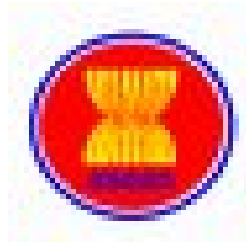


**Annex I, Part 6**



**ASEAN**

**GUIDELINES FOR THE  
SAFETY ASSESSMENT OF  
A COSMETIC PRODUCT**

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## OBJECTIVE:

1. The purpose of this Guideline is to help the Cosmetic Industry in assessing the safety of the product as well as the Regulators in auditing the data contained in the Product Information File (PIF). This guideline serves to highlight some of the important considerations in the safety assessment of cosmetic product in line with Article 8 d of the ASEAN Cosmetics Directive <sup>1</sup> which requires an *assessment of the safety for human health of the finished product, its ingredients, its chemical structure and its level of exposure*. This safety assessment is to be performed by a qualified professional defined as the *Safety Assessor*.

### 1. GENERAL APPROACH

2. The provisions of Article 3 of the ASEAN Cosmetic Directive stipulates that *A cosmetic product put on the market must not cause damage to the human health when applied under normal or reasonably foreseeable condition of use taking into account in particular of the product presentation, its labeling, instruction for its use and disposal warning statements as well as any other information provided by the manufacturer or his authorized agent or by any other person responsible for placing the product on the market.*

3. Hence cosmetic products have to be safe both for consumers and, if relevant, for involved professionals (e.g. hairdressers, beauticians, etc.).

4. As far as skin is concerned, the two main untoward reactions to be avoided are skin irritation and skin sensitisation <sup>2</sup>. Cosmetic products are often applied on areas exposed to environmental factors. Thus, care has also to be taken to avoid photo-induced reactions such as photoirritation and photosensitisation <sup>2</sup>.

5. Products applied on the scalp or the face may come in contact with the eye. Consequently, eye tolerance has to be addressed with optimal attention as a major component of the safety assessment for a cosmetic product.

6. Systemic toxicity that may result from percutaneous absorption or from accidental (children) or reasonably foreseeable (e.g. oral hygiene products, lipsticks) oral intake should also be considered.

7. Ensuring the safety of a cosmetic product requires a global approach throughout the life of the product from the choice of raw materials to the marketing follow-up. A number of issues have to be taken into account, including:

- Applying Cosmetic Good Manufacturing Practice Guidelines (ASEAN Cosmetic Directive - Technical Documents) or approved equivalent;
- Careful selection of cosmetic ingredients, making sure that they will be safe at a given concentration in a given finished product;
- Checking local tolerance of the finished product;

- Selection of adequate packaging to maintain the quality of the product and to avoid, as far as possible, risks of misuse or accident;
- Quality control, mainly microbiological and chemical;
- Stability studies e.g. to evaluate shelf life, preservative effectiveness (challenge test), compatibility of the product and the packaging, etc;
- Appropriate labelling - presentation of the product, instructions for use and disposal, warnings (if relevant) and appropriate action to take in case of accident;
- Adequate procedures in case of side effects with the marketed product - case-by-case treatment, appropriate medical, dermatological, ophthalmological etc., advice as necessary, follow-up of the product on the market and consumer comments, information storing etc. In case of Serious Adverse Event, the procedure must be identical to the ASEAN Cosmetic Committee approved Guidelines (Annex I)
- Ensuring corrective action/ follow-up, if any visible product change or adulteration is advised from the market place;

8. Although it is not possible to attain zero risk or to obtain absolute safety in any kind of human activity, including cosmetology, reasonable efforts have to be made to reduce the risk from cosmetic products to the minimum, according to the state of the art at the time.

9. There is no formalistic approach to the safety evaluation process. The actual process will vary from product to product according to the novelty of the product composition and to the relevance and adequacy of information available. However, as a general rule, the major basis for safety evaluation is provided by considering the toxicological profile of its ingredients<sup>3</sup>.

10. From a scientific point of view, in almost all cases finished product testing does not require the use of toxicological tests in animals. In general, all questions which are posed at this stage can be answered by utilising other information sources, including human data from skin compatibility tests ethically performed on the skin of human volunteers<sup>4</sup>.

## 2. INGREDIENTS

11. Cosmetic ingredients are mostly chemicals and often mixtures of chemicals of synthetic origin or natural extracts. The careful selection of ingredients is the key issue for ensuring the safety of the finished product.

12. The structure of the chemical determines its chemical and biological reactivity e.g., Barratt, 1995<sup>5</sup>. This has to be considered from two points of view: cosmetic interest and safety. Other considerations are the degree of chemical purity, the possible interactions with other ingredients in the formulation and potentiation of skin penetration. In general, the presence of impurities is technically unavoidable. But these impurities have to be of no significant toxicological relevance in the finished product. Particular attention should be taken to the possibility of interaction between impurities (e.g. formation of nitrosamines) and the presence of pesticide residues, toxic metals and/or transmissible spongiform encephalopathies (TSE) in ingredients of botanical origin or extracted from animals.

13. Based on the state of knowledge, possible interactions between ingredients with potential safety relevance have to be considered. Influence on skin penetration may also be of importance, especially for sensitisation and systemic risks<sup>6</sup>. Skin penetration can be assessed using *in vitro* methods<sup>6</sup>. Determination of allergic potential may also require testing of ingredients formulated with suitable vehicles.

14. On the other hand, the safety-in-use of an ingredient largely depends on the exposure conditions (type of formulation, concentration, frequency and duration of contact, body area involved, effect of the sun, etc.) taking into account normal conditions of use and foreseeable misuse.

### 2.1 INGREDIENTS TO BE AVOIDED

15. For each raw material, it is necessary to check whether it is covered by current legislation and, if so, whether the proposed usage is within the prescribed parameters. The following ingredients must be excluded:

- Ingredients prohibited under the ASEAN Cosmetics Directive in Annex II<sup>1</sup>;
- Ingredients restricted under the Cosmetics Directive when used beyond the allowed conditions and restrictions laid down in Annex III<sup>1</sup>;
- Ingredients with toxicological data incompatible with the intended concentration and use;
- Ingredients which do not have sufficient toxicological data and/or safety in use experience;
- Ingredients which are not properly characterized either chemically or through the extraction process for natural extracts
- For colouring agents, preservatives and/or UV filters, ingredients must be substances listed in Annexes IV, VI or VII respectively, within the limits and under the restrictions laid down in these annexes

16. Data to be taken into consideration, besides those directly relating to toxicity, include positive identification of the ingredient, potential impurities of relevance, physico-chemical properties and analytical chemistry, potential interaction with other ingredients of the formulation and possible role in skin penetration.

17. The toxicological profile of a raw material is obtained by analysing available data, published or not, concerning the raw material. These data may include results of *in vitro*, *in vivo* and clinical testing, as well as results of epidemiological studies where available. It is clear that new ingredients or ingredients used in a novel application require particular attention.

## 2.2 SOURCES OF TOXICOLOGICAL DATA

18. The main sources of toxicological data on ingredients are the suppliers. Raw material manufacturers have to comply with national legislation on chemicals / dangerous substances (occupational safety, transport, packaging and labelling). Most effort should be made to collect toxicological data and other relevant information from the suppliers. It may be necessary to encourage the supplier to conduct additional studies. Because these data can be needed for regulatory purposes other than the Cosmetics Directive, the use of alternative (non-animal) test methods is restricted to those which are generally accepted (e.g. OECD guidelines).

19. Other sources of toxicological data may be obtained from:

- Scientific literature, databases (e.g. Toxline, Medline), reports issued by the US Cosmetic Ingredient Review (CIR) program, the EU Scientific Committee on Consumer Products (SCCP) or the ASEAN Cosmetic Scientific Body (ACSB), the Research Institute for Fragrance Materials (RIFM) monographs, reports by ECETOC, NTP, BIBRA, etc.;
- Safety Data Sheets;
- In-house experience with the particular ingredient and cosmetic products containing it;
- Expert judgment based on similarities with chemically related substances.

20. Ingredients listed in Annexes III to VII of the ASEAN Cosmetics Directive do not need supporting evidence provided that they are used as specified in the Annexes. In the case of substances in Annex VI in which concentrations higher than those specified may be used for other functions, supporting information is likely to be necessary.

21. The composition of fragrances and flavours is generally not available to the cosmetic manufacturer and use should be made of the safety evaluation as well as conformity to the latest International Fragrance Association (IFRA) Guidelines which have to be provided by the supplier<sup>7</sup>.

## 2.3 CONDITIONS OF USE AND EXPOSURE

22. Evaluation of the safety of ingredients is certainly not adequate as a stand-alone procedure but has to include considerations of exposure (magnitude, route, duration, frequency, etc.)<sup>3</sup>

23. The following parameters have to be considered<sup>8</sup>:

- Class of cosmetic product(s) in which the ingredient is used;
- Method of application (e.g. rubbed-in, sprayed, applied and washed off, etc.);
- Concentration of ingredient in product;
- Quantity of product used for each application;

- Frequency of application;
- Total area of skin contact;
- Site of contact (e.g. mucous membrane, sunburnt skin);
- Duration of contact (e.g. rinse-off products, leave-on products);
- Reasonably foreseeable misuse which may increase exposure;
- Type of consumers (e.g. children, people with sensitive skin);
- Projected number of consumers;
- Application to skin areas exposed to sunlight;
- Quantity likely to enter the body.

This last point, which relates to systemic availability, is a critical issue in safety evaluation - the information is mainly provided by percutaneous absorption data.

### 3. SAFETY EVALUATION OF FINISHED PRODUCTS

24. The assessment of the safety of any cosmetic product clearly relates to the manner of use. This factor is most important since it determines the amount of substance which may be absorbed through the skin or mucous membranes, or ingested or inhaled.

25. As mentioned above, the main sources of information are the toxicological characteristics of ingredients and the available human experience (including market experience, beauticians, factory workers, etc.) with similarly composed products. Each ingredient has to be considered carefully. Particular attention should be paid to new and novel ingredients. Open questions of safety assessment are defined by expert judgement in each individual case after careful review of all available information.

26. In general, the potential of a cosmetic product for sensitisation, genotoxicity and all other types of systemic (toxic) effects will be evaluated on the basis of the properties of the ingredients. Adequate consideration of human exposure is, however, of paramount importance for the interpretation of available data. This involves an examination of the potential role of the vehicle. This holds particularly true for percutaneous absorption or quantitative data concerning any other route of entry into the systemic circulation. The question of possible interaction between different ingredients will usually be evaluated on the basis of experience (similarities, published data on related compounds/mixtures, theoretical considerations, etc.) and may be controlled using *in vitro* testing and/or skin compatibility tests.

27. For assessing the safety-in-use of a finished product, especially the local tolerance, it can be very useful to compare it with other formulae successfully marketed by the company.

28. If the new product is a simple variant of an existing product, or if the formulation only consists of raw materials or ingredients previously used in similar products at common use levels, then it is likely that no additional safety data will be needed.

29. If raw materials are used in new ways, then additional safety data may be required by the safety assessor.

30. If novel raw materials or raw materials new to the company are to be used, then more detailed information will be necessary.

31. Local tolerance largely depends on the whole formulation. Consequently, even with known and safe in-use ingredients, it may be necessary to check the skin compatibility of a new formulation by appropriate testing.

32. When exhaustive analysis of toxicological data on ingredients appears insufficient to define with certainty the local tolerance of the finished product, additional experiments can be performed *in vitro* and/or in human volunteers.

33. *In vitro* testing may be carried out to complement available information with the necessary use of appropriate benchmarks. For ocular safety, methods such as those listed below are available:

- BCOP - Bovine Cornea Opacity and Permeability Test;
- FLT or TEP - Fluorescein Leakage Test or Trans Epithelial Permeability



- HET-CAM - Hen's Egg Test - Chorioallantoic Membrane;
- RBC - Red Blood Cell Test;
- TEA - Tissue Equivalent Assay.

34. Skin compatibility or tolerance may be checked using reconstructed skin models and/or ethically conducted trials on human volunteers.

35. Clinical trials in man should be based on the principles of Good Clinical Practice (GCP) such as that of the EU. The following type of tests may be performed:

- Open epicutaneous application (single or repeated);
- Closed epicutaneous application (single or repeated);
- Controlled application tests;
- Further testing may involve in-use tests and /or market tests.

#### 4. SAFETY CLAIMS

36. If a safety claim is to be made, e.g., "dermatologically tested", it has to be supported by adequate evidence. In most cases, appropriate human testing on the finished product will be necessary rather than animal testing. The testing must meet all necessary ethical requirements for a clinical trial<sup>9; 10</sup>. One important prerogative in this respect is the safety assessment by a suitably qualified and experienced person before the trial starts<sup>4</sup>.

## 5. RESPONSIBILITIES OF THE SAFETY ASSESSOR

37. The person in charge of assessing the safety of the product is called the safety assessor. The safety assessor is responsible for determining:

- Whether or not the ingredients present in the formula meet the requirements of the legislation in respect of the concentration for authorised substances, absence of substances prohibited by the law and, more generally, in respect of all legal requirements;
- Whether or not particular endpoint(s) have to be considered for a given ingredient;
- Whether the data available are relevant and sufficient;
- Whether or not interactions of toxicological relevance and/or modifications to penetration are likely to occur;
- Whether or not complementary data are needed either on ingredients or on the finished product.

38. A modern approach to safety assessment is based on a thorough analysis of available data and conditions of exposure. Ideally, the development of the formulation should take into account these elements from the start by a close collaboration between safety assessor and formulator.

39. A proper choice of ingredient at an adequate concentration level is sufficient to avoid the major risks (e.g. genotoxicity, carcinogenicity, systemic toxicity) and also to avoid, to a large degree, sensitisation. Testing on finished products is unnecessary in most cases to assess these risks, provided potential interactions between ingredients and role of vehicle are considered.

In most cases, the knowledge of all information available is sufficient to assess the safety of finished products. In the case of totally new ingredients, new combinations of ingredients or new formulation processes without safety-in-use experience, additional testing may be needed.

However, in all cases, all information on ingredients and formulations should be made accessible by the suppliers and formulator to the safety assessor to ensure an adequate safety assessment.

40. The Safety Assessor should possess qualification in relevant fields *for example* a diploma in the field of pharmacy, toxicology, dermatology, medicine or a similar discipline and be suitably trained in the safety assessment of cosmetics.

41. The role and responsibility of the safety assessor have to be emphasised. It is in the interest of the company to select a person knowledgeable in the field of safety evaluation applied to cosmetics and who is responsible and ethical.

42. The Safety Assessor does not need to be an employee of the company and can belong to an external organization or institution, as long as he has the required qualification.

43. The safety assessor must:

- Have recognised competence and ethics in the field;

- Have access both to the toxicological and to the analytical information pertinent from a safety view point. Some questions are likely to be raised by the safety assessor concerning, e.g. purity of raw materials, impurity profile - if available, and control procedures applied, detailed information on a test mentioned or referred to by the supplier, quantitative analysis of an impurity with a potential toxicological relevance, etc;
- Not be involved with the commercial aspects related to the product;

44. Safety assessment may require human testing to check skin compatibility of both cosmetic ingredients and finished products. Any such trials have to be carried out following the appropriate ethical requirements<sup>9; 10</sup>.

45. The judgment of the safety assessor relies on:

- The knowledge and experience of toxicological properties and safety-in-use of the known ingredients;
- The history of safety-in-use of products containing the same or similar ingredients;
- The expert judgment of the set of data available on an unknown, new or novel ingredient;
- If necessary, the results of additional data obtained either on one or more ingredients or on the finished product.

46. The safety assessor may conclude:

- The product is safe as such without special warnings or precautions;
- The product is safe provided a given type of packaging is used or provided a warning is added or the mode of use and usage instructions are defined more precisely or provided a complementary test with favourable results is performed;
- The product is not safe for the proposed use;
- That available data are not sufficient to determine whether or not the product will be safe and that further studies need to be carried out to obtain the required information;
- Specific safety claim(s) may or may not be used.

47. A product cannot be marketed if the conclusion of the safety assessor is that the product may not be marketed safely under the normal or reasonably foreseeable conditions of use. Recommendations by the safety assessor which are relevant for the safety-in-use of the product have to be followed. They are part of the safety statement the assessor signs which should be presented, together with the qualifications of the safety assessor, to the relevant regulatory authorities (inspectors) when required.

48. Selecting the safety assessor thus appears to be a key issue for the manufacturer of cosmetic products. It is not only a legal issue: it may also have importance for other aspects such as, for example, the image of the company as well as product liability implications.

## 6. Raw Material Supplier Responsibilities

### 1. Chemicals

49. Provide its customers with adequate information as to the safety of the ingredients supplied:
- Physical/chemical/microbiological specifications-purity
  - Absence of Annex II ingredients beyond unavoidable traces (e.g. heavy metals)
  - Toxicity studies:
    - Acute toxicity
    - Dermal absorption
    - Skin (and eye) irritation
    - Mucous membrane irritation (if necessary)
    - Skin sensitisation
    - Sub-chronic toxicity
    - Mutagenicity
    - Photo toxicity and photo mutagenicity (if necessary)
    - Human data (if available)

### 2. Botanicals Extracts:

50. Provide its customers with adequate information as to the safety of the ingredients supplied:
- Proper identification of the plant/part used
  - Physical/chemical/microbiological specifications-purity
  - Pesticide level
  - Absence of Annex II ingredients beyond unavoidable traces (e.g. heavy metals)
  - Toxicity studies:
    - Skin irritation . sensitisation
    - Photo toxicity . photo sensitisation (if necessary)
    - Mutagenicity

### 3. Animal Extracts:

51. Provide its customers with adequate information as to the safety of the ingredients supplied:
- Proper identification of the animal/part used
  - Physical/chemical/microbiological specifications-purity
  - Absence of Transmissible Spongiform Encephalopathy
  - Absence of Annex II ingredients beyond unavoidable traces (e.g. hormones, antibiotics, etc)
  - Toxicity studies:
    1. Skin irritation . sensitisation
    2. Photo toxicity . photo sensitisation (if necessary)
    3. Mutagenicity

#### **4. Fragrances and flavours:**

52. Provide its customers with adequate information as to the safety of the fragrances supplied:
- Certificate of compliance with latest IFRA Guidelines
  - Maximum safe concentration depending of the product type

#### **7. Manufacturer Responsibilities**

53. Including:

- É Careful selection of cosmetic ingredients, making sure they will be safe at a given concentration in a given finished product
- É Checking local tolerance of the finished product
- É Selection of adequate packaging to maintain the quality of the product and to avoid, as far as possible, risks of misuse or accident
- É Applying ASEAN Cosmetic Good Manufacturing Practices
- É Quality control, mainly microbiological and chemical
- É Appropriate labelling: presentation of the product, instruction for use and disposal, warnings (if relevant) and appropriate actions to take in case of accident
- É Adequate procedures in case of side effects with the marketed product
- É Ensures corrective action, follow-up if visible product change or adulteration is advised from the market place
- É Proper selection of the Safety Assessor

#### **8. Distributor Responsibilities**

54. Including:

- É Make sure the manufacturer has the adequate systems to ensure product safety (including GMP)
- É Collect information on post marketing experience and transfer such information to the manufacturer on a timely basis, determine trends and keep adequate records
- É Report any Serious Adverse Event to the Authorities

#### **9. Regulator Responsibilities**

55. Including:

- É Ensure public health and safety
- É Audits samples from the market
- É Audit PIF
- É Inspection of company premises
- É In case of Serious Adverse Event collaborate with the Industry to take proper actions
- É In case of product testing showing potential risk for human health or adulterated product, take appropriate measures to remove the product from the market, communicate with the public and take appropriate action on the responsible company/person

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