



**Safety Assessment of a
Cosmetic Product
ASEAN Guidelines
Workshop
June 12-13, 2006**

Article 3 ASEAN Cosmetic Directive

A cosmetic product placed on the market 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 labeling, instructions for its use and disposal, warning statements 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 market

Cosmetic products have to be safe for the consumers and, if relevant, for involved professionals (i.e. hairdressers, beauticians)

Main concerns

- Skin irritation
- Skin Sensitization

Cosmetic products are often used in areas exposed to environment:

- Photo Irritation
- Photo Sensitization

For products applied on the face or scalp

- Eye tolerance

Systemic toxicity

This may come from percutaneous absorption, accidents (children) or reasonably foreseeable (oral hygiene, lipsticks) intake of the products

Safety Assessment

This should have a global approach throughout the life of the product i.e. from the choice of raw materials to the post marketing surveillance

Safety Assessment

- Careful selection of RM: making sure they will be safe at a given concentration in a given product
- Checking local tolerance of the finished product
- Selection of adequate packaging to maintain quality of product and minimize risks of misuse
- Applying ASEAN Cosmetic GMP

Safety Assessment

- Quality Control: chemical and microbiological
- Appropriate labelling
- Adequate procedures in case of side effect with marketed product (complaint management)
- Ensuring follow-up actions in case of product change or adulteration in the market place

Ingredients

Cosmetic ingredients are chemicals or mixture of chemicals of natural or synthetic origin. Careful selection is key to product safety and to product efficacy.

Importance should be given to the presence of impurities, to the interactions between ingredients in the formulation and potentiation of skin penetration

Ingredients

Particular attention should be given to the possibility of interaction between impurities, the presence of pesticide residues, toxic metals or transmissible spongiform encephalopathies (TSE) in ingredients of botanical or animal origin

Ingredients

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.

Ingredients

To be avoided:

- Ingredients prohibited under Annex II
- Ingredients from Annex III when used beyond permissible use
- 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 naturals

Ingredients

- For colouring agents, preservatives or UV filters, ingredients must be listed in annexes IV, VI or VII respectively, within the limits and under the restrictions laid down in these annexes
- No other ingredients than those listed in these respective annexes, can be used as colours, preservatives or UV filters

Ingredients

- Ingredients listed in Annexes III to VII of the ASEAN Cosmetics Directive do not need supporting safety 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

Fragrances

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 IFRA Guidelines which have to be provided by the supplier

Condition of use and exposure

The following parameters have to be considered:

- 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 (mainly provided by percutaneous absorption data); this relates to a critical safety issue: systemic availability

Safety Evaluation of Finished Products

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

- 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.

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.

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

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.

Responsibilities of 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.

Safety Assessor

- 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
- 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.
- 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.

Safety Assessor

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;

Safety Assessor

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.

Safety Assessment

The safety assessor may conclude:

1. The product is safe as such without special warnings or precautions;
2. 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;
3. The product is not safe for the proposed use;
4. 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;
5. Specific safety claim(s) may or may not be used.

Safety Assessment

- 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 to the relevant regulatory authorities (inspectors) when required

Safety Assessor

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.

RM Supplier Responsibilities

Chemical

- Provide its customers with adequate information as to the safety of the ingredients supplied:
 - Physical/chemical/microbiological specifications-purity
 - 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)

RM Supplier Responsibilities

Botanical Extracts

- 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
 - Toxicity studies:
 - Skin irritation – sensitisation
 - Photo toxicity – photo sensitisation (if necessary)
 - Mutagenicity

RM Supplier Responsibilities Animal Extracts

- 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)

Manufacturer Responsibilities

- Careful selection of cosmetic ingredients, making sure 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

Manufacturer Responsibilities

- Applying ASEAN Cosmetic Good Manufacturing Practices
- Quality control, mainly microbiological and chemical
- Appropriate labelling: presentation of the product, instruction for use and disposal, warnings (if relevant) and appropriate actions to take in case of accident
- Adequate procedures in case of side effects with the marketed product
- Ensures corrective action, follow-up if visible product change or adulteration is advised from the market place

Distributor Responsibilities

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

Regulators responsibilities

- Ensure public health and safety
- Audits samples from the market
- Audit PIF
- In case of Serious Adverse Event collaborate with the Industry to take proper actions
- 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

Recommendations to ACC

- Adopt the Safety Evaluation Guidelines
- Disseminate the Guidelines to Regulators and Industry, especially SME's, through training Seminars

Recommendations to ACC

- Create a Curriculum (including examination) for the certification of Safety Assessor: Industry as well as Regulators. The following technical assistance can be used for a start:
 - ITC
 - PTB
 - APRIS II
- Involve the ACSB in the preparation of the training modules as well as the examination
- Involvement of Universities for the longer term

Thank you