REPORT FOR INTERNATIONAL COOPERATION ON COSMETIC REGULATION

Principles of Cosmetic Product Safety Assessment

Report is:[1]

☒ Prepared For ICCR ICCR Report ICCR Guidance

Author:

Authors: Daisuke Araki (1), Dan Bagley (2), John Bailey (3), Rolf Fautz (4), Gulnara Gabidullina (5), Kazuko Ito (6), Linda Loretz (3), Beta Montemayor (7), Pushpa Rao (8), Hitoshi Sasa (9), Takahiko Suwa (10), Florian Schellauf (11)

Affiliations:
(1) Kanebo Cosmetics, 3-28, Kotobukicho 5-chome, Odawara, Kanagawa 250-0002, Japan.
(2) Colgate Palmolive, 909 River Road, PO Box 1343, 08855-1343 Piscataway, USA
(3) Personal Care Products Council, 1101 17th Street, NW, Suite 300, 20036-4702 Washington DC, USA
(4) Kao/Kanebo, Pfungstaedter Strasse 92-100, 64297 Darmstadt, Germany
(5) Procter and Gamble, Rusham Park, Whitehall Lane, TW20 9WN, Egham, UK
(6) JCIA, Toranomon 45MT Building, 1-5 Toranomon-5chome, 105-0001Minato-ku, Japan
(7) CCTFA, 420 Britannia Road East, Suite 102, L4Z 3L5, Mississauga ON, Canada
(8) Energizer
(9) Shiseido, 2-12-1Fukuura, Kanazawa-ku, Yokohama, Japan
(10) Shiseido, 2-2-1 Hayabuchi Tsuzuki, 224-8558 Yokohama, Japan
(11) COLIPA, Avenue Herrmann Debroux 15A, 1160 Auderghem, Brussels, Belgium.

Date of Preparation: May 25, 2011	**Status:** Final – for adoption

[1] Documents submitted to ICCR by industry working groups or other interested parties may have "for ICCR" in their title, e.g. "Report Prepared **for ICCR**". Only documents that are endorsed by ICCR Steering Committee or that produced by the Steering Committee or an ICCR WG are to be titled "ICCR Guidance", "ICCR Report", etc.

TABLE OF CONTENTS

1. PURPOSE

The purpose of the ICCR Document on Principles of Cosmetic Product Safety Assessment is to provide a general framework for use in different jurisdictions in the development of safety substantiation principles for cosmetic products. The use of this framework will help to promote development of approaches and supporting principles that will be consistent and, to the fullest extent possible, aligned across jurisdictionsIt is recommended that this document be used in the overall development of approaches to cosmetic ingredient and product safety substantiation necessary to meet the legal and regulatory requirements in different countries/regions

2. SCOPE

This document describes the ICCR consensus on cosmetic product safety assessment principles and provides a core document which may be complemented with further safety-related ICCR documents on specific issues.

The definitions of a cosmetic product in the various jurisdictions are provided in annex I.

It does not replace the need for in-depth training and experience for a person performing a safety assessment or conducting in-market control nor does it provide a list of specific toxicological endpoints or study protocols.

3. ACRONYMS AND DEFINITIONS

ICCR International Cooperation on Cosmetic Regulation

4. RESPONSIBILITIES

The document has been prepared for ICCR by an industry working group comprised of safety and regulatory experts from the four ICCR jurisdictions.

5. DISCUSSION

5.1 General Principles

Cosmetic products are formulations comprised of specific combinations of substances or mixtures[2]. In general, it is possible to assess their safety by considering and examining the relevant toxicological endpoints of their ingredients, and the likely local and systemic consumer exposure to the product.

The following general safety assessment principles are applied:

[2] For easier readability, these are referred to as 'ingredients' in the remainder of the document, although this latter term may also have specific, narrower regulatory meaning in relation to some regional specific regulatory requirements.

- The safety assessment of cosmetic ingredients is not a standardized procedure, but should be performed on a case-by-case basis using best science. In particular, checklist approaches and decisions based on hazard alone are considered inappropriate and not adequate to thoroughly assess safety.
- The safety assessment of cosmetic ingredients involves a systematic stepwise approach that starts from conservative assumptions and includes refined approaches, as required and/or appropriate.
- The safety assessments should utilize the most up to date approaches available while taking into account current legal/regulatory requirements[3].
- The assessment should utilize the entire scope of information available to reach science-based decisions using a weight-of-evidence approach.
- Local and systemic human exposure is of the greatest importance for the safety assessment of cosmetic ingredients; the route, the magnitude and nature of human exposure are the key drivers for the definition of the package of safety data needed. All relevant endpoints need to be addressed but not necessarily with specific study data. ("Data need is exposure-driven").
- The exposure assessment should cover the normal and reasonably foreseeable use of products. When appropriate, specific consideration has to be given to vulnerable sub-groups of a user population.
- All relevant existing data should be evaluated before new animal testing is undertaken. New safety testing may be warranted when the existing information is not adequate to support the safety of an ingredient or when new potential safety issues arise[4].
- The availability of adequate information on the toxicity of the ingredients should in all cases prevent the requirement to study systemic toxicity of the finished product or repetition of already existing studies.

A safety assessment process includes:

- Ingredient characterization through relevant physico-chemical data, purity and profile of impurities, and chemical structure of constituent ingredients comprising a product.
- Assessment of all relevant toxicological hazard information. Data on closely related structural analogues, and structure-activity modeling data, may be considered.
- Considerations with regard to the stability of ingredients and product formulation as well as their microbiological status.
- Exposure assessment including an understanding of how the product is used: the amount, frequency, and duration of intended use; and target users.
- Calculation of safety or exposure margins (as appropriate), using the relevant dose metric for the endpoint considered.
- Post Market Surveillance to support continued product safety.

[3] Examples for available safety assessment guidance:
- The SCCS's Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, 7th Revisionhttp://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_004.pdf
- CTFA Safety Evaluation Guidelines (2007)
- Nohynek GJ, Antignac E, Re T, Toutain H. Toxicol Appl Pharmacol. 2010 Mar 1;243(2):239-59

[4] Animal testing for cosmetic purposes is not allowed in the EU.

5.2 Considerations with regard to animal testing

Data for assessing the safety of finished products have traditionally been obtained from animal tests either on the ingredients or the final formulation or both. The cosmetic industry has been at the forefront of research into the development of non-animal alternative methods for more than 25 years, and is committed to continuing this work to eventually eliminate animal testing as soon as possible.

The result of these efforts are a number of alternative test methods formally accepted by OECD and included in OECD test protocols that should be used for the safety assessment.

The use of suitable alternative methods in the context of safety assessment should not be limited to methods that have undergone formal validation by a national validation body. There are a number of useful alternative methods and approaches available that contribute useful safety information in the context of a weight-of-evidence safety assessment. Examples are *in vitro* tests, cell and tissue culture models, read-across approaches, structure-activity modeling data ((Q)SAR)), and results of *in-silico* computational methods. Scientific evidence of the ability of an alternative test to predict a certain aspect of toxicity of an ingredient is of fundamental importance.

When there are no validated alternative methods, authorities may still require manufacturers to predict the toxicity of ingredients/chemical substances and formulations with or without using animal assays. However, the use of animal assays should in all cases be minimized as much as possible.

Approaches to non-animal safety assessment related to endpoints specifically relevant for cosmetic safety assessment have been published in the literature.[5]

5.3 Role of the party responsible for safety assessment

The party responsible for assessing the safety of a cosmetic product has an integral role in the process of safety assessment and has to possess the necessary qualifications to fulfill this role in a responsible and ethical way.

Those responsible for the safety assessment should:

- Have training and competence in analysis, evaluation and interpretation of toxicological data
- Have access both to the toxicological and analytical information relevant to safety. Consider the safety of the product impartially and objectively.
- Carry out the safety assessments based on a thorough analysis of all available data, conditions of exposure and appropriate consideration of weight of evidence.

In case of a written safety assessment , the credentials and the contact address of the party responsible for the safety assessment should be included.

5.4 Reasoning of the safety assessment

The reasoning of the safety assessment relates to the considerations, which lead the safety assessor from all available safety related information to an overall conclusion on the safety of a product.

[5] http://dx.doi.org/10.1016/j.yrtph.2009.04.004,
http://dx.doi.org/10.1016/j.yrtph.2009.04.003
http://dx.doi.org/10.1016/j.yrtph.2010.03.012

5.5 Selection of the appropriate toxicological endpoint(s) as the driver for the safety assessment

Theoretically, all toxicological endpoints have to be considered for all ingredients in a safety assessment for a cosmetic product. However, this does not mean data or testing are required for all endpoints.

Decisions on whether or not specific data is required for any given endpoint needs to be documented and scientific justification for these decisions must be incorporated into the reasoning of the safety assessment.

Guidance on the appropriate selection of relevant endpoints can be found in the references listed in footnote 1.

5.6 Weight of evidence approach

"Weight of evidence" is terminology often used in safety assessments to describe a risk-based approach to assess the likelihood of adverse findings in humans. It is based on data obtained from all available sources, including multiple toxicological studies in both humans and animals, but also alternative data, with consideration to the quality of the data obtained. In essence, it means the integration of existing toxicological information where ever possible.

The weight of evidence approach is a framework which, rather than using a checklist approach of standard toxicological testing, instead uses a tiered assessment strategy incorporating many different types of safety data (see also annex II).

5.7 Considerations for products for specific target populations

Cosmetic products must be safe for all potentially vulnerable subpopulations likely to purchase or use such products unless a specific user group is clearly defined by a special presentation of the product. Besides, the performance, positioning and claims of a cosmetic product can selectively address or exclude certain consumer groups. A safety assessment must take this into account.

Examples for considerations that relate to specific subpopulations are provided in annex III.

5.8 Safety Assessment Conclusion

Based on all the available data, the conclusion of the person responsible for the safety assessment may be:

- The product is safe for the proposed use without restrictions.
- The product is safe with restrictions and may need specific warnings or precautions (risk reduction measures).
- The product is not safe.

Any recommendations by the person responsible for the safety assessment, which are relevant to ensure consumer safety when using the product, are included in the safety related documentation for a cosmetic product.

An illustrative example for such a safety statement is shown below:

"After analysis of all available information including formulation, toxicological profile of the ingredients and clinical reports, it is concluded that, according to the current state of scientific knowledge, product XXX is not expected to cause damage to the human health and can be marketed for the intended and foreseeable use as [insert product type]."

APPENDICES

Appendix 1: Regulatory definitions of a cosmetic product

Canada	"Cosmetic" includes any substance or mixture of substances manufactured, sold or represented for use in cleansing, improving or altering the complexion, skin, hair or teeth, and includes deodorants and perfumes;
EU	A 'cosmetic product' shall mean any substance or preparation intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition.
Japan	The term "Cosmetic" means any article intended to be used by means of rubbing, sprinkling or by similar application to the human body for cleaning, beautifying, promoting attractiveness, altering the appearance of the human body, and for keeping the skin and hair healthy, provided that the action of the article on the human body is mild. Such articles exclude the articles intended, besides the above purposes, for the use of drugs […] and quasi-drugs
USA	The term "cosmetic" means: (1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap.

Appendix 2: Weight of evidence approach

Examples of safety data that are used as part of a weight of evidence approach to fill pivotal toxicological data gaps include, but are not necessarily limited to:

- Existing animal data that may not have been generated in accordance with the latest test guideline method, but which are considered valid. This ensures that generation of new animal data is minimised.
- A TTC approach (Threshold of Toxicological Concern) is a pragmatic risk assessment tool that is based on the principle of establishing a human threshold exposure for all chemicals, below which there is a very low probability of an appreciable risk to human health (Kroes et al, 2004).
- In vitro data or alternative data from valid test systems to use as a screening study to predict toxicity.
- Human (clinical) data, including data from clinical trials and applications in other industries such as food and medicinal products. Data from human studies can also be required, if the formulation is considered innovative. Such studies can evaluate safety or local tolerance within the clinical setting for a relevant target population whilst at the same time accurately reflecting safety of the product under use as intended.
- Also data gathered from post-marketing surveillance including information from self-reporting from consumers as well as information from medical professionals such as dermatologists.
- Read-across approaches, based on the chemical structure and properties in order to predict toxicity of the ingredient.

Several governmental and non-governmental regulatory agencies have taken up this approach in their safety assessment practice and guidance documents:

- The EU REACH Guidance on Information Requirements recommends the use of all available information and the application of expert judgment.
- OECD recommends the use of weight of evidence in the compilation of Screening Information Database Sets (SIDS) and in the Globally Harmonised System (GHS); this approach is given prominence for classification.
- The SCCS Guidelines do acknowledge data not conducted in accordance with current guidelines can be included in cosmetic ingredient submissions to this committee, provided full justification is given (SCCS guidelines *SCCS/1416/11*).
- The US Cosmetic Ingredient Review have used read across data from structurally similar ingredients, on numerous occasions to fill safety data gaps on cosmetic ingredients. Similarly a weight of evidence approach is commonly adopted.
- International Life Science Institute (ILSI) report on screening tools for risk assessment of toxic chemicals. The following report cites numerous examples of ITS (Integrated Testing Strategies): Framework for use of toxicity screening tools in context based decision making. Doull et al, 2007. Food Chem Toxicol 2007: 45; 759-796.