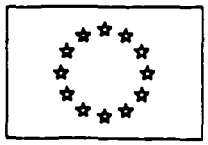

COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 05.05.1997
COM(97) 182 final

1996 COMMISSION REPORT ON THE DEVELOPMENT, VALIDATION AND LEGAL ACCEPTANCE OF ALTERNATIVE METHODS TO ANIMAL EXPERIMENTS IN THE FIELD OF COSMETICS.

TABLE OF CONTENTS

Summary

1 INTRODUCTION AND BACKGROUND

This 1996 report is the third report to be presented by the Commission. It reviews the situation at October 1996, i.e. just before the date by which the Commission had to present draft measures postponing the date for the ban on animal testing in cases where alternative methods of testing have not been scientifically validated as offering an equivalent level of protection for the consumer, taking into account OECD guidelines. It belongs in the context of the sixth amendment to the basic Cosmetic Products Directive adopted by the Council on 14 June 1993 (Directive 93/35/EEC), which provides for the banning of cosmetic products which contain ingredients or combinations of ingredients tested on animals as of 1 January 1998 unless alternative methods are not available by this date, in which case the Commission must present draft measures to postpone the ban. The sixth amendment also provides that the Commission shall present annual progress reports to the EP and Council.

The 1996 report consists of two parts. The first, more general part:

- describes the objectives and constraints which have to be addressed,
- summarises the existing and expected results,
- specifies the conclusions drawn by the Commission from these objectives, constraints and results in preparing its draft proposal for a Directive postponing the deadline of 1 January 1998.

The second part of the report is more scientific. It explains:

- the initiatives taken in 1996 by the various parties involved in the research, validation and legal acceptance of alternative methods.
- the difficulties involved in obtaining statistics,
- the state of progress in each individual domain.

2 OBJECTIVES AND CONSTRAINTS

There are *two key objectives* – namely ensuring the safety of cosmetic products for human health and the elimination/reduction of animal suffering.

- Cosmetic products, which include personal hygiene products, are used throughout a person's life. The Cosmetic Products Directive makes it incumbent on manufacturers to ensure that cosmetic products are safe for human health and, as of 1 January 1997, to keep a safety information

dossier which will be accessible to the monitoring authorities. The Cosmetic Products Directive has also established a system of lists of substances that are banned, subject to restrictions, or authorised respectively. These lists are regularly adapted to technical progress, on the basis of an opinion delivered by the Scientific Committee on Cosmetology, which takes into account the results of tests.

The banning of all new ingredients would not make tests superfluous because the safety of ingredients must be regularly reexamined in the light of scientific progress. Neither can one outlaw all innovation – a measure which would bankrupt numerous SMEs.

– The reduction and elimination of animal suffering is an ethical imperative. Although animal tests in the field of cosmetic products account for a mere 0.03% of all animal tests, they have been given priority.

The report describes the work done in 1996 by the following parties:

* the Commission and notably ECVAM, the European Centre for the Validation of Alternative Methods, a unit of the Joint Research Centre; DG XI "Environment, Nuclear Safety and Civil Protection, which manages Directive 86/609 on the protection of animals used for scientific and experimental purposes; DG XII "Science, Research and Development", in funding research programmes; DG XXIV "Consumer Policy", which manages the Cosmetic Products Directive and the Scientific Committee on Cosmetology.

* the Scientific Committee on Cosmetology;

* COLIPA/the European Cosmetic, Toiletry and Perfumery Association;

* the OECD.

However, the report emphasises that the development, validation and acceptance of alternative methods is a process which has proven more complex and arduous than initially foreseen and that, as in all scientific research, it is impossible to guarantee a precise result by a given date. The report also stresses that the utmost prudence is called for as regards the use of human volunteers, who cannot serve as a substitute for animal experiments pure and simple.

The constraints that have to be borne in mind are mainly:

* compliance with the rules of international trade, notably those of the WTO (World Trade Organisation). The point is that any measure having the effect of banning products from third countries on the grounds that these products have been tested on animals poses problems of compatibility with the rules of international trade. It would appear necessary to investigate the subject in greater detail in the context of preparing an EP

and Council Directive which the Commission intends to propose during the coming months, designed to amend the basic Cosmetic Products Directive so as to address, in a legally appropriate text, the ban on animal testing by regulating in particular the question of finished products.

* the interests of the employment-generating SMEs, which also must be taken into account. Measures must be taken to ensure that they are trained and informed.

3 EXISTING AND EXPECTED RESULTS

The results are summarised in the first part of the report and described in greater detail in the second part.

A distinction must be made between (a) ingredients and combinations of ingredients and (b) finished cosmetic products.

As regards *tests on ingredients/ combinations of ingredients* the report makes it clear that no alternative method offering an equivalent degree of protection is available to date, or likely to be available by 1 January 1998.

Methods which do not involve animal trials will however become progressively available in the fields of percutaneous absorption and local risks to the eye and skin: photoirritation, eye irritation and skin irritation.

However, as regards tests concerning the system risks – i.e. risks involving exposure of the organism as a whole as opposed to local risks – there is no hope that animal trials can be replaced on schedule. However, the number of animals used is being steadily reduced.

In general it will be possible to evaluate the safety of the *finished products* after 1 January 1998 without recourse to animal trials, thanks notably to existing knowledge on the safety of the ingredients, and by methods not involving the use of animals, even if these methods are not liable to be the subject of an OECD guideline, which deals exclusively with ingredients and combinations of ingredients. However, in certain cases there may be a risk of toxic effects, due for example to the interaction of the ingredients or to the fact that skin penetration of the ingredients is facilitated by the vehicle used. In such cases tests on animals would remain necessary.

4 CONCLUSIONS DRAWN BY THE COMMISSION FROM THESE OBJECTIVES, CONSTRAINTS AND RESULTS

The Commission's draft directive designed to postpone the deadline of 1 January 1998 takes into account the objectives, constraints and results described in the report.

The Commission notes that, while progress has been made in research into alternative test methods, notably in the fields of percutaneous absorption and local risks to the eyes and skin, the fact remains that no alternative method has yet been scientifically validated and accepted andthat the OECD has not yet adopted pertinent guidelines on toxicity tests in the field of alternative testing methods.

The situation is unlikely to change before 1 January 1998.

Hence the draft Directive proposes the postponement of the date mentioned in Article 4(1)(i) of Directive 76/768/EEC, in compliance with the second sentence of that provision, until 30 June 2000, before which date it can be foreseen that no alternative testing method will have been adequately scientifically validated and accepted.

It also provides that before 1 January 2000 the Commission shall present draft measures taking into account progress made by that date.

The Commission also wishes to promote research into and the validation of alternative methods.

As regards finished products, the Commission will take measures to promote the dissemination among SMEs of methods not involving the use of animals.

The Commission has also initiated reflections and intends, in the coming months, to present a proposal for a European Parliament and Council Directive on the amendment of Article 4 (1) (i) to address, in a legally appropriate text, the ban on animal testing in respect of finished cosmetic products – barring exceptional cases – as of 1 January 1998, in order to comply with the requirements of Directive 76/768.

This proposal for a Directive should also regulate aspects relating to products from third countries and clarify certain concepts and references in the text that have given rise to questions.

Since the Directive will be based on Article 100a, this Commission proposal requires the approval of the European Parliament and the Council.

PART 1

1996 Commission Report

on the development, validation and legal acceptance of alternative methods to animal experiments in the field of cosmetics.

A. INTRODUCTION AND BACKGROUND

The Commission has already presented two annual reports on 1994 and 1995 data concerning progress in the development, validation and legal acceptance of alternative methods to animal experiments in the field of cosmetics.

This 1996 report reviews the scientific situation at October 1996.

This 1996 report belongs in the context of Directive 76/768/EEC on cosmetic products, whose new Article 4 (1) (i), introduced by Council Directive 93/35 of 14 June 1993, provides that Member States shall ban the placing on the market of cosmetic products containing ingredients or combinations of ingredients tested on animals after 1 January 1998 in order to meet the requirements of this Directive.

However, this Article specifies that "if there has been insufficient progress in developing satisfactory methods to replace animal testing, and in particular in those cases where alternative methods of testing, despite all reasonable endeavours, have not been scientifically validated as offering an equivalent level of protection for the consumer, taking into account OECD toxicity test guidelines, the Commission, shall, by 1 January 1997, submit draft measures to postpone the date of implementation of this provision, for a sufficient period, and in any case for no less than two years, in accordance with the procedure laid down in Article 10. Before submitting such measures, the Commission will consult the Scientific Committee on Cosmetology".

This 1996 report comprises two parts. The first, more general part, describes the objectives and constraints that have to be addressed, the existing and expected results as regards ingredients and combinations of ingredients on the one hand and finished products on the other, and the conclusions drawn by the Commission from these objectives, constraints and results in preparing its draft proposal for a Directive to postpone the deadline of 1 January 1998.

The second part of the report is more scientific. It describes:

- the initiatives taken in 1996 by the different parties involved in the development, validation and legal acceptance of alternative methods, specifying wherever possible the cost of these initiatives

- the difficulties in obtaining statistics

– the state of progress in each individual domain.

B. OBJECTIVES AND CONSTRAINTS

Two principal objectives must be pursued and wherever possible reconciled in the field of cosmetic products: (a) ensuring consumer safety and (b) reducing and, ideally, eliminating animal suffering.

Moreover, various constraints must be borne in mind, the two primary ones being (a) the international arena and the need to comply with WTO rules and the rules of free competition, and (b) the interests of firms, notably employment-generating small and medium-sized enterprises.

1. Consumer safety

Consumer safety must remain paramount. Here it should be noted that the notion of "cosmetic products" encompasses not only so-called "decorative" products, such as lipstick or nail varnish, but also articles such as soap, shampoos, toothpaste which are used throughout a person's lifetime from early childhood on. It is essential that these products should not cause harmful, immediate and visible effects, such as irritation, or long-term, latent effects such as risks of carcinogenicity or teratogenicity, etc.

To ensure that cosmetic products are safe for human health in all these respects, it is necessary to check not only the safety of the finished product but also – and primarily – that of the ingredients used in its manufacture. It is for the manufacturer to ensure the safety of the ingredients, in compliance with Article 2 of the Cosmetic Products Directive, according to which cosmetic products must not be liable to cause damage to human health when they are applied under normal conditions of use; manufacturers may also be held liable in the event of damages pursuant to Council Directive 85/374/EEC on liability for defective products. Pursuant to Council Directive 93/35/EEC of 14 June 1993 amending for the sixth time the basic Cosmetic Products Directive, the manufacturer must, as of 1 January 1995, keep certain information readily accessible to the competent authorities, including "assessment of the safety for human health of the finished product. To that end the manufacturer shall take into consideration the general toxicological profile of the ingredient, its chemical structure and its level of exposure."

The Cosmetic Products Directive also includes a series of annexes featuring positive and negative lists of substances. The general principle is that substances may be used freely, unless they are prohibited (Annex II), or subject to certain limitations and conditions (Annex III). There are three exceptions to this general principle: the only colouring agents, preservatives and UV filters authorised are those featuring in positive lists (Annexes IV, VI and VII).

A substance can only be included in these lists, which are adapted to technical progress each year by a Commission Directive, if it has been the subject of an opinion delivered by the Scientific Committee on Cosmetology concerning its toxicity for human health. This SCC opinion is prepared on the basis of all the existing scientific data and notably the test results furnished by industry, which may concern sensitisation, mutagenicity, eye irritation, skin irritation, photoirritation, carcinogenicity, teratogenicity, and acute, subchronic and chronic toxicity, etc.

While some 7 000 substances are already used in cosmetic products and while for many cosmetic substances new tests are not generally required, it should however be stressed that such tests may sometimes be crucial in reevaluating, on the basis of technical progress and new scientific knowledge, certain substances which have been in use for a very long time. Hence each year the SCC examines a series of banned substances (numbering approximately 400) and substances subject to certain limitations and requirements (numbering approximately 50).

It must also be possible to examine the risks associated with the use of these products in combination. Thus on safety grounds it is not possible to dispense entirely with animal trials, even in respect of substances already in use. Moreover, in the cosmetic products sector – as in all other industrial sectors – it would be neither wise nor reasonable to bring innovation to a standstill. Even if consumers were to foresake their quite legitimate hope of obtaining ever better products, a blanket ban on innovation by outlawing the use of new substances would certainly spell ruin for numerous European cosmetic product manufacturers, mainly employment-generating SMEs.

2. The reduction and elimination of animal suffering

Reduction and, where possible, elimination of animal suffering is an objective that deserves the closest attention and in respect of which resources should be mobilised at all levels.

This objective reflects ethical imperatives concerning respect for life, deep-seated public aspirations, and the wishes of the European Parliament. It finds expression in several European instruments, including Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes and Directive 93/35/EEC (the sixth amendment to the initial Cosmetic Products Directive).

While consumer safety must be assured, we must also do our utmost to ensure that animal tests are replaced by alternative tests as soon as possible, provided these afford an equivalent level of protection. Although animal trials in the cosmetics field account for a mere 0.03% of all animal tests and although all chemical substances already have to be tested in

order to provide the toxicity data required under Directive 92/32/EEC, cosmetic products have been prioritised and there has been a major drive in recent years, notably since the adoption of Directive 93/35/EEC, to promote the development of alternative methods. These endeavours, as well as progress to date and the outlook for the future, are described in the 1994 and 1995 annual reports on the development, validation and legal acceptance of alternative methods to animal experiments in the field of cosmetic products, already presented by the Commission to the EP and the Council.

Notably, these reports describe the work done by a number of players. Part II reviews the activities of these players in 1996.

In particular, these players are:

ECVAM (the European Centre for the Validation of Alternative Methods), a unit of the Ispra Joint Research Centre, which coordinates the validation of alternative methods at Community level, provides a forum for pooling information and works on the development, updating and management of a database and promotes dialogue between all interested parties.

In 1996 *ECVAM* continued to organise workshops of direct relevance to evaluating the safety of cosmetic products (based on e.g. data concerning alternative methods); it published in ATLA recommendations methods for assessing percutaneous absorption and for skin sensitisation testing, and recommendations on the application of biostatistical methods to the development and validation of alternative toxicological methods; it subsidised and coordinated a study for testing UV filters listed in Annex VII to the Cosmetic Products Directive (photoirritation); it conducted a formal validation study on four tests of skin corrosion, and maintained regular contacts with the OECD and began a number of prevalidation studies relevant to the cosmetics industry.

The Commission (*DG XI* "Environment, Nuclear Safety and Civil Protection") which manages Directive 86/609/EEC on the protection of animals used for experimental or other scientific purposes, has continued to follow the matter. The Commission (*DG XII* "Science, Research and Development") has also subsidised research programmes including the development of alternative methods.

In the context of its consumer policy, the Commission *(DG XXIV)* has funded research and participated in or organised meetings with all the partners involved and organised and followed up the meetings of the SCC.

The Scientific Committee on Cosmetology – whose mandate is to deliver scientific opinions to the Commission on ingredients listed in the Annexes to the Cosmetic Products Directive and on the applicability of alternative methods validated in the process of evaluating the safety of cosmetic products, and on the proposal for a Directive which the Commission must

present concerning the postponement of the deadline for the ban on animal tests in cases in which alternative methods will not be available by 1 January 1998 – met on numerous occasions in 1996 both in plenary and in its Alternative Methods Subcommittee, sometimes jointly with the European Industry. Besides the activities documented in Part II, the SCC adopted in 1996 a document titled "The use of alternatives to animal studies in the safety evaluation of cosmetic ingredients or combinations of ingredients".

Finally, at *OECD* level, work has been done on percutaneous absorption (meeting of the national coordinators in Paris in September 1996).

It is important to note that the development, validation and acceptance of alternative methods cannot be achieved overnight, despite all the effort that is being invested.

Hence the validation phases – i.e. the complex process by which the pertinence, reliability and reproducibility of a test developed for routine application and legal acceptance is evaluated and monitored – have turned out to be more numerous and complex than initially foreseen, and new phases have had to be incorporated.

Moreover, as in the case of all scientific research, it is well-nigh impossible to guarantee a precise result by a given date, and certain studies, which were thought to be on the verge of completion – such as the EU/HO study on alternatives to the Draize test – turned out to be disappointing as regards the predictability of the risk.

As regards alternative tests on human volunteers, for example in the field of skin irritation, the utmost prudence is called for; such tests should only be countenanced in the proven absence of real risks.

For all that, progress to date has already made it possible to substantially reduce the number of animals used and to mitigate their suffering, - for example the use of three basic in vitro mutagenicity tests will obviously lead to further improvements in the future.

3. International aspects and the GATT/TBT rules

It is important to note that any measure that leads to banning the importation of cosmetic products into the Community solely because these products or their ingredients have been tested on animals might prove incompatible with the rules of international trade. The main restriction that public international law imposes on a state is to forbid - except in the event of a specific rule to the contrary - any exercise of its power on the territory of another state.

Firstly, the WTO outlaws quantitative restrictions on imports (Art XI§1). Moreover, Article III§4 proscribes all discriminatory measures between *like* products, i.e. in accordance with the accepted interpretation, products which do not present physical differences. Since the test method clearly has no physical effect on the product, a discrimination based on this criterion might be held to fall foul of Article III§4.

Finally, such a measure would not be easy to justify in the context of the general exceptions featured in Article XX of the GATT (and more specifically subsection b), which authorises – within the terms of Article XX – measures "necessary to protect human, animal or plant life or health". In the absence of case law in this area, it is not possible to claim that protection of animal welfare could be covered by the exception.

Secondly, as regards measures designed to verify compliance with the provisions of the Cosmetic Products Directive – viz. requirements in regard to the protection of human health – the provisions of the Agreement on Technical Barriers to Trade (TBT) and notably those of Article 6 must be borne in mind. Article 6 promotes the mutual recognition of conformity evaluation procedures: "Members shall ensure that, whenever possible, that results of conformity assessment procedures in other Members are accepted, even when these procedures *differ* from their own, provided they are satisfied that those procedures offer an assurance of conformity with applicable technical regulations or standards *equivalent* to their own procedures".

Bearing these provisions in mind, the extraterritorial application of a Community measure banning animal trials could be considered as contrary to the Community's international commitments. Moreover, Article 4(1)(i) of this Directive specifies that the ban on animal testings may be postponed if there are no scientifically validated alternative methods which offer the consumer an *equivalent* degree of protection. Hence it would be difficult to deny the equivalence, from the viewpoint of human health protection, of animal tests with alternative test methods which are recognised as equivalent.

It should be noted that the rationale behind the ban is not that animal tests do not permit correct assessment of compliance with the provisions of the Cosmetic Products Directive, but is based purely on ethical considerations.

Thus any decision on the use of alternative methods could also be challenged if it were adopted on a unilateral basis. Moreover the TBT Agreement strongly encourages the members of the WTO to adopt the pertinent international systems for assessment of the conformity of a technical regulation (Article 9). However, Article 9 also specifies that this applies only to the extent that these international systems are in compliance with the provisions of Articles 5 and 6 of the selfsame TBT Agreement (Article 9§3).

Thus it is very important to remain at least within the framework of the Organisation for Economic Cooperation and Development (OECD), to which moreover Directive 93/35 refers.

Part II of this report explains the role played by the OECD in regard to alternative methods in the different domains of the safety of cosmetic products and highlights the close links which the Commission has also developed and maintains with the OECD in this specific field.

The Commission is reflecting on to all matters relating to the rules of international trade in the context of preparing a proposal for a European Parliament and Council Directive designed to amend the basic Cosmetic Products Directive to address, in a legally appropriate text, the ban on animal testing, notably by regulating the question of finished cosmetic products.

4. The interests of the SMEs

Finally, apart from consumer safety and the ethical imperative to reduce/eliminate animal suffering, the reasonable interests of the cosmetics industry should also be taken into consideration, notably those of the employment-generating SMEs. The alternative methods to be developed should be accessible to SMEs, even if they do not have as many "in-house" toxicologists or the same amount of experience or field data, or the internal laboratories and financial resources available to the large firms.

In this context, COLIPA will be launching a major drive to provide information and training, in collaboration with its large member firms. Moreover, it seems that specialised laboratories are springing up whose services the SMEs will be able to draw on for alternative trials, as and when such trials reach maturity.

ECVAM could also be involved – possibly together with COLIPA (Scaat) – in training SMEs in the use of alternative methods for evaluating the safety of cosmetic products.

C. EXISTING AND EXPECTED RESULTS

1. Tests on ingredients and combinations of ingredients

It should be noted that, as shown in Part II, no alternative method offering consumers an equivalent degree of protection has yet been scientifically validated and accepted by the regulatory authorities. The OECD has not yet adopted pertinent guidelines for toxicity tests in the field of alternative testing methods for ingredients and combinations of ingredients used in cosmetic products.

However progress has been made and it looks as though alternative methods will progressively become available in the various safety domains pertaining to percutaneous absorption and local risks to the eye and skin (photoirritation, eye irritation and skin irritation).

However, these methods will not be validated *and accepted* by 1 January 1998, despite the high expectations that were had, mainly in regard to percutaneous absorption and photoirritation.

In regard to percutaneous absorption and local risks, the situation is as follows:

Photoirritation

Photoirritation mainly concerns UV filters. A special study to follow the EU/COLIPA validation study is scheduled for 1996. This is directed by Zebet, and subsidised and coordinated by ECVAM. The study should make it possible to test UV filters in Annex VII to the Cosmetic Products Directive and to prepare a protocol with a view to submitting a draft guideline to the OECD. The first results of this special study should be available by September 1997.

Percutaneous absorption

In May 1996, after discussions with the Commission, the industry presented the OECD with a draft new guideline on in vitro percutaneous absorption. "In-house" data were provided to support this dossier. A meeting of the OECD national coordinators' group was held in Paris in September 1996, but the rate of progress toward acceptance slow.

The Scientific Committee on Cosmetology has emphasised that the test protocols used by industry had not yet been subjected to the formal validation study and that the documentation was incomplete. However, the SCC has in recent years agreed to use in vitro percutaneous absorption data in evaluating the safety of several cosmetic ingredients.

Eye irritation

The 1995 Report stressed that the results of the validation studies of alternative methods to the Draize eye irritancy test had been disappointing (EU/Home Office study and COLIPA study).

ECVAM and COLIPA held a meeting in December 1996 to discuss the outcomes of the EC/HO and COLIPA studies and plan new initiatives.

Skin irritation

ECVAM has conducted a formal validation study involving four skin corrosion tests, whose results are expected in 1997.

The OECD is also planning a draft testing strategy to determine the skin irritation potential of chemical substances.

The draft OECD strategy is to use a hierarchical approach by eliminating severe skin irritants through consideration of the structure activity relations (SAR's) and structure property relations (SPR's) and data obtained from in vitro corrosion tests, before considering the use of conventional in vivo tests on rabbits or the use of human volunteers.

A summary of the situation regarding local risks shows that progress should proceed apace but that 1 January 1998 is too early for the replacement of animal trials. However, as regards reducing the number of animals and their suffering, it may be noted that in practice in vitro tests are already used as screening or guideline tests and that certain data have already been provided to the SCC.

Skin sensitisation

Research has led to a better understanding of the scientific bases of skin sensitisation.

ECVAM is to take action in the light of the report of the ECVAM workshop on this topic.

Mutagenicity

The combination of three basic in vitro tests already makes it possible to demonstrate a mutagenic potential and this combination is already being applied in evaluating the safety of cosmetic ingredients.

All tests on ingredients relating to systemic effects

(Acute toxicity, subchronic toxicity, carcinogenicity, teratogenicity). Because they are linked to exposure of the organism as a whole, there is no hope that alternative methods to replace animal trials will be available in the foreseeable future.

However, the refinement of the methods used has already made it possible to reduce the number of animals used and mitigate their suffering, and this trend is likely to continue.

2. Finished cosmetic products

As regards finished cosmetic products, progress to date suggests that it will generally be possible to evaluate their safety on the basis of available knowledge on the toxicity of their ingredients and their physicochemical properties, using methods which do not involve the use of animals, even if these methods are not liable to be the subject of an OECD guideline which deals dealing only with ingredients and combinations of ingredients.

Hence it will only be necessary to resort to animal testing in rare, exceptional cases, where there are grounds to fear that the toxic effects of the ingredients may be potentiated, notably when skin penetration of the ingredients is facilitated by the vehicle used or when such effects result from the interaction of the ingredients. The SCC has emphasised this fact in its Guidelines on the use of alternative methods to animal studies in the safety evaluation of cosmetic ingredients or combinations of ingredients of 24 May 1996.

Certain cosmetics firms already very often use methods which do not involve the use of animals to test their finished products.

COLIPA (the European Cosmetic, Toiletry and Perfumery Association) has announced that it could progressively establish a voluntary ban on animal testing for finished cosmetic products – except in the exceptional cases referred to above – for the entire European cosmetics industry, and that it would be willing to organise technology transfer in this respect. COLIPA has also said that it could ensure the widest possible dissemination of findings in this area and promote training in European companies and laboratories; this training could be coordinated by the Commission's services. The Commission, in particular, will promote the dissemination of methods not involving animals among the SMEs. It could also endeavour to promote such measures at international level.

D. CONCLUSIONS DRAWN BY THE COMMISSION FROM THESE OBJECTIVES, CONSTRAINTS AND RESULTS IN ITS DRAFT DIRECTIVE PARTIALLY POSTPONING THE DEADLINE OF 1 JANUARY 1998 AND IN ITS REFLECTIONS ON THE PRESENTATION OF A PROPOSAL FOR A EUROPEAN PARLIAMENT AND COUNCIL DIRECTIVE AMENDING ARTICLE 4(1)(I) OF THE BASIC DIRECTIVE

1. The draft Directive prepared by the Commission takes account of the fact that, while progress has been made in research into alternative test methods, notably in the fields of percutaneous absorption and local risks to the eyes and skin, the fact remains that no alternative method has yet been scientifically validated and accepted. The OECD has not yet adopted pertinent guidelines for toxicity tests in the field of alternative testing methods.

The situation is unlikely to change before 1 January 1998.

Hence the draft Directive proposes the postponement of the date mentioned in Article 4(1)(i) of Directive 76/768/EEC, in compliance with the second sentence of that provision, for not less than two years.

Currently it is difficult to predict precisely when certain alternative methods for testing certain ingredients or combination of ingredients will be scientifically validated. However as it is likely that alternative methods will progressively become available in the field of percutaneous absorption, photoirritation, eye irritation skin irritation and skin sensitivation, and whereas, besides, the Commission is mindful of the objective of Article 4(1)(i), the draft Directive postpones the deadline to a date by which it can be foreseen no alternative method will have been adequately scientifically validated and accepted, viz. 30 June 2000. It also stipulates that before 1 January 2000 the Commission shall present draft measures taking into account progress made by that date.

Finally, in the context described above, and also in compliance with the provisions of Article 130f(3) of the Treaty and Fourth Research Framework Programme, the Commission will take the necessary measures to promote research into and the validation of alternative methods to animal testing in the field of ingredients and combinations of ingredients in cosmetic product formulations. This could take the form of a recital in the draft proposal for a Directive.

2. Presentation of a proposal for a European Parliament and Council Directive amending Article 4(1)(i) of the basic Directive

In the context described in point C.2. above relating to the existing and expected results for finished cosmetic products, the Commission has initiated reflections and intends, in the coming months, to present a proposal for a European Parliament and Council Directive amending Article 4 (1) (i) in order to address, in a legally appropriate text, the ban on animal testing in regard to finished cosmetic products – barring exceptional cases – as of 1.1.1998, in order to respect the obligations of Directive 76/768.

This proposal for a Directive should also regulate, in a legally appropriate text, aspects concerning products from third countries, and clarify the concept of "finished products".

Since the Directive will be based on Article 100a, this Commission proposal requires the approval of the Council and the European Parliament.

E. CONCLUSIONS AND OUTLOOK

1. This report reviews the situation in the immediate run-up to the date by which the Commission must present a draft measure postponing the deadline of 1 January 1998 in areas in which alternative methods for testing ingredients and combinations of ingredients will not be available by that date.

2. Two objectives must be pursued: consumer safety, which the Commission insists must not be compromised in any way, and the elimination/reduction of animal suffering.

* Banning all new ingredients would not remove the need for animal tests because the safety of ingredients has to be reexamined in the light of new scientific knowledge. Moreover, blocking all innovation could put firms out of business and in particular the employment-generating SMEs. It should be noted also that cosmetic products include personal hygiene products, products for babies (...) and not only so-called "decorative" products.

* Priority should be given to eliminating animal suffering in the field of cosmetic products, even if tests in this domain account for a mere 0.03% of all tests. The Commission (ECVAM, DG XI, XII, XXIV), the Scientific Committee on Cosmetology, the OECD and Industry continued to work to this end in 1996.

However the validation process has turned out to be more complex than foreseen. In the SCC's opinion the utmost prudence is called for as regards the use of human volunteers, who cannot simply serve as a stand-in for animal experiments.

3. Two constraints must also be borne in mind:

a) compliance with the rules of international trade, notably those of the WTO(World Trade Organisation). The point is that any measure having the effect of banning products from third countries on the grounds that these products have been tested on animals poses problems of compatibility with the rules of international trade. It would appear necessary to investigate the subject in greater detail in the context of preparing an EP and Council Directive which the Commission intends to propose during the coming months, designed to amend the basic Cosmetic Products Directive so as to address, in a legally appropriate text, the ban on animal testing by regulating in particular the question of finished products.

b) the interests of the SMEs, which must be trained and informed.

4. As regards the existing and expected results, a distinction must be made between ingredients/ combinations of ingredients and finished products.

a) As regards ingredients and combinations of ingredients, no alternative method will be ready by 1 January 1998. However, methods should progressively become available for percutaneous absorption, photoirritation, eye irritation skin irritation and skin sensitivation.

However, in the case of tests concerning system risks, i.e. exposure of the entire organism, there is no hope for alternative methods maturing in the foreseeable future.

b) In general, it should be possible to ensure the safety of finished products, thanks mainly to our knowledge of the ingredients, without resorting to animal testing, after 1 January 1998. However, the SCC has emphasised the need for exemptions to this rule in the case of toxic effects caused, for example, by interactions of the ingredients.

c) Progress has however already made it possible to reduce the number of animals used.

5. The Commission has drawn conclusions from these objectives, constraints and expected results:

– the Commission has prepared a draft Directive postponing the date of 1 January 1998 in regard to ingredients and combinations of ingredients.

The Commission has also decided to pursue its deliberations on presenting a proposal for a European Parliament and Council Directive amending Article 4 (1) (i) of the basic Directive in order to address the ban on animal testing, notably by regulating the question of finished products.

PART 2

SCIENTIFIC ASPECTS

A. INITIATIVES TAKEN IN 1996

1. ECVAM

Of the workshops organised and/or published by ECVAM in 1995 and 1996 on the development and validation of alternative tests, those of direct interest to the assessment of consumer safety are as follows:

– Workshop 13.	Methods for Assessing Percutaneous Absorption Angera, Italy; 30 May-3 June 1994 Howes et al. (1996) ATLA 24, 81-106
– Workshop 16	Acute toxicity testing in vitro and the classification and labelling of chemicals Angera, Italy; 18-22 April 1994 Seibert et al. (1996) ATLA 24, 499-510
– Workshop 19	Alternative methods for skin sensitisation testing Angera, Italy; 24-28 April 1995 de Silva et al. (1996) ATLA 24, 683-705
– Workshop 24	The development and validation of expert systems for predicting toxicity Angera, Italy; 1-4 October 1996 Dearden et al. (1997) ATLA 24, in press
– Workshop 25	Current Status and Future Development of Databases on Alternative Methods Neublberg, Germany; 12-15 September 1996. Report in preparation.

ECVAM has also published in ATLA recommendations on the application of biostatistical methods in the development and validation of alternative toxicological methods (ATLA 24, 511-530, 1996).

Of the other ECVAM Task Forces, those dealing with Prevalidation, Skin Irritation and Integrated Testing are also particularly relevant to the cosmetic testing issue.

In addition to the ECVAM validation studies on skin corrosivity and phototoxicity, prevalidation studies were begun on modified protocols for the bovine corneal capacity and permeability (BCOP) test and the fluorescein leakage (FL) test.

2. Scientific Committee on Cosmetology (managed by DG XXIV)

The Alternative Methods/Guidelines Subcommittee of the SCC organised three joint meetings with COLIPA/SCAAT (15 February 1996, 19 March 1996, 24 April 1996), a meeting with the Director of ECVAM (6 March 1996) and a meeting designed to draw conclusions and adopt an opinion (6 May 1996), following consultations with DG XXIV.

During these meetings the following points were addressed:

a) Preparation of a discussion document on the use of alternative methods to animal studies in the safety evaluation of cosmetic ingredients or combinations of ingredients.

b) Examination of the final report on the EC/HO study on the validation of the Draize eye irritancy test.

c) Examination of the statistical assessment data of phase 1 of the COLIPA study – validation of the eye irritancy test in the rabbit.

d) Discussion with ECVAM's Unit head on the implementation of the provisions of Article 4 of Directive 93/35/EEC, involving a general review of the validation studies.

e) Discussions with COLIPA/SCAAT on Industry's approach to the implementation of Directive 93/35/EEC, which is based on the experience of the cosmetic firms and the outlook for replacing animal tests.

3. DG XII

Since 1985 the Commission has been supporting research in the field of new in vitro alternatives to animal experiments in pharmaco-toxicology applicable to the cosmetic industry.

The BIOTECH II programme launched after the BAP, BRIDGE and BIOTECH I programmes is also contributing to the development of these in-vitro alternatives applicable to cosmetic products. Following the second call for proposals, three projects are being funded with a total budget of ECU 3 825 000.

The projects are:

* BIO4-CT96-0086:
  New immuno-pharmaco-toxicological model: human reconstructed epidermis containing Langerhans cells
  Coordinator: Dr. Rainer Schmidt
  L'OREAL S.A.
  Centre Charles Zviak
  9a, rue du Général Roguet
  F - 92383 Clichy Cedex

* BIO4-CT96-0036:
  Development of *in vitro* systems using human immortalized cell lines for testing skin irritancy
  Coordinator: Professor Charles Lapière
  Laboratory of Experimental Dermatology
  Université de Liège
  Tour de Pathologie, B 23
  B - 4000 Liège

* BIO4-C96-0246:
  Development for *in vitro* tests for drug allergenicity and B cell switching to IgE synthesis
  Coordinator: Dr. I. W. Coleman
  Department of Pharmacology & Therapeutics
  New Medical Building
  Ashton Street
  GB - Liverpool L69 3BX

4. COLIPA

COLIPA/SCAAT (the European Cosmetic, Toiletry and Perfumery Association/ Steering Committee on Alternatives to Animal Testing)

Following the international two-day scientific symposium organised at the end of 1995, Scaat has continued its efforts towards getting validated alternative methods accepted and introduced into the regulatory framework.

On EYE IRRITATION, the results of the COLIPA validation study became fully available and were submitted for review to ECVAM and to the SCC and DG XXIV. The relevant working party has drafted a first paper on the outcome of the study, which has been accepted for

publication in *Toxicology In Vitro*. Further statistical analysis of the data generated by the study is in progress.

On SKIN IRRITATION, the specific working party is drafting guidelines on human testing of cosmetic ingredients, expected to be available early 1997. This follows the issuing of guidelines on human testing of finished products, issued in 1995 and now published in *Food and Chemical Toxicology*. Both guidelines incorporate the need for strict ethical standards for such testing.

On PERCUTANEOUS ABSORPTION, a working party has been collecting data generated by the cosmetic industry substantiating the validity of in vitro testing, as laid down in the COLIPA guidelines prepared in 1995. An extensive data package has been made available to ECVAM, to OECD, and to the SCC and DG XXIV.

On PHOTOIRRITATION, a second phase of the EU/COLIPA validation study has been successfully completed and discussed with the SCC. The SCC has asked for a special study to verify the applicability of the in vitro method for UV-filters listed in Annex VII of the Cosmetics Directive. This special study will be sponsored by ECVAM and carried out over the next year.

SCAAT has also created a working party "SKIN SENSITISATION". The main objective of this new group is to define and execute a research programme on mechanisms, which could pave the way to suitable in vitro test methods.

5. OECD

OECD Guidelines for the Testing of Chemicals and the Principles of Good Laboratory Practice (GLP) are developed in the broader context of the concept of mutual acceptance of data. Both of these instruments for ensuring harmonized data generation and data quality are an integral part of the 1981 OECD Council Decision on the Mutual Acceptance of Data (MAD). In accordance with this decision, OECD's 28 Member Countries agree that data generated in the testing of chemicals in any OECD Member Country, when in accordance with OECD Test Guidelines and Principles of GLP, shall be accepted in any other Member Country for the purpose of assessment and other uses relating to the protection of man and the environment. The practical consequence of this decision is that data developed in a Member Country under these conditions and submitted for fulfilling regulatory requirements in another Member Country, cannot and will not be refused. Consequently, OECD Test Guidelines are globally accepted as the standard methods for safety testing and as such enhance the validity and international acceptance of test data. Recognising the significance of OECD Test Guidelines, the European Commission strongly supports work on the development of new test guidelines and the updating of existing ones.

B. STATISTICS ON ANIMAL EXPERIMENTS

On numerous occasions the Commission has urged the Member States, both orally and in writing, to provide the necessary statistics.

1995:

1. Eight Member States reported that finished cosmetic products had not been tested on animals on their territory (Italy, Greece, Belgium, Ireland, Sweden, Finland, Luxembourg, Germany).

2. Six Member States reported that cosmetic ingredients had not been tested on animals on their territory (Greece, the Netherlands, Ireland. Sweden, Finland, Luxembourg).

3. Only three Member States (Austria, France, the United Kingdom) communicated figures on the number of animals used, while emphasising that these figures were not interpretable and that there was uncertainty as to what they really signified. In these circumstances the 1995 Report could not present comparative tables comprising numerical data, because such a table would have given a false picture of reality.

4. As regards the declarations on the absence of tests, it is worth mentioning that certain Member States that do not manufacture ingredients will certainly be using ingredients tested in other Member States or in third countries and that certain ingredients used in cosmetic products may have been tested for other purposes.

Following the final reminder from the Commission in October 1996:

- Ireland and Finland confirmed that cosmetic products had not been tested on animals in their countries in 1996. Sweden did likewise for 1995 but reported that in November 1996 it did not have data relating to 1996.

- Portugal reported that cosmetic products were not tested on animals in its country.

- Germany confirmed that finished products were not tested on animals and that it had no data as regards ingredients testing.

- Finally, in the Netherlands the Experiments on Animals Act, which entered into force on 5 February 1997, provides that animal experiments may not be carried out with a view to developing new cosmetics or to testing existing cosmetics which come within the remit of the Commodities Act.

The Commission regrets that it does not have more statistics and is pursuing its efforts to obtain them.

C. STATE OF PROGRESS IN 1996 IN EACH INDIVIDUAL AREA

1. Photoirritation/phototoxicity

ECVAM/COLIPA

The biometric analysis (= statistical evaluation) of the data produced during the second validation phase has been completed for the 3T3 NRU PI[1] cell viability test.

The raw data were imported into an EXCEL file and checked for internal consistency. A new mathematical model was developed to analyse the complex dose-response relationships.

The predictive value was evaluated by comparing the in vivo photoirritation classification of the materials tested with the classification based on the values and biological endpoint of the in vitro test.

The variability of the in vitro classification was calculated on the basis of the rate of classification errors.

The degree of association between the results of the tests conducted by the different laboratories was subjected to statistical analysis.

The results of the biometric analysis (dated 29° March 1996) **indicate that the NRU assay is capable of correctly predicting the irritation potential in man** in regard to most of the substances tested. It may be noted that:

a. (In many cases) the PIF does not represent the exactly measured values but estimates which are below or above the critical value (>5<) established in phase I of the validation study.

b. The prediction model proposed in the SOP (Standard Operation Procedure) of the 3T3 NRU test predicts well the in vivo phototoxicity of most of the substances tested.

c. The variability of the PIF values grows with the increase in absolute PIF values.

The number of independent tests in each laboratory was too small to authorise a valid estimate of intralaboratory variability data;

---

1 NRU: Neutral red uptake assay", which uses the cells as target and cell toxicity as the outcome.

d. The effects of data variability on the in vitro classification are negligible, as the computer analysis of the classification errors demonstrates.

The technical problems responsible for the incorrect classification of certain test materials have been identified and will be taken into account in evaluating the performance of the 3T3 NRU PI test in the final report.

In particular, one should bear in mind:

- possible in vivo classification errors
- errors in preparing the solution due to the total lack of information on the coded test substances
- the deviations in regard to the SOP.

SCC

Following an SCC recommendation, which emphasised the importance of verifying the applicability of the NRU test in evaluating the safety of Annex VII UV filters and creating a database, **a third experimental phase**, *directed by ZEBET, and subsidised and coordinated by ECVAM*, **is planned for 1996**. The objectives of this study are **to test the Annex VII UV filters** and to prepare an optimised protocol with a view to **submitting a draft guideline on in vitro photoirritation to the OECD. The first results** of the third phase **should be in by September 1997.**

OECD

The OECD group of national coordinators has decided not to develop the in vivo method on its schedule before termination of the third in vitro validation phase at end 1997. If the in vitro method has not been completed by that date, the OECD will try to develop the in vivo method.

2. Percutaneous absorption

COLIPA

In May 1996 a method proposed in the ECVAM workshop report, as discussed by the industry, ECVAM and OECD secretary, was presented to the OECD.

This draft, which is currently being studied by the OECD group of national coordinators, explicates the general principles governing the design of protocols for skin penetration tests using the excised skin of different mammalian species post mortem. The skin is excised from the dead animals:

[– "know-how" regarding the substance tested and choice of vehicle;

- choice of the type of cell, receptor fluid, cutaneous membrane and control of membrane integrity;
- potential significance of the skin metabolism;
- (finite or infinite) dose and duration of application;
- temperature and humidity conditions;
- sample collection and analysis;
- presentation of the results and content of the final report.]

To support this guideline COLIPA submitted to the OECD, ECVAM and the SCC a dossier consisting of "in-house" data and articles from the literature designed to demonstrate the predictive value, reliability and robustness of the in vitro approach.

It may be summarised as follows:

* Predictive value

  The in vitro tests are useful predictors of in vivo cutaneous absorption.

  [Bearing in mind the variability of in vivo data, there is good correlation between
  - in vitro (pig) and in vivo (rat) data for 10+8 hair dyes;
  - in vitro (rat) and in vivo (rat) data for 8 coded substances of different solubility;
  - in vivo (pig) and in vitro (man) data for 7 colouring agents;
  - in vitro (pig) and in vivo (man) data for 1 UV filter in ethanol solution.

The skin of the pig's ear is a very good model of the human skin in in vitro cutaneous absorption tests of oestradiol.]

It is possible to design prediction models of skin pharmacokinetics on the basis of in vitro tests.

[The in vitro data in the rat can be used in combination with a skin pharmacokinetic mode.

The model correctly predicts experimental in vivo measurements in man for an ester in suspension in a mixture of organic solvents and surfactants.]

* *Reliability*

  "In-house" experience in this domain pertained to different categories of cosmetic ingredients, including UV filters, hair dyes, surfactants, mineral hydrocarbons, etc.

* *Robustness*

The dossier contains scanty information on the intra- and interlaboratory variability of the results and their statistical analysis.

[The skin penetration coefficients (Kp) and their standard deviations give an idea of the degree of reproducibility of the results obtained in a series of in vitro tests conducted on benzyl alcohol. Good interlaboratory reproducibility is observed in *one* study conducted in two laboratories using the same in vitro protocol (rat) to measure the skin penetration of two UV filters.]

* Influence of operating conditions

There are some articles in the literature that provide patchy and unsystematic information on the influence of storage conditions, the type of cell used, and the batches of skin used.

[– The use of the excised skin of fresh or deep-frozen pig does not influence the results for two UV filters (lipophiles) and lactic acid (a hydrophile);
– the type of cell used (static or continuous flux) does not influence the cutaneous absorption of water-soluble substances through various types of membranes taken from different species (pig, rat, man) into different destination solutions;
– the choice of the destination solution is crucial for substances which have low solubility in water;
– batches of skin taken from three different animals (rats) do not influence the data on cutaneous absorption and distribution through the skin in respect of two UV filters tested using the same vehicle.]

OECD

The USA and the EU are at odds about the in vitro approach within the OECD's group of national coordinators.

At its 7th meeting, held in Paris on 18 and 19 September 1996, **the group of national coordinators decided:**

1. **to devote a forthcoming workshop to the study of existing in vitro percutaneous absorption data;**
2. **to base the decisions on** a guideline document to be prepared in the coming year by the OECD Secretariat on **the criteria for the validation and acceptance of alternative methods** (on the basis of the Solna workshop report);
3. to develop a dual guideline on in vivo and in vitro tests, in the event of rapid development of the in vitro dossier.

SCC

Although the SCC has emphasised that **the test protocols used by industry were not subjected to a formal validation test** and although it recommended that the existing documentation be supplemented, notably as regards intra- and intra-laboratory reproducibility and the influence of the vehicle on the release of the cosmetic ingredients, **the SCC is convinced of the relevance of the in vitro methods** and has in recent years agreed to draw on in vitro percutaneous absorption data in the evaluation of the safety of several cosmetic ingredients for human use.

3. **Eye irritation**

ECVAM/COLIPA

The international EC/HO validation study of alternatives to the Draize eye irritancy test did not achieve the expected objectives but it inspired the organisation of an ECVAM/ERGATT workshop on the practical aspects of validation and the preparation of a prevalidation schedule by ECVAM, as well as the planning of the COLIPA study.

Limited results were obtained for a small number of protocols **in COLIPA's first international validation phase** of alternatives to the Draize test, where prediction models had been prepared for each test.

Statistical evaluation of the results of the first validation phase indicate that the most promising protocols are FLtest[2], TEA[3] and RBCtest,[4] which conform reasonably with their prediction models; however, for the first two more reproducibility data is required because in each case they have only been used by two large laboratories, while the utility of the FL and RBC tests has been challenged because the pertinence of their classification models is not universally supported. Moreover, no attempt has been made to evaluate the idea of a battery of two or more tests to replace in vivo assays.

Currently there are no validated alternative methods capable of replacing the OECD-405 in vivo eye irritancy test.

4. **Skin irritation**

ECVAM

---

2 Fluorescein leakage test, measures the damage caused to a cell barrier.

3 Tissue Equivalent Assay, measures the time required to cause a 50% reduction in the viability of cells in reconstituted human skill.

4 Red blood cell haemalysis test, used to evaluate damage to the cell membranes.

Following a prevalidation exercise in 1995 on skin corrosion tests (TER, CORROSITEX and SKIN and EPISKIN), **ECVAM undertook a formal validation study** involving four skin corrosion tests and 60 test materials, whose results are expected in 1997.

Considerable progress has been made in developing a database to predict irritation potential. However the in vitro tests currently being validated concern highly irritant substances and so this research – which is very useful for classifying and labelling dangerous substances – is only of limited use in evaluating the skin tolerance of cosmetic ingredients, which are a priori weakly- or non-irritant substances (at their concentration of use).

There are to date no validated alternative methodologies capable of replacing the OECD 404 in vivo skin irritancy test. An ECVAM workshop on human skin equivalents and their uses is planned for 1997.

OECD

A draft test strategy for determining the skin irritation potential of chemical substances is **on the programme of the OECD** group of national coordinators.

The strategy proposed by the OECD envisages first eliminating the most irritant substances through examination of the structure activity relations and structure property relations, as well as by using information derived from in vitro corrosion tests, before considering recourse to conventional tests on rabbits, in vivo, or the use of human volunteers.

5. Skin sensitisation

Identifying skin irritation potential which manifests itself as contact allergy is important in evaluating the safety of cosmetic ingredients.

The impressive research work done up to now has helped clarify our understanding of the mechanistic bases of skin sensitisation. It seems that predicting sensitisation potential is feasible only by combining information derived from several supplementary tests.

ECVAM

The report of ECVAM workshop 19 reviews the situation and contains recommendations for research aimed at replacing current animal tests, viz.:

* refine the DEREK expert system identifying the structural alerts of skin sensitisation and develop supplementary systems based on the SARs (Structure Activity Relationships)

- standardise the tests "on cultures" of the most promising in vitro cells, and notably study the essential role of mediators derived from human dendritic cells and standardise the methods of isolating and cultivating these cells
- develop other in vitro models, notably on skin explants
- develop an in vitro skin metabolism system
- develop an adequate database on the basis of these tests, through a validation exercise using a suitable in vivo database.

ECVAM hopes to support a prevalidation study on an in vitro test, in 1997.

Bearing in mind the complexity of the process and the fact that predicting sensitising potential is a difficult task because of the variability of individual response, **definitive results in this domain can be expected only in the medium term, if not indeed the long term.**

6. Skin compatibility of the finished product

The guidelines prepared by COLIPA in November 1995 on evaluating the skin compatibility of ***finished cosmetic products*** in the framework of strictly controlled clinical studies, which were informed by ethical considerations and based on prior knowledge of the composition and stability of the tested products and prior evaluation of the toxicity data pertaining to the ingredients used in the product, have been published in *Food and Chemical Toxicology* [34 (1996) 651-660].

ISSN 0254-1475

COM(97) 182 final

DOCUMENTS

EN 10 15 02

Catalogue number : CB-CO-97-176-EN-C

ISBN 92-78-19036-5

Office for Official Publications of the European Communities

L-2985 Luxembourg