All relevant toxicological information is gathered via several sources: official instances, Supplier's Material Safety Data Sheets (MSDS), and CD-ROM's from individual companies, commercial databases including bibliographical as well as factual databases (10). A first problem is that MSDSs do not always exist, since they are not required when the substance / preparation is not classified in any danger class (harmful, irritating, toxic, ...). A second problem can be encountered with some substances taken up in EINECS (European Inventory of Existing Commercial Chemical Substances), which are very old and therefore

may have a very poor and incomplete toxicological data package. On the contrary, new chemical substances (after 1981) are regulated by the Seventh Amendment of Directive 67/548/EEC (Dangerous Substances) and do have a dossier. Its content depends on the annual volumes placed on the market, but the summaries of these studies are not confidential. It is, however, often difficult to get access to this critical information.
All chemical, toxicological and technical information on the ingredients present in a particular finished product are brought together in a TIF. It is used by the safety assessor together with all available information relevant to human exposure to make the risk assessment of the finished product (table 2).

Safety aspects	Tools
Hazard	- Animal studies
	- 3R studies (replacement, reduction, refinement)
	- Human data, clinical studies
Exposure	- Product type
	- Use pattern, application mode
	- Application site
	- Concentration
	- Frequency
	- Amount applied
	- Chemical composition
	- Stability
	- Microbiological purity
	- Target population
	- Percutaneous absorption
Risk	- Risk assessment

Table 2: Tools of safety assessment for cosmetic ingredients and finished products (10).

The cosmetic risk to be evaluated usually is restricted to a local one and is centred on irritation (and photoirritation if relevant) and immunobiological reactions (contact allergy and eventually photoallergic reactions). Potential systemic effects can occur (11) and should be particularly taken into consideration when considerable skin penetration and/or oral intake occur.
The safety assessor must indicate in writing whether a cosmetic product can be brought onto the EU market without risks to human health when applied under normal and reasonably foreseeable conditions of use.

5. NEW CHALLENGES IN SAFETY ASSESSMENT OF COSMETICS

With the implementation of the Sixth Amendment a number of new challenges came up in the safety assessment of cosmetics. These can be summarised as follows:
- Shift from *in vivo* to *in vitro* testing;
- New role of raw material suppliers;
- The need for appropriate training;

- Ethical constraints in human testing;
- Special problems for SME's (small and medium enterprises);
- Consumer concerns and risk perception.

5.1. Moving from *in vivo* to *in vitro* testing

The challenge of moving from *in vivo* to *in vitro* testing for the cosmetic industry and in particular for safety assessors, is achieving the same level of consumer protection and at the same time respecting the consumers desire for reduction or even elimination of animal testing. An updated list of validated *in vitro* and 3R methods suitable to be used for cosmetics is present in the Notes of Guidance of the SCCNFP (8, 9). In table 3, the actual situation of validated alternative *in vitro* methods useful for safety testing of cosmetic ingredients and prospects for the near future are shown.

-	+/-	+
• Subacute toxicity	• Acute (oral) toxicity	• Skin corrosivity
• Chronic toxicity	• Skin irritation	• Phototoxicity
• Reproductive toxicity	• Ocular irritation	• Percutaneous absorption*
• Carcinogenicity (non mutagenic)	• Skin sensitisation (Local Lymph Node Assay**)	• Mutagenicity
• Biokinetics	• Embryotoxicity***	• Acute toxicity (LD_{50})*

Table 3: Actual situation of validated alternative/*in vitro* methods useful for safety testing of cosmetic ingredients and prospects for the near future.

* Not validated by ECVAM (European Centre for the Validation of Alternative Methods), but accepted by ESAC (ECVAM Scientific Advisory Committee) and SCCNFP (European Scientific Advisory Committee) as a replacement alternative.

** Not validated by ECVAM, but accepted by ESAC and SCCNFP as a refinement alternative.

*** Validated by ECVAM but not yet accepted by SCCNFP.

5.2. New role of raw material supplier

With the requirements of the Sixth Amendment to keep a TIF ready for inspection for the competent authorities and containing a safety assessment based on the structure, toxicological pattern and exposure of the ingredients, the availability, substantivity and completeness of high quality toxicological data of raw materials and new ingredients became of key importance. Raw material suppliers, surfactant suppliers and speciality chemical suppliers should be made better aware of this problem.

5.3. The need for appropriate training

All parties involved in the preparation of cosmetics, importation within the EU, supply of raw materials, safety assessment, development or application of alternative methods, regulation, etc. should be appropriately trained by taking specific training courses in the safety assessment of cosmetics. Such a course existed at the national level in Germany and was

organised by the Deutsche Gesellschaft für Wissenschaftliche und Angewandte Kosmetik. An academic course with a legal course certificate exists since 3 years at the European level in Belgium at the Vrije Universiteit Brussel, Department of Toxicology (http://Safetycourse.vub.ac.be).

5.4. Ethical constraints in human testing

By eliminating animal testing, the need for human testing is increased since alternative methods have a limited predictive value for human exposure. Confirmatory safety tests are sometimes necessary and can be carried out in man.
Ethical concerns, however, should be considered. The SCCNFP stated that confirmatory tests on humans can be done when the toxicological profiles of all ingredients and of the finished cosmetic product, based on animal or alternative methods, are available and safe (SCCNFP/0003/98).
Human tests, however, should not be preferred to animal tests and cannot be considered as an alternative to the use of animals. The SCCNFP made guidelines for potential cutaneous irritant ingredients (SCCNFP/0003/98), finished products (SCCNFP/0068/98) and potentially cutaneous sensitising cosmetic ingredients (SCCNFP/0120/99 Final).

5.5. Special problems for SME's

Safety assessment of cosmetics and the application of *in vitro* methodologies require specialised personnel, which often is not available in SMEs. This means that extra resources become necessary for advice by competent consultants and for *in vitro* testing by contract laboratories.

5.6. Consumer concerns and risk perception

Awareness of the consumer is a key issue, which should be taken seriously. A drastic change in attitude should be made: until now, a traditional approach was applied by using a standard battery of *in vivo* tests and this was sufficient. Today not only should one move to the application of a standard battery of *in vitro* tests but better to a balanced *in vitro*/alternative strategy for each category of cosmetic products.
Risk perception, although subjective and completely dissimilar from the scientific determination of hazard and risk, really does matter, since it can importantly affect the cosmetic market. A typical example is the recent "problem" of the UV-filter 4-methylbenzylidene camphor, which was perceived by the general public and the Danish Ministry to be an endocrine disruptor having estrogenic activity which could damage human health and particular that of small children (12, 13), while scientific evidence showed that there was no need for any regulatory action to protect the consumer.

6. CONCLUSIONS

The European Cosmetic Directive as it is today guarantees safe cosmetic products on the EU market. This is for a great part due to the community decision to leave the experimenter and therefore also the manufacturer to their own responsibility. This has resulted in a refinement of the different evaluation criteria and also in better cosmetics.
A disadvantage, however, is the heavy task for SMEs that are not really equipped to take such a high responsibility and to deal with the high costs resulting from the implementation of the Sixth Amendment.
New challenges are to come with the Seventh Amendment and a potential animal testing ban on cosmetic products and cosmetic ingredients in the EU, and a potential EU marketing ban of animal tested cosmetic products. They seem to be quite threatening for the safety of cosmetics and their free circulation within, and especially outside the EU market.
In vitro methods will replace more and more *in vivo* regulatory testing, but it would be wise to allow 3R testing (Reduction, Replacement, Refinement = strategy proposed by Russell and Burch) (14) in cases where validated *in vitro* methods are not yet available.

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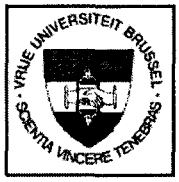
SAFETY EVALUATION OF COSMETICS IN THE EU



Vera Rogiers
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Dermato-Cosmetology and Pharmacognosy
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Belgium

CONTENTS

CONTENTS

- ❑ BACKGROUND & PHILOSOPHY OF EU COSMETIC LEGISLATION
- ❑ EU COSMETIC LEGISLATION
- ❑ KEY PRINCIPLES FOR SAFETY OF COSMETICS IN ACTUAL EU LEGISLATION
- ❑ SAFETY EVALUATION OF COSMETIC INGREDIENTS
- ❑ NEW CHALLENGES IN SAFETY EVALUATION OF COSMETICS
- ❑ CONCLUSIONS

❑ BACKGROUND & PHILOSOPHY

EU: 15 MEMBER STATES
➡ ENLARGEMENT

SINGLE MARKET

free movement of
- people
- capital
- goods
- services

COSMETICS

similar:
- packaging
- labelling
- safety requirements

SIMILAR LEGISLATION

CONTENTS

- ❑ BACKGROUND & PHILOSOPHY OF EU COSMETIC LEGISLATION
- ❑ EU COSMETIC LEGISLATION
- ❑ KEY PRINCIPLES FOR SAFETY OF COSMETICS IN ACTUAL EU LEGISLATION
- ❑ SAFETY EVALUATION OF COSMETIC INGREDIENTS
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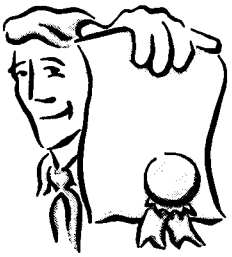
❑ EU COSMETIC LEGISLATION



COUNCIL DIRECTIVE 76/768/EEC

- consumers needs
- commercial exchange
- elimination of trade barriers
- human safety (no pre-marketing, responsibility, product composition & information)

ANNEXES ⟵ ⟶ **ARTICLES**

ADAPTATIONS TO TECHNICAL PROGRESS

- recent scientific data & SCCNFP opinions
- 26 updates

AMENDMENTS

- change in philosophy, new policy
- 6 amendments

❑ EU COSMETIC LEGISLATION

COUNCIL DIRECTIVE 93/35/EC: 6th AMENDMENT

- ☞ Adjusted cosmetic definition
- ☞ Compilation of an inventory of ingredients
- ☞ Stricter safety requirements
- ☞ Additions in labelling requirements for ingredients and product function
- ☞ Package of information on each cosmetic product (safety and efficacy)
- ☞ Notification requirement, information to poison information centres
- ☞ Restrictions on animal testing; ban on animal testing of ingredients on 30-6-2002 (Commission directive 2000/41/EC)

CONTENTS

❑ KEY SAFETY PRINCIPLES

① **STRICT SAFETY REQUIREMENTS**

② **SAFETY OF FINISHED PRODUCT BASED ON SAFETY OF INDIVIDUAL INGREDIENTS & EXISTENCE OF SPECIFIC LISTS**

③ **SAFETY OF FINISHED PRODUCT BASED ON SAFETY OF INDIVIDUAL INGREDIENTS & REQUIREMENT OF A EUROPEAN DOSSIER**

④ **USE OF VALIDATED ALTERNATIVE METHODS & POSTPONEMENT POSSIBILITIES**

❑ KEY SAFETY PRINCIPLES

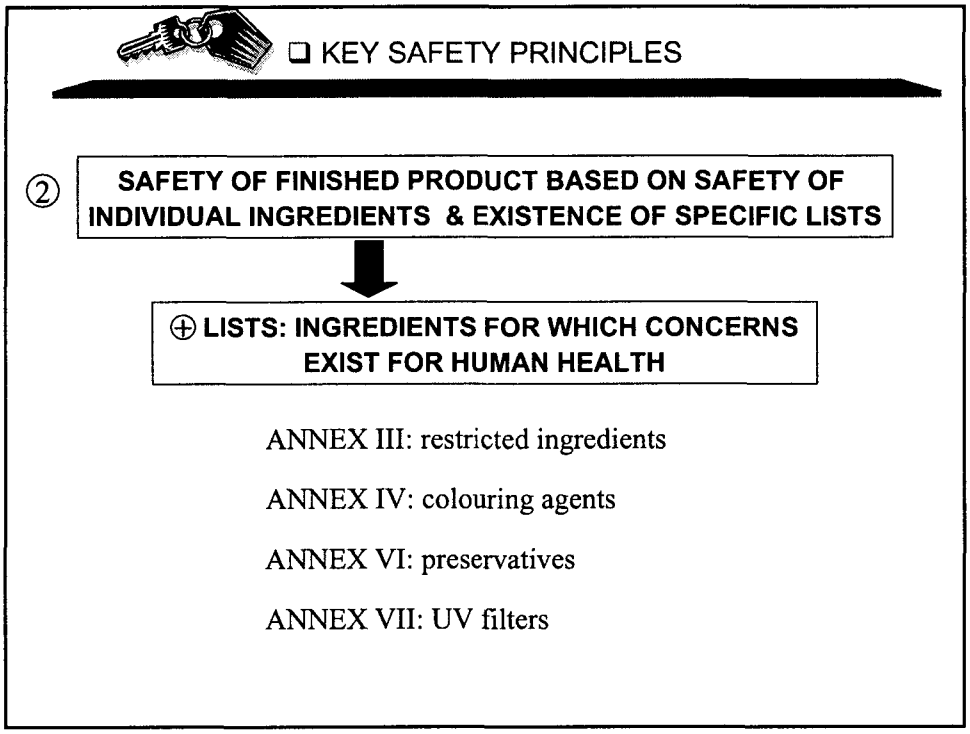
① **STRICT SAFETY REQUIREMENTS**

☞ a cosmetic must be **safe** under normal or reasonable foreseeable condtions of use (art 2)

☞ **full responsibility** lays with manufacturer/first importer/marketer (art 2)

☞ **labelling requirements** (art 6)

- name & address
- nominal content
- date of minimal durability < 30 months
- precautions of use
- batch number
- product function
- ingredients (INCI)
- off-pack labelling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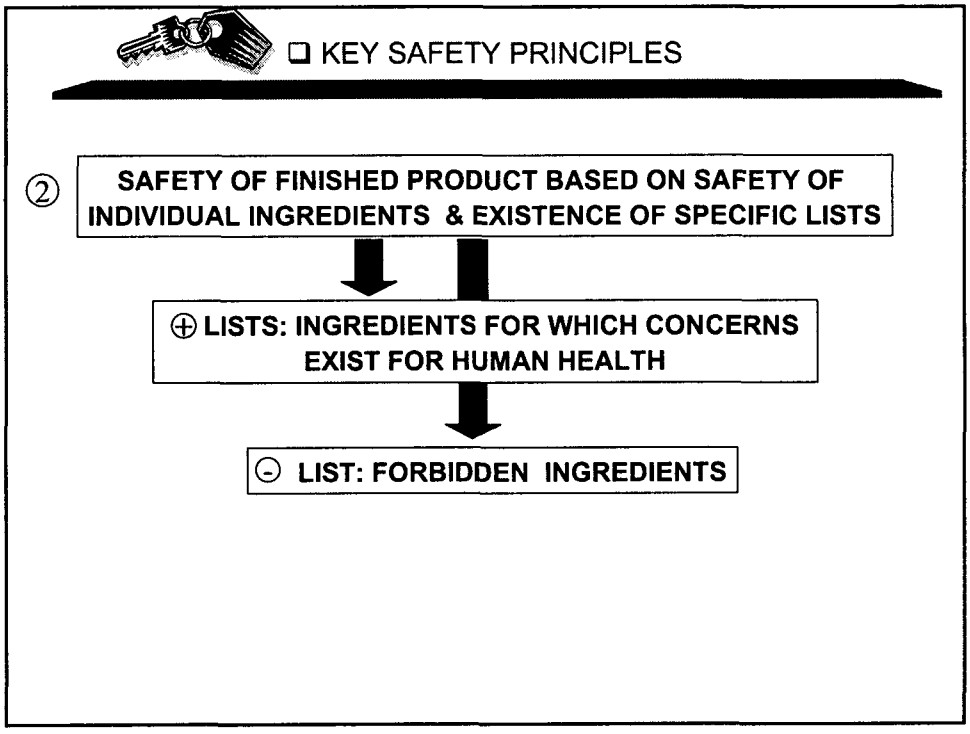
⊕ LISTS: INGREDIENTS FOR WHICH CONCERNS EXIST FOR HUMAN HEALTH
ANNEX III: restricted ingredients
ANNEX IV: colouring agents
ANNEX VI: preservatives
ANNEX VII: UV filters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⊕ LISTS: INGREDIENTS FOR WHICH CONCERNS EXIST FOR HUMAN HEALTH
⊖ LIST: FORBIDDEN INGREDIENTS

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⊕ **LISTS: INGREDIENTS FOR WHICH CONCERNS EXIST FOR HUMAN HEALTH**

⊖ **LIST: FORBIDDEN INGREDIENTS**

RESTRICTION LIST: ANNEX III (conc./application field)

- RESPONSIBILITY OF DG ENTERPRISE
- AFTER ADVICE OF SCCNFP

❑ KEY SAFETY PRINCIPLES

③ **SAFETY OF FINISHED PRODUCT BASED ON SAFETY OF INDIVIDUAL INGREDIENTS & REQUIREMENT OF A EUROPEAN DOSSIER**

☞ for each cosmetic product an **information package** must be kept available for inspection: TIF or PIR

☞ responsibility lays with manufacturer/ importer or marketer

☞ content:
- administrative dossier
- ingredients dossier
- finished product dossier
- "follow-up in market" dossier

❑ KEY SAFETY PRINCIPLES

④ **USE OF VALIDATED ALTERNATIVE METHODS & POSTPONEMENT POSSIBILITIES**

COUNCIL DIRECTIVE 93/35/EC: 6th AMENDMENT

guaranteed safety without animal tests on ingredients from 1/1/ 1998 on when validated alternatives are available

↓

COMMISSION DIRECTIVE 97/18/EC

ban on animal testing of ingredients postponed to 30/6/2000

↓

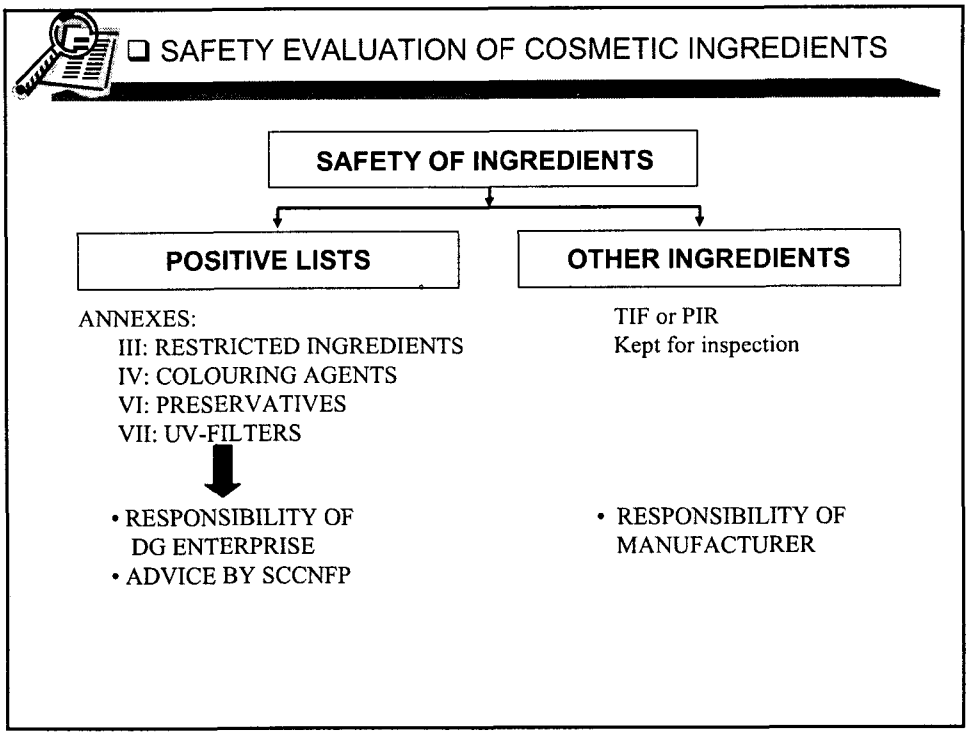
COMMISSION DIRECTIVE 2000/41/EC

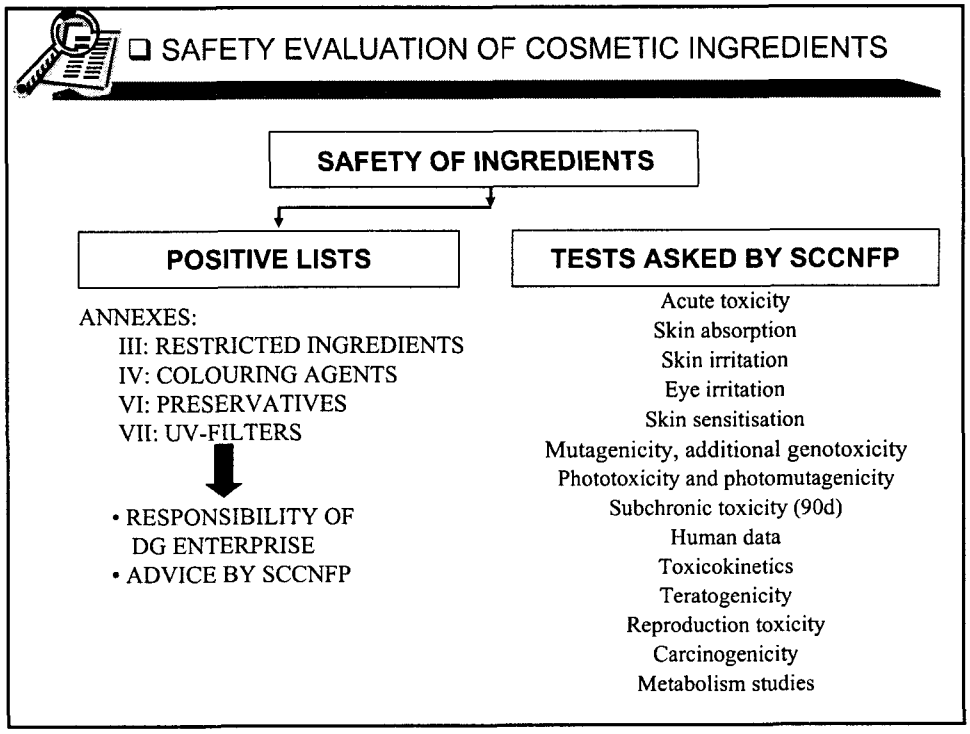
ban on animal testing of ingredients postponed to 30/6/2002

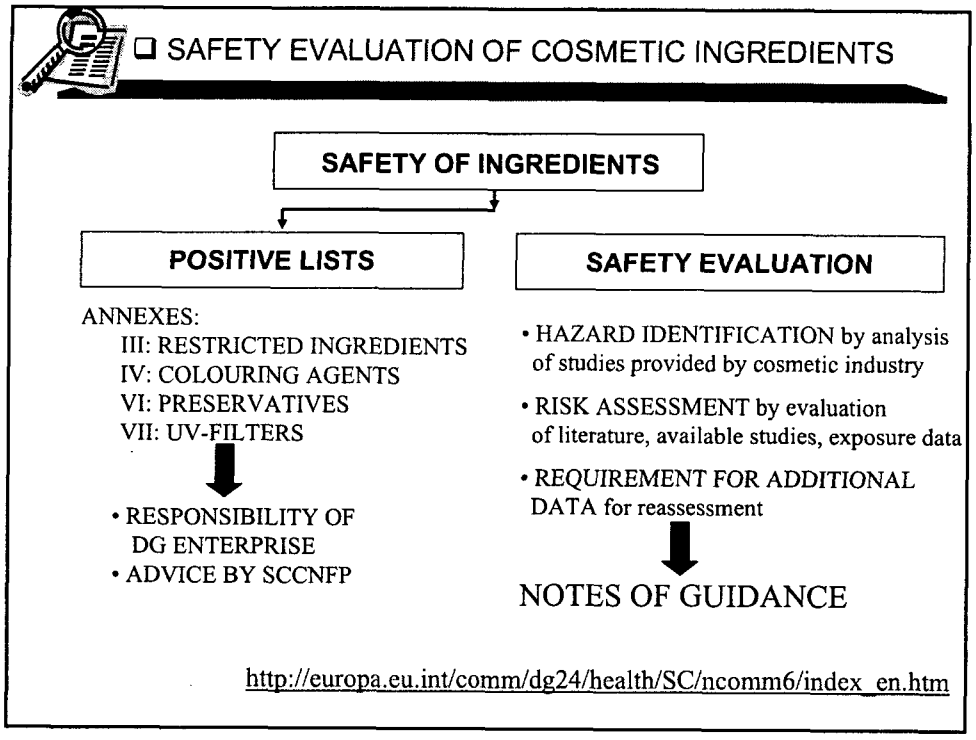
↓

SEVENTH AMENDMENT PROPOSAL

CONTENTS


❑ SAFETY EVALUATION OF COSMETIC INGREDIENTS
SAFETY OF INGREDIENTS
POSITIVE LISTS
OTHER INGREDIENTS
ANNEXES:
III: RESTRICTED INGREDIENTS
IV: COLOURING AGENTS
VI: PRESERVATIVES
VII: UV-FILTERS
• RESPONSIBILITY OF DG ENTERPRISE
• ADVICE BY SCCNFP
TIF or PIR
Kept for inspection
• RESPONSIBILITY OF MANUFACTURER


❑ SAFETY EVALUATION OF COSMETIC INGREDIENTS
SAFETY OF INGREDIENTS
POSITIVE LISTS
TESTS ASKED BY SCCNFP
ANNEXES:
III: RESTRICTED INGREDIENTS
IV: COLOURING AGENTS
VI: PRESERVATIVES
VII: UV-FILTERS
• RESPONSIBILITY OF DG ENTERPRISE
• ADVICE BY SCCNFP
Acute toxicity
Skin absorption
Skin irritation
Eye irritation
Skin sensitisation
Mutagenicity, additional genotoxicity
Phototoxicity and photomutagenicity
Subchronic toxicity (90d)
Human data
Toxicokinetics
Teratogenicity
Reproduction toxicity
Carcinogenicity
Metabolism studies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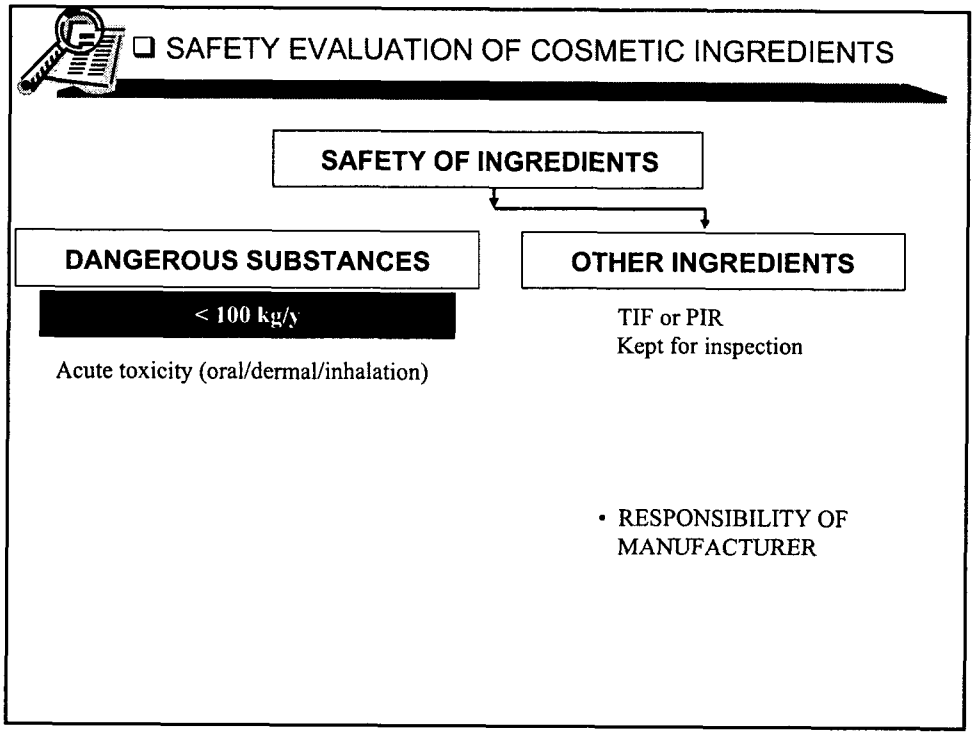
IV: COLOURING AGENTS
VI: PRESERVATIVES
VII: UV-FILTERS
• RESPONSIBILITY OF DG ENTERPRISE
• ADVICE BY SCCNFP
• HAZARD IDENTIFICATION by analysis of studies provided by cosmetic industry
• RISK ASSESSMENT by evaluation of literature, available studies, exposure data
• REQUIREMENT FOR ADDITIONAL DATA for reassessment
NOTES OF GUIDANCE
http://europa.eu.int/comm/dg24/health/SC/ncomm6/index_en.htm


❑ SAFETY EVALUATION OF COSMETIC INGREDIENTS
SAFETY OF INGREDIENTS
DANGEROUS SUBSTANCES
OTHER INGREDIENTS
< 100 kg/y
Acute toxicity (oral/dermal/inhalation)
TIF or PIR
Kept for inspection
• RESPONSIBILITY OF MANUFACTURER

❑ SAFETY EVALUATION OF COSMETIC INGREDIENTS

? ? ? CONTENT OF TIF ? ? ?

☞ Administrative dossier

- Name product
- Product category
- Quantitative composition
- Responsibles

❑ SAFETY EVALUATION OF COSMETIC INGREDIENTS

? ? ? CONTENT OF TIF ? ? ?

☞ Administrative dossier

☞ Ingredients dossier

- Identity supplier(s) & composition of ingredients
- Physico-chemical properties
- Microbiological properties
- Toxicity data
- First aid measures
- Risk & safety instructions

❑ SAFETY EVALUATION OF COSMETIC INGREDIENTS

? ? ? CONTENT OF TIF ? ? ?

- ☞ Administrative dossier
- ☞ Ingredients dossier
- ☞ Finished product dossier

- Manufacture details
- Stability
- Physico-chemical properties
- Microbiological data
- Safety data
- Poison Control Centre correspondence
- SAFETY ASSESSOR and credentials
- SAFETY EVALUATION
- Efficacy & claim substantiation
- Packaging & labelling

❑ SAFETY EVALUATION OF COSMETIC INGREDIENTS

? ? ? CONTENT OF TIF ? ? ?

- ☞ Administrative dossier
- ☞ Ingredients dossier
- ☞ Finished product dossier
- ☞ "Follow-up of the market" dossier

- Post-market complaint system
- Complaints + follow-up

❑ SAFETY EVALUATION OF COSMETIC INGREDIENTS

SAFETY ASSESSOR

RISK ASSESSMENT

HAZARD

- **Structural data, QSAR, physico-chemical data, …**
- **Animal studies**
- **3R studies**
- **Human data, clinical studies**

EXPOSURE

- **Type product**
- **Use pattern**
- **Application site**
- **Concentration**
- **Frequency**
- **Amount applied**
- **Chemical composition**
- **Stability**
- **Microbiology**
- **Target group**
- **Percutaneous absorption**

CONTENTS

❑ NEW CHALLENGES

- ☞ SHIFT FROM "*IN VIVO*" TO "*IN VITRO*" TESTING
- ☞ NEW ROLE OF RAW MATERIAL SUPPLIERS
- ☞ NEED FOR APPROPRIATE TRAINING
- ☞ ETHICAL CONSTRAINTS IN HUMAN TESTING
- ☞ SMEs
- ☞ RISK PERCEPTION BY CONSUMER

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❑ NEW CHALLENGES "*IN VIVO*" TO "*IN VITRO*"

3 R's CONCEPT

FORMALLY VALIDATED ALTERNATIVE METHODS (ECVAM, ESAC, SCCNFP, EC)

- skin corrosivity: TER, EPISKIN®,EPIDERM®
- skin sensitisation: LLNA
- phototoxicity: 3T 3NRU-PT
- percutaneous absorption with pig skin
- mutagenicity, photomutagenicity
- acute toxicity: LD50

"VALID" ALTERNATIVE METHODS AS USED BY MAJOR COSMETIC COMPANIES (FINISHED PRODUCT TESTING)

- eye irritation : HET-CAM, ISOLATED EYE TEST, BCOP CYTOTOXICITY TEST
- Skin irritation HUMAN SKIN MODELS + CYTOTOX

Updated list SCCNFP :
http://www.europa.eu.int/comm/dg 24/health/SC/ncomm6/index_en.htm

❑ NEW CHALLENGES "*IN VIVO*" TO "*IN VITRO*"

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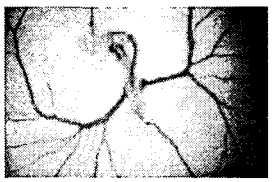

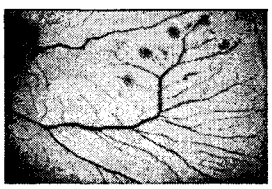

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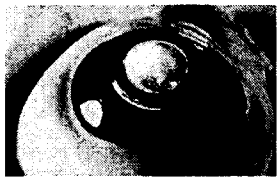

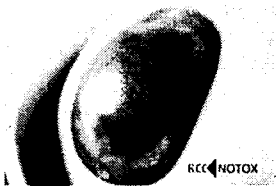

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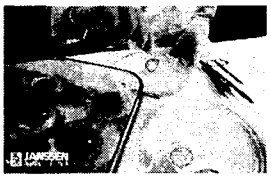

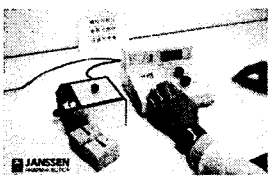

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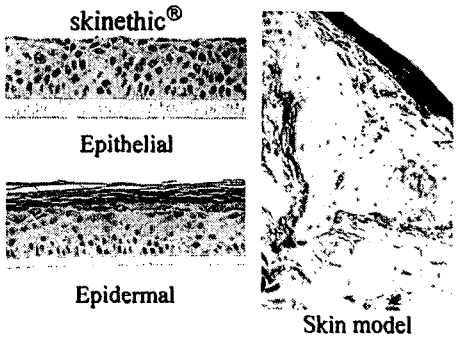

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❑ NEW CHALLENGES "*IN VIVO*" TO "*IN VITRO*"

PROSPECTS FOR NEAR FUTURE

	
- SUBACUTE TOXICITY - CHRONIC TOXICITY - REPRODUCTIVE TOXICITY - CARCINOGENICITY (non-mutagenic) - BIOKINETICS	- ACUTE (ORAL)TOXICITY - SKIN IRRITATION - OCULAR IRRITATION - SKIN SENSITISATION - EMBRYOTOXICITY

❑ NEW CHALLENGES "*IN VIVO*" TO "*IN VITRO*"

FINISHED COSMETIC PRODUCT TESTING USING ALTERNATIVE METHODS

INTERMEDIATE STEP BETWEEN ASSESSMENT OF THE TOXICOLOGICAL PROFILE OF THE COMPOSING INGREDIENTS AND COMPATIBILITY TESTING ON HUMAN VOLUNTEERS

REDUCTION OF POTENTIAL RISK FOR CONSUMER

❑ NEW CHALLENGES "*IN VIVO*" TO "*IN VITRO*"

SAFETY ASSESSMENT OF A FINISHED COSMETIC PRODUCT

1) PHYSICO-CHEMICAL AND QSAR DATA
2) AVAILABLE TOX DATA ON INGREDIENTS OBTAINED *IN VIVO*
3) AVAILABLE TOX DATA ON INGREDIENTS OBTAINED USING ALTERNATIVE METHODS (validated methods)
4) PRODUCT EXPOSURE
5) ADDITIONAL *IN VITRO* TESTS OF FINISHED PRODUCT (validated and "valid" methods)
6) COMPATIBILITY TESTING OF FINISHED PRODUCT ON HUMAN VOLUNTEERS

ETHICS !!!

❑ NEW CHALLENGES "*IN VIVO*" TO "*IN VITRO*"

NEED FOR INTENSIVE TRAINING

SAFETY ASSESSMENT OF COSMETICS IN THE EU

COURSE AT THE VRIJE UNIVERSITEIT BRUSSEL

7-12 APRIL 2003

HTTP://SAFETYCOURSE.VUB.AC.BE