

Attachment 1:

“The Cosmetics Safety Risk Assessment Guideline”

(Draft for Comments)

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Cosmetic Safety Risk Assessment Guideline

This guideline is made to identify and control safety risks of cosmetic to ensure the health and safety of consumers.

1. Scope of application

It is applied to risk assessment of cosmetic ingredients and safety evaluation of the products, including risk assessment on the unavoidable safety risk substances which were introduced by the manufacturing process of ingredients and products.

2. Basic principles and requirements

2.1 Cosmetics can be generally considered as a combination of various ingredients, the safety of ingredients is the premise of cosmetic safety. The safety evaluation of cosmetics shall be based on the risk assessment of all ingredients and risky substance. If chemical or biological interactions between the ingredients exist, the evaluation to the generated risk substances shall be performed.

2.2 The cosmetic safety evaluation shall be based on existing scientific data and relative information, following the principles of science, fairness, transparency, and case by case approaches, and ensuring the in-

dependence of risk assessment work during the implementation.

2.3 The cosmetic safety risk assessment work shall be done according to the requirements of this guideline by safety risk assessors who have corresponding qualification.

2.4 The safety risk assessment documents of cosmetic product shall be renewed in time and be kept for 10 years after the expired date of the last launched products.

2.5 Where the conclusion of the cosmetic product safety risk assessment report is not enough to exclude potential risks of the product to human health, traditional toxicological tests shall be conducted to evaluate the safety of the products.

3. Qualifications on safety risk assessors of cosmetic products

The safety risk assessors of cosmetic products shall meet the following requirements:

3.1 Shall has professional knowledge of cosmetic products, and understand the requirements on quality and safety control during the manufacturing process of cosmetic products.

3.2 Shall be able to review and analyze toxicological information, and have the ability to analyze, evaluate and explain toxicological data.

3.3 Shall be able to analyze the safety of cosmetic products fairly and objectively, and conduct the risk assessment based on analyzing all

available data and exposure conditions.

3.4 Shall have professional knowledge related to medical science, pharmacy, chemicals, toxicology or similar subjects, shall have a bachelor or higher degree or other formal qualification certificates, and shall have more than 5 years of relevant professional working experience.

3.5 Shall receive periodical professional training. Shall continue to have in-depth study on risk assessment, shall understand and master new means of risk assessments, and the information related to safety risk assessment of cosmetic products.

4. Risk assessment procedures

The risk assessment procedures of cosmetic ingredients and risk substances include the following four steps:

4.1 Hazard identification

Based on the results of the toxicological studies, clinical researches, undesirable effects monitoring, human epidemiological studies, and according to their physical, chemical and toxicological characteristics to confirm whether an ingredient or a risk substance has potential hazards to human health.

4.1.1 Cosmetics health hazard effects

Mainly include:

(1) Acute toxicity: includes acute toxic effects by oral, percutaneous, or inhalation routes.

(2) Irritation: includes skin irritation and eye irritation.

(3) Sensitization: mainly skin sensitization.

(4) Phototoxicity: includes the phototoxicity and photosensitization caused by the ultraviolet irradiation.

(5) Mutagenicity: includes gene mutations and chromosome aberrations effect, etc.

(6) Chronic toxicity: includes the functional and / or organic changes of tissues and target organs caused by long-term exposure to

(7) Developmental and reproductive toxicity: includes a change in the fetus developmental malformation.

(8) Carcinogenic: includes the type, location, rate of the tumor, etc.

4.1.2 Hazard identification

(1) The hazard identification is determined by the results of the toxicological tests of the raw material or the risk substance. The acute toxicity, skin irritation, skin corrosion, acute eye irritation/corrosion, sensitization, phototoxicity, mutagenicity, chronic toxicity, developmental and reproduc-

tive toxicity, carcinogenicity and other toxic characteristics of cosmetics ingredients and the risk substance should be determined, and the determination should comply with China's current cosmetic technology standards or the evaluation principles of the international universal toxicological tests results. The main toxicity including the property of the hazard of the raw material or risk substances should be identified.

(2) The potential hazard of the ingredients and the risk substance on human could be identified based on the data from epidemiological study, human monitoring, clinical adverse event reports, and other relevant data.

(3) When determining the hazard, the purity and stability of the raw material shall be considered, the possible reaction of this raw material to other components in the finished product, and the percutaneous absorption rate or other factors such as the impurities which unavoidable introduced by manufacturing process should be taken into account.

(4) For the raw material contain different components, the hazard of each ingredients shall be identified.

4.2 Dose-response assessment

It is used to determine the relationship between the toxic response and the exposure dose of an ingredient or a risk substance. In the case of an effect with a threshold, the dosage at which No Observed Adverse Ef-

fect Level (NOAEL) shall be determined. If the NOAEL is not available, the lowest dosage at which an adverse effect level is observed (LOEL) shall be applied. In the case of non-threshold carcinogens, a dose descriptor shall be determined.

4.2.1 For the ingredient with a dose-response relationship, it is necessary to identify the no observed adverse effect level (NOAEL).

Data obtained from systemic toxicological profiles or repeated dose toxicity studies such as sub chronic and/or chronic studies, carcinogenicity studies, teratogenicity studies, or reproductive/developmental studies, etc.) should be applied in the determination of NOAEL, which is used for the calculation of MoS.

Experimental conditions that NOAEL to be determined should be taken into consideration. The conditions should be most relevant to the intended use conditions of ingredients and species susceptibility.

If a NOAEL is not acquirable, the LOAEL or Bench Mark Dose (BMD) could be used as an alternative. However, an additional uncertain factor which is 3 should be taken into account when using LOAEL to calculate the MoS.

4.2.2 For ingredients with non-threshold carcinogenicity, an appropriate dose-descriptor (T_{25} , etc.) should be identified to evaluate the dose-

response relationship.

4.2.3 Magnusson Kligman Guinea Pig Maximization Test (GPMT), Buehler Test, and other appropriate methods can be used to evaluate the potential of skin sensitization of a substance.

4.3 Exposure assessment

Exposure assessment is intended to evaluate the application area, concentration, frequency, and duration of human exposure to determine the exposure level of an ingredient or a risk substance.

4.3.1 The exposure of an ingredient or a risk substance shall be based on the use conditions of the product contains these ingredient or the risk substance. The use conditions are the zone of application, use amount, frequency, duration, etc. which described as following:

- (1) The category of cosmetics;
- (2) The application area or route of the application: skin, mucous membrane, and possible inhalation exposure.
- (3) The frequency of exposure: including intermittent exposure or daily exposure, and the frequency of application per day, etc.
- (4)The duration of exposure: including leave-on and rinse-off, etc.

(5) The amount of exposure: including the amount of each usage and total amounts, etc.

(6) Dermal absorption.

(7) The specificity of the exposure target: such as infants, child, pregnant women, women in lactation, etc.

(8) Others: such as misuse or exposure in accident.

4.3.2 Calculation of Systemic Exposure Dosage

(1) When dermal absorption is reported as $\mu\text{g}/\text{cm}^2$ of the ingredient per application, the calculation of SED shall be as follows :

$$SED = \frac{DA_a \times SSA \times F}{BW} \times 10^{-3}$$

With: SED: Systemic Exposure Dosage ($\text{mg}/\text{kg} \cdot \text{bw}/\text{day}$);

DA_a : Dermal Absorption reported as $\mu\text{g}/\text{cm}^2$, is the amount of ingredient absorbed per square centimeter, resulting from an assay under in-use mimicking conditions; In case no dermal absorption data is available, 100% dermal absorption is used.

SSA: skin surface area expected to be exposed to the finished cosmetics products

F: frequency of application of the finished product (day^{-1})

BW: default human body weight (60 kg)

- (2) When dermal absorption is reported as a percentage of the amount of ingredient applied, the calculation of SED will be as follows :

$$SED = A \times C \times DA_p$$

With: SED: Systemic Exposure Dosage ($\text{mg/kg} \cdot \text{bw/day}$);

A: Daily exposure amount of a cosmetic product per kg body weight, and the retention of the product is taken into account.

C: The concentration (%) of the ingredient in finished product.

DA_p : Dermal Absorption expressed as a percentage of the test dose. In case no dermal absorption data is available, 100% dermal absorption is used. However, in case $MW > 500 \text{ Da}$ and $\log P_{ow}$ is less than -1 or higher than 4, the value of 10% dermal absorption is considered.

Other toxicological profile of cosmetics (for example, calculation of skin surface and body weight per unit area) should also be taken into consideration when calculate the exposure as well as other possible exposure (for example, inhalation and lip products that could be ingested).

4.4 Risk Characterization

Risk characterization indicates the possibility and damage extent of the ingredients or the risk substances to the health of the human. It can be described by the methods such as calculating margin of safety (MoS), the dose description parameter T_{25} or the internationally recognized carcinogenic guidelines, etc.

4.4.1. Risk characterization for threshold ingredient

For the compound with threshold, the risk characterization is assessed via calculation of margin of safety (MoS) to conduct the assessment. The calculation formula:

$$MoS = \frac{NOAEL}{SED}$$

Among them:

MoS: margin of safety.

NOAEL: Non Observed Adverse Effect Level.

SED: Systemic Exposure Dosage (mg/kg·day)

Normally, when the MoS of an ingredient is ≥ 100 , it can be considered to be safe, this value (MoS ≥ 100) can be applicable to children as well.

If the MoS of an ingredient is < 100 , the ingredient is considered to have some risk and there are safety concerns in term of its application.

4.4.2. Risk characterization for an ingredient has non-threshold

For non-threshold ingredients, the characterization is calculated by the lifetime cancer risk (LCR). Lifetime cancer risk (LCR) is calculated as follows:

(1) Firstly, convert the T_{25} obtained from animal test to T_{25}

(HT_{25}): according to the following formula:

$$HT_{25} = \frac{T_{25}}{(BW_{(人)}/BW_{(动物)})^{0.25}}$$

In the formula:

- T_{25} is the dose which induces 25% of the experimental animals to get cancer.

- HT_{25} is human T_{25} converted from animal T_{25}

- BW is body weight kg

(2) Based on the acquired HT_{25} by calculation and the exposure amount, lifetime cancer risk is calculated as follow.

$$LCR = \frac{SED}{4 \times HT_{25}}$$

In the formula:

- LCR: lifetime cancer risk.
- SED: Systemic Exposure Dosage (mg/kg/day).

If the lifetime cancer risk of the ingredient is less than 10^{-6} , it is considered that the risk of carcinogenicity is low, it is safe to use.

If the lifetime cancer risk of the ingredient is more than 10^{-6} , it is considered that the risk of carcinogenicity is high; and there is a safety concern in term of its application.

5. Toxicology studies

Via a series of toxicological studies, the toxicology profiles of an ingredient or a risk substance are determinate. The toxicological profiles are part of the hazard identification; it is the basis of the risk assessment of cosmetics product and ingredients.

5.1 Acute toxicity

The acute toxicity includes toxicological data from the tests via administration rout by oral and / or percutaneous and / or inhalation. Relevant data shall be provided according to the usage of ingredients and possible exposure route. The acute toxicity test is the first step to evaluate toxic

properties of an ingredient and a risk substance. The hazard information to health could be collected via a short term exposure. The study results of an ingredient and a risk substance can be used as the basis of its toxicological classification, labeling, and to justify the dose level selection for sub chronic toxicity study and other toxicological studies.

5.2 Irritation / corrosion

Irritation/corrosion includes the single dose skin irritation / corrosion test and repeated skin irritation / corrosion study, acute eye irritation study/ corrosion study, etc. Those studies are used to determine and to evaluate whether the ingredient is irritant or corrosive to mammalian skin and eye, and its degree.

5.3 Skin sensitization

Skin sensitization study is used to determine whether repeated exposure to an ingredient can cause allergic reaction to mammals and its degree.

5.4 Skin phototoxicity.

Skin phototoxicity studies are used to evaluate the possibility of an ingredient causing the skin phototoxicity.

5.5 Mutagenicity / Genetic toxicity

Mutagenicity / genetic toxicity studies include *Salmonella typhimurium* / reverse mutation assay, vitro mammalian cell chromosome aberration test, in-vitro mammalian cell gene mutation test, mammalian bone marrow cell chromosome aberration test, in vivo mammalian cells micronucleus test, testicular germ cell chromosome aberration test and etc. These tests can be used to evaluate the possibility of ingredient causing mutation. The gene toxicity evaluation of a raw material should include at least one gene mutation test and one chromosome aberration test data.

5.6 Sub chronic toxicity

The sub chronic toxicity includes sub chronic oral toxicity study and sub chronic dermal toxicity study.

Sub chronic oral toxicity study will provide not only the data in terms of health effect after repeated exposure to tested material for a certain period, tested material's action on target organs, and the in-vivo tested material's accumulation capacity, but also the estimation of no observed adverse effect level. The latter can be used to choose and determine the exposure levels of chronic study and to calculate the primarily human exposure safety level.

Sub chronic dermal toxicity study can provide not only the health effect of repeated exposure to tested material after a certain period, but also

the skin permeability of the test material, target organ and justification for chronic skin toxicity test dose selection.

5.7 Developmental and reproductive toxicity

Developmental and reproductive toxicity tests aim to detect the possibility of causing abnormal fetal rat after the exposure of ingredients or risk substances in pregnant animals.

5.8 Chronic toxicity / carcinogenicity

The accumulation of chemicals in the body is the basis of chronic intoxication. The chronic toxicity test is a test to detect the toxicological effects in animals as a result of long term exposure to substances in a certain way. When a chemical substance is proved to be potentially carcinogenic by short-term screening test, or its chemical structure is very similar to a known carcinogen, and when the chemical substance has a certain practical application value, it is necessary to be verified by a carcinogenicity test. Animal carcinogenic test provides the data for the probability of causing tumor under long-term exposure to the substance in human.

5.9 Toxicokinetics

The toxicokinetic test is a test to quantitatively study an ingredient's absorption, distribution, metabolism, excretion and characteristics in ani-

mal body, and then to explore the pattern of occurrence and development of an ingredient's toxicity, and to understand the distribution of an ingredient in animals' body and its target organs.

After the skin absorption of an ingredient, the metabolic transformation may have an important influence on its potential toxicity, distribution and excretion. Therefore, in some specific circumstances, it is necessary to conduct in vivo or in vitro biological transformation studies, to prove or exclude certain undesirable effects.

5.10 Skin absorption

The data from skin absorption test. For polymers, if the average molecular weight of the polymer is over 1000, no need to provide relevant data.

5.11 Other toxicological test data: data from other toxicology tests that can help to explore the toxicity of an ingredient shall be provided when necessary.

5.12 Human safety test data

Human safety test data includes clinical safety test data and epidemiological data.

After an ingredient is tested in the toxicology tests, a human skin patch test could be performed when necessary to test the potential adverse reactions on human skin.

Safety data of the cosmetic products which contain the ingredients, including epidemiological studies, population monitoring, clinical adverse event reports, accident reports and other relevant information should be collected.

6. The risk assessment of an ingredient

6.1 The principles of risk assessment

6.1.1 Risk assessment on each ingredients and risk substances should be conducted following the assessment procedure to ensure the safety use of ingredients.

6.1.2 All ingredients meet the cosmetics safety technical standard requirements such as preservatives, sunscreen, colorant, hair dye, etc. which in the positive list shall be exempt from the risk assessment.

6.1.3 For the ingredients of which safety evaluation conclusion has been published by well-known organizations, such as the U.S. cosmetic ingredients review (CIR) committee, the European Scientific Committee on Consumer Safety (SCCS), the relevant assessment shall be analyzed. As-

assessment conclusions could be adopted while in compliance with China cosmetics regulations. If inconsistent assessment results from different organizations exist, the most restrictive should be used.

6.1.4 If the safety limit of an ingredient have been published by authorities, such as World Health Organization (WHO), the United Nations Food and Agriculture Organization (FAO), the Organization for Economic Co-operation and Development (OECD), domestic and international governments and other authorities (such as acceptable daily intake, tolerable daily intake, reference dose, etc.), the relevant assessment data should be analyzed. Assessment conclusions could be adopted while in compliance with China cosmetics regulations. If inconsistent assessment results from different authorities exist, the most restrictive should be used. Additional risk assessment of the ingredient on the local toxicity (irritation, corrosion, etc.) shall be conducted.

6.1.5 If a fragrance conforms to the International Fragrance Association (IFRA) standards, relevant assessment data should be analyzed. Assessment conclusions could be adopted while in compliance with China cosmetics regulations.

6.2 Physical and chemical property of ingredients

Physicochemical properties of an ingredient are the most critical information that can be used to predict certain toxicological profiles. Accord-

ing to product formulation, physicochemical properties of each ingredient should be obtained.

The physicochemical properties including:

6.2.1 Name of the ingredient

The names of ingredients include generic name, trade name, INCI name, CAS number, EINCES number etc.

6.2.2 Physical state

Such as solid, liquid, volatile gas, etc.

6.2.3 Molecular structure and relative molecular weight

For the preparations, the molecular structure and relative molecular weight of each component must be explained.

6.2.4 Chemical properties and purity

Technical conditions when characterizing the chemical properties (UV or IR, NMR, MS, elemental analysis, etc.) should be described, as well as test results and so on.

Purity of ingredients, test methods, and the validation of the analytical methods should be clarified. The substance used in physicochemical ex-

periments and toxicological studies must represent the ingredient used in the products on the market.

6.2.6 The characteristics of impurity or the accompanying pollutant

In addition to the purity of the material, it is necessary to indicate the concentration or content of the impurities that may exist.

6.2.7 Solubility

The solubility of the ingredient in water and/or any other relevant organic solvents should be indicated.

6.2.8 Partition coefficient (Log P_{ow})

Partition coefficient should be indicated. The method should be explained when the value is calculated.

6.2.9 Other related physical and chemical indicators

For the component that can absorb ultraviolet light, the wavelength and spectrum of the ultraviolet absorbed should be indicated.

6.2.10 Homogeneity and stability

The homogeneity of the test solution used for testing the ingredients under the test conditions should be reported.

The stability of ingredients in the experimental conditions should be reported. In addition, the storage conditions of the ingredients should also be explained.

6.2.11. UV-VIS absorption spectra

Based on the structure of an ingredient, UV-VIS absorption spectra should be provided.

6.2.12 Isomers formation

When there are isomers in an ingredient, each relevant isomer should also be carried out risk assessment.

6.2.13 Function and usage

The purpose or efficacy of the ingredient are intended to use or have been used in cosmetics, the highest concentration of the raw materials are intended to use or have been used shall be provided. If an ingredient is to be used in spray or aerosol products, it should be explicitly mentioned that the exposure through inhalation is possible, and the risk assessment of inhalation exposure should be taken into account.

In addition, when the ingredient has been used for other purposes (such as in consumer goods, industrial products), the concentration should be described as far as possible.

6.3 Ingredients from the minerals, animals, plant and biological technology sources

6.3.1. The ingredients from minerals shall include the following information:

- (1) Source of the ingredient;
- (2) Manufacture process: physical process, chemical modification, purification method and cleaning up method, etc.;
- (3) Characteristic elements: characteristic components (%);
- (4) Physical and chemical properties of components;
- (5) Microbiological quality;
- (6) Preservatives and /or other additives.

6.3.2 The ingredients from animals shall include the following information:

- (1) The origin of the species (cattle, sheep, shell, etc.) and organ tissues (placenta, serum, cartilage, etc.);
- (2) Country of origin;
- (3) Manufacture process: extraction conditions, hydrolysis type, purification method, etc.
- (4) Efficacy component content;
- (5) Form: powder, solution, suspension, etc.

(6) Characteristic elements: characteristic amino acids, total nitrogen, polysaccharides, etc.

(7) Physical and chemical properties;

(8) Microbiological quality (including viral pollution);

(9) Preservatives and /or other additives.

6.3.3 The ingredients from plants should include the following information:

(1) Generic names of plants;

(2) The Species, Genus and family name;

(3) Part of the plant used;

(4) Sensory description: powder, liquid, color, smell, etc.;

(5) Morphological anatomy;

(6) Natural ecological and geographical distribution;

(7) The sources of the plants including the geographical origin and whether it is cultivated or wild;

(8) The specific preparation process: collection, washing, drying, extraction, etc.;

(9) Storage conditions.

10) Characteristic elements: characteristic elements;

(11) Physical and chemical properties;

(12) Microbial quality including fungal infection;

(13) Pesticide, heavy metal residues, etc.

(14) Preservatives and /or other additives;

(15) If it is an extract, the content of the solvent and the active ingredient should be stated.

6.3.4 The ingredients from biotechnology should include the following:

(1) Manufacture process;

(2) The description of the organism: the donor, acceptor, and modified microorganisms;

(3) Host pathogenicity;

(4) The toxic constituents include the biological metabolites, the produced toxins, etc.;

(5) Physical and chemical properties;

(6) Microbiological quality;

(7) Preservatives and / or other additives.

For the ingredients from special biological technology, in which the modified microorganisms or potential toxic substances that cannot be completely removed, the data need to be provided to explain.

6.4 Flavors and fragrances

Fragrance and fragrance should comply with the International Fragrance Association (IFRA) standards or other relevant national standards, in addition, the following contents should be included :

6.4.1 Semi quantitative concentration of the ingredients in the fragrance

(i.e., < 0.1%; 0.1 < 1%, 1% to < 5%, 5% to < 10%, 10% to < 20%, 20% and to above);

6.4.2 Natural ingredients should have following information:

- (1) The composition analysis of this batch of the natural ingredient.
- (2) The highest content of each component in ingredients, the differences among batches should be taken into account.

6.4.3 The type of cosmetics that use the highest concentration of the compound should be clearly stated.

7. Safety Evaluation of Cosmetic Products

7.1 Principles of the evaluation

7.1.1 To ensure the safety of a cosmetic product, safety evaluation of the product shall be based on the data of risk assessment on the ingredients it contains, together with the product application method, the amount of usage, and the exposure of impurities.

7.1.2 The risk assessments of ingredients of a cosmetic product shall be based Risk Assessment Process described in part 4. All the ingredients listed in cosmetic technical standard such as preservatives, sun filters, colorants, and hair dyes could be exempt from the risk assessment.

7.1.3 Risk assessment of risk substances that introduced by ingredients or production process shall be conducted according to Risk Assessment Process described in part 4.

7.1.4 After the risk assessment of a finished product, human patch test could be applied to exclude skin irritation or sensitization when the ethical requirements could be met.

7.1.5 It is not necessary to provide the risk assessment data for those ingredients which already have the limit in relevant cosmetic regulations in China; For the ingredients which already have the limit or safety conclusions from foreign authorities, applicant could provide corresponding assessment report, it is not necessary to do a risk assessment. In case inconsistency occurs between the different authorities' reports, the conclusion of the risk assessment should be applied strictly.

7.1.6 Risk assessment report should be prepared for each product, and should be properly kept and updated in a timely manner.

7.2 Assessment of physical and chemical stability of products

7.2.1 For each batch of the cosmetic products launched in the market, the following physical and chemical parameters should be controlled.

(1) Physical state

(2) Formula type (oil in water or water-in-oil emulsion, emulsion, powder, etc.)

(3) Sensory characteristics (color, odor, etc.)

(4) PH of aqueous solution preparation (under the condition of ..°C)

(5) Viscosity of liquid preparation (under the condition of ...°C)

(6) Other aspects based on specific needs

7.2.2 Whether if there is a chemical or biological interaction between ingredients and whether if a risk exists shall be identified.

If chemical or biological interaction between ingredients exists, specific physical and chemical experimental data should be provided and risk assessment shall be carried out.

7.2.3 Ensure no changes that affecting product quality and safety would happen during product transport and storage.

Experimental data on stability and the data on content change of active ingredients could be used for explanation.

7.2.4 Risk assessment of physical stability of the container which in contact with the content and its compatibility with cosmetic product shall be conducted.

The risk assessment on physical stability of the container could be based on the safety data or safety attestation from packaging suppliers.

7.2.5 For cosmetic products that have similar formulation systems and same packaging material, the product risk assessment on physical and chemical stability could be based on existing data and experimental result with provisions of reasons and explanations.

7.3 Microbiological Assessment of the Cosmetic Product

7.3.1 Microbial contamination usually has two sources: the ingredients and product manufacturing process, and the product application of

consumers. From the time of consumers open the product packaging to the last time the consumers use the product, different microbial could be introduced into the cosmetic due to the surrounding environment and contact of human skin (hand and body).

To ensure product quality and consumers' safety, it is necessary to conduct routine microbial test on each batch of products launched in the market. In the on-the-spot report, standards, methods and items of the test, as well as the test result of each batch should be provided and included in the corresponding archive files.

7.3.2 For cosmetic products under development, assessment on the effectiveness of preservatives in the products should be conducted through a test, to ensure their function of preservation to stabilize microbe during storage and using. In the R&D phase of the cosmetic product, microbial challenge test should be conducted, and the test data should be used in assessing the effectiveness of the product's preservatives.

For cosmetic products that could deteriorate or generate hazardous substances which may infect the consumers under normal storage and usage condition, effectiveness of the preservatives should be guaranteed.

7.3.3 For cosmetic products having same preservation system and similar formulation, risk assessment of microbiology could be conducted based on existing data and experimental result with provisions of reasons and explanations.

7.4 Safety Monitoring of Cosmetic Products in the Market

7.4.1 The safety of products launched in the market shall be monitored, documented and be kept on file. The information includes undesirable effect occurred during normal use and improper use, complaints from consumers and follow-up visits.

7.4.2 In case the following situations occur for the cosmetic products in the market, the safety of the product should be reassessed.

(1) There are new toxicological findings of the ingredients in the products launched in the market, and these findings may affect the existing safety evaluation conclusion of the product.

(2) The changes of ingredient specification are significant enough to impact the current risk assessment result of the product in the market.

(3) Undesirable effect of the products in the market show a continuous and significant increasing trend, or serious undesirable effect take place.

(4) Other situations impacting the product quality and safety.

8. Safety Risk Assessment Report;

8.1 Risk Assessment Report on Cosmetic Ingredients

See Appendix 1 for contents generally should be included in the risk assessment report on cosmetic ingredients

8.2 Safety Assessment Report of Cosmetic Finished Products

See Appendix 2 for contents generally should be included in the safety assessment report of cosmetic finished product.

9. Terms and Definitions

The following terms and definitions are applicable to this guide.

9.1 Cosmetics

Any daily use industrial chemical products intended to be placed in contact with the external parts of human body (skin, hair, nail, lips, etc.) to cleaning them, perfuming them, protecting them, beautifying them, and changing their appearance by the methods of daubing, spraying and other means.

9.2 Ingredients of Cosmetic Products

It means the ingredients in the formula of a cosmetic product

9.3 Risk Substances

Substances that are introduced from the ingredients or manufacturing process, which could be a potential hazard to human health.

9.4 Hazard

The property of ingredients or impurities that causing adverse effect on human body when are exposed.

9.5 Risk

The possibility and characteristics of harmful effects of ingredients or impurities to users under the condition of consumer exposure.

9.6 Dose

Amount that can be absorbed through direct contact sites (digestive tract, mucosa, skin, etc.) of organisms, generally expressed as mg/kg·bw.

9.7 No Observed Adverse Effect Level (NOAEL)

The highest dose or concentration within organisms under specified exposing condition through experiment and observation, where no adverse effect findings are observed.

9.8 Lowest Observed Adverse Effect Level (LOAEL)

The lowest dose or concentration within organisms under specified exposing condition through experiment and observation, where adverse effect findings are observed.

9.9 Benchmark Dose (BMD)

A dose, at which a substance causes a certain and relatively low health risk (usually 1% - 10%). The dose is related to the clear tolerance or change of a biological effect.

9.10 Threshold Compounds

Compounds that are not harmful to animals or humans under certain exposure dosage, including non-carcinogens and non-genotoxic carcinogens.

9.11 Non-Threshold Compounds

Compounds which are mostly genotoxic carcinogens already known or assumed as having no threshold for their effect, i.e. compounds

that could have adverse effect at any dose known or assumed to be greater than 0.

9.12 Systemic Exposure Dosage (SED)

Predicted amount of chemicals that enter into human body by various exposure means, generally expressed as mg/kg·bw/day

9.13 Margin of Safety (MoS)

The ratio of experimental NOAEL obtained from proper tests to the predicted SED.

9.14 Acceptable Risk

The possibility of lifetime cancer risk is acknowledged by the society and accepted by the public, which is generally less than 10^{-6} and may vary with time, place, conditions and public tolerance.

9.15 T₂₅

The dosage at which tumor will occur at a specific tissue site of 25% of the experimented animals after correction for spontaneous incidence. It can be obtained by chronic toxicity/carcinogenicity test.

9.16 Acceptable Daily Intake (ADI)

The amount of a chemical a person can be exposed to on a daily basis from food and drinking water over a lifetime and without suffering any known undesirable effect.

9.17 Tolerable Daily Intake (TDI)

The amount of a certain hazard a person can be exposed to on a daily

basis over a lifetime and without suffering any known undesirable effect.

9.18 Reference Dose (RfD)

An estimated dosage of daily exposure from environment (air, water, soil, food, etc.), to human population (including sensitive subgroup) that is likely to be without an appreciable non carcinogen or non-mutagen risk, or the risk is acceptable or negligible

9.19 Undesirable Effect

Undesirable effects refers to any adverse effect happened in skin or their appendages as well as partial or whole human body, which are caused by normal use of cosmetics in daily lives. But the adverse effects caused by production or occupational exposure, or by using of fake products or unqualified products are not “adverse effects” defined in this “guideline”.

APPENDIX 1

Risk Assessment Report on Ingredients of Cosmetic Products

Title: Risk Assessment Report on (Name of the ingredient)

Assessment Company

Assessed by:

Assessed on dd/mm/yy

I. Summary of the Risk Assessment:

II. Descriptions of the Ingredients' Characteristics

1. Name of the ingredient, including chemical name, general name, trade name, INCI name, CAS No. or EINCES No., etc.
2. Molecular formula and structural formula :
3. Physical and Chemical Form:
4. Solubility:
5. Stability:
6. pH-value:
7. Partition coefficient:
8. Purity:
9. Impurity and content:

10. Use intention or function:
11. Use concentration:
12. Others: ingredients, flavors or fragrances that are derived from minerals, animals, plants, or through biotechnology shall be described in accordance with the requirements specified in this Guideline.

III. Risk Assessment Steps:

1. Hazards Identification:

1.1. Toxicological Endpoints:

- (1) Acute toxicity
- (2) Irritation/ Corrosion
- (3) Skin sensitization
- (4) Skin phototoxicity
- (5) Mutagenicity / Genotoxicity
- (6) Sub chronic toxicity:
- (7) Developmental and reproductive toxicity
- (8) Chronic toxicity/carcinogenicity;
- (9) Toxicokinetics
- (10) Human safety data.

1.2 Hazard Identification:

2. Assessment on Dose-response Relationship

3. Exposure Assessment

4. Description of Risk Characteristics

IV. Analysis of the risk assessment result: including analysis on the integrity, reliability and scientificness of the material, and uncertainty of the data source.

V. Measures or suggestions of the risk control

VI. Risk Assessment Conclusion on Ingredients

VII. Special Note:

VIII. Supporting Material, including literature references, testing/analyzing reports and specification certificate of related ingredients.

When risk substances are in the ingredient, then conclusions and materials of assessment on the risk substances or their analysis report shall be provided.

Appendix 2

Safety Assessment Report on Cosmetic Products

Title: (Product Name) Safety Assessment Report

Product Formula Number:

Assessment Company

Assessed by:

Assessed on dd/mm/yy

I. Summary of the Safety Assessment

II. Description on Product Characteristics

1. Product Name
2. Product Formula (function of each ingredient shall be included)
3. Physical and Chemical Information of Ingredients
4. Information on Potential Risk Substance
5. Use Method:
6. Use Intention or Function
7. Application Amount:
8. Others:

III. Risk Assessment Steps of Ingredients or Risk Substances in Cosmetic

Products.

1. Hazards Identification

1.1 Toxicological Endpoint

- (1) Acute toxicity
- (2) Irritation/Corrosion
- (3) Skin sensitization
- (4) Skin phototoxicity
- (5) Mutagenicity / Genotoxicity
- (6) Sub chronic toxicity:
- (7) Developmental and reproductive toxicity
- (8) Chronic toxicity/carcinogenicity;
- (9) Toxicokinetics
- (10) Human safety data.

1.2 Hazard Identification

2. Assessment on Dose-response Relationship

3. Exposure Assessment

4. Description of Risk Characteristics

IV. Analysis of the risk assessment result: including analysis on the integ-

riety, reliability and scientific of the material, and uncertainty of the data source

V. Measures and Suggestions for Safety Risk Control

VI. Safety Assessment Conclusion of Cosmetic Products:(including physical and chemical stability of the products, microbiological assessment; human safety data of the products or their similar formula, such as clinical data, survey from the consumers and reports of undesirable effect.)

VII. Supporting Material, including literature references, testing/analyzing reports and specification certificate of related ingredients.

VIII. Special Note:

1. If there are 2 or more than 2 ingredients that share similar systemic toxicity mechanism in the same product formula, aggregation exposure should be taken into consideration for safety margin calculation, and a specific case analysis should be made.
2. For products whose formula or technology is brand new, a human patch test or a human use test should be conducted for safety confirmation of local tolerance. Otherwise, safety assessment on the products shall be followed by adopting traditional toxicology tests on finish products.