UK-CHINA BUSINESS ENVIRONMENT PROGRAMME – STANDARDS STRAND

Outcome 1: Adoption and use of International Standards in China

Sector: Cosmetics

A COMPARISON STUDY BETWEEN CHINESE AND EU TECHNICAL GUIDELINES FOR COSMETIC SAFETY ASSESSMENT

FINAL REPORT

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GENERAL INTRODUCTION:

This comparison study is conducted under the framework of the "UK-China Business Environment Programme – Standards Strand" (BEP-S), which is funded by the UK Government Prosperity Programming and delivered by the British Standards Institution (BSI). The purpose of this study is to provide technical guidance and theoretical basis for the development of a training programme targeting cosmetics safety assessors, PIF (Product Information File) evaluators, and inspectors in China. It also aims to provide a comprehensive understanding for international players about the Chinese standards for cosmetics safety assessment.

In this report, a comparison is made between the draft version of the 'Technical Guidelines for Cosmetic Safety Assessment' (TGSA) (draft for comment), recently released by the Chinese authority, and the 'Scientific Committee on Consumer Safety (SCCS) Notes of Guidance (NoG) for the Testing of Cosmetic Ingredients and their Safety Evaluation', 10th Revision (SCCS/1602/18). This is the second version of the report. The assessment is carried out on the basis of a non-official translation in which some issues/ambiguities may also be due to translation. For this second report, references and abbreviations have been added and reference has also been made to the 11th Revision of the NoG which has just been compiled by the SCCS, but not yet officially made available. Also, the remarks made by BSI Group and industry experts have been taken into consideration.

This report is for the Phase I of the comparison study, which looks into the similarities and differences of the principles, framework, and key technical requirements between the Chinese and EU standards. It will serve as the basis for the in-depth analysis of Phase II, which will be conducted when the final version of the TGSA is published.

The Technical Guidelines for Cosmetic Safety Assessment (TGSA) is one of the technical guidelines under the framework of China's new cosmetic regulation, 'Regulations for Supervision and Administration of Cosmetics' (CSAR), which became effective on January 1, 2021. This is a basic framework regulation the implementation of which relies on a series of secondary, tertiary regulations and technical guidelines such as risk assessment. As one of the key secondary regulations, the Administrative Measures for Cosmetics Registration and Notification will come into force on 1 May 2021. In support of the implementation of these Measures, the aim of TGSA is to clarify the basic requirements of safety assessors and operating guidelines for their reports, in order to ensure a smooth transition from the now repealed 'Regulation Concerning the Hygiene Supervision over Cosmetics', which had been in force since 1990, to CSAR.

The SCCS is an independent Scientific Committee that actually counts 17 members. The SCCS provides scientific advice to the European Commission, based on best available scientific knowledge as a basis for EU policy on public health, consumer safety and the environment. The members are scientists from academia, research or other scientific bodies. They are appointed in their personal capacity, following an open call. Selection criteria are scientific excellence, experience in risk assessment, independence and transparency. As far as possible, geographic origin and gender balance are considered in the composition of the Committee. External experts may be invited to working groups when special expertise is required. Most work of the SCCS is related to answers on mandates issued by the European Commission. The

mandates are a result of consultations of the Commission with representatives of the different Member States. The SCCS has regular contacts with the Agencies ECHA (European Chemicals Agency), EFSA (European Food Safety Authority), EMA (European Medicines Agency) and ECDC (European Center for Disease Prevention) and other EU risk assessment bodies, Commission's scientific bodies SAM (Scientific Advisory Mechanism), SCOEL (Scientific Committee on Occupational Exposure Limits) and JRC (Joint Research Centre), academia & research bodies.

SCCS opinions are the basis for adopting new or adapting existing legislation *e.g.* ingredients present in the Annexes of the Cosmetics Regulation. The opinions also feed the debate in Regulatory Committees and Working Groups and recommendations mostly focus on research gaps to suggest further areas of research. Opinions are used not only in debates at the EU level but also in an international context. Over the years, SCCS opinions became worldwide reference for other national and international scientific and regulatory bodies.

It is important to know that the SCCS does not assess the safety of cosmetic products but only of specific cosmetic ingredients for which some concern could exist for human health. The safety of individual finished cosmetic products is, in the EU, the responsibility of the Responsible Person (RP), who brings the cosmetic product on the EU market and depends for the risk assessment of the product on a certified safety assessor. The risk assessment is for a particular cosmetic product present in the form of a 'Cosmetic Product Safety Report' (CPSR) present in the PIF for that product. The contents of the CPSR and the PIF are described in Regulation (CE) N° 1223/2009. The Authorities of the Member States may carry out compliance controls. For those ingredients for which SCCS opinions exist, these opinions are an important element in the safety assessment of the finished product, but such opinions only exist for a minority of ingredients (i.e., those ingredients listed in the Annexes of the Cosmetics Regulation). For all other ingredients and each finished cosmetic product, the RP and safety assessor need to establish the safety on the basis of all other available toxicological data.

The SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation are compiled in order to guide companies in a transparent way through the process of submitting a safety dossier to the European Commission for those substances present in their products for which concern could exist for human health. These are the so-called Annex substances to the EU Cosmetic Regulation (CE) N°1223/2009. The Annex substances consist of 2 negative and 3 positive lists: Annex II contains forbidden ingredients; Annex III consists of forbidden ingredients that are only allowed in certain applications and concentrations (*e.*g. hair dyes); Annex IV contains the allowed colorants; Annex V contains the allowed preservatives and Annex VI includes the allowed UV-filters. The SCCS NoG are regularly updated and actually the 10th Revision (SCCS/1602/18) is available. The 11th Revision (SCCS/1628/21) is on the agenda of the plenary meeting scheduled on the 30th of March 2021. Where there are some changes introduced in comparison with the 10th Revision, this is indicated in this second report.

As the TGSA in China is dealing not only with all cosmetic ingredients, but also with the finished cosmetic product, it seems necessary to include in the comparison also the content of a European PIF.

A Product Information File (PIF) needs to be prepared by the industrial companies for all cosmetic products that they place on the EU market. The RP of a company, as described in Regulation (EC) N° 1223/2009, Art 4., is responsible for the compliance with the obligations set out in the Cosmetic Regulation, which includes the safety of the cosmetic product and its ingredients. According to the provisions stipulated in Regulation (EC) N°1223/2009, Art 11. and Annex 1., the PIF content has to contain the relevant safety information for both, the ingredients and the finished cosmetic product. The Authorities of the Member States may, at the premises of the RP, control the PIF of the cosmetic products that are present on their market.

I. COSMETIC INGREDIENTS: COMPARATIVE ANALYSIS OF THE TGSA WITH THE NoG

As indicated in the general introduction, the safety assessment process of cosmetic ingredients presented in the TGSA is compared with the process described in the NoG of the SCCS, 10th Revision (SCCS/1602/18). In this comparison, similarities and differences are highlighted and some gaps have been identified. In this second report, additional information as indicated in the introduction has been added.

II.1. Basic Principles and requirements for the safety assessor

-A first important conclusion is that both documents put a lot of emphasis on the safety of the ingredients of the cosmetic products on their market.

-Similar in both documents is the basic principle that the safety for human health of cosmetic products is based on the safety and high quality of the product's ingredients. Key factors in this process are the chemical structure, the exposure to the user and the toxicological profile of the ingredients. This includes deliberately added ingredients and possible impurities. There is, however, a difference between both: impurities are in the TGSA defined as 'special ingredients' and are thus considered as ingredients of the cosmetic product. In the NoG and in the PIF, impurities are determined and characterised, but are not considered as ingredients. They should as such also not appear on the 'Ingredients list', which is in the EU obliged labelling on the packaging.

- The risk assessment and following safety evaluation are both carried out by trained safety assessors. For the SCCS, its members (and thus its safety assessors) are European safety experts who have been recruited via an open call in the Official EU Journal. For the industry preparing the PIF part A, the safety assessors need to have the requirements as described in the Cosmetic Regulation Art. 10.2, being in the possession of a university diploma (pharmacy, toxicology, medicine, chemistry ….). It is important to recognise that in the TGSA (Art. 3.1), it is clearly expressed that safety assessment will be carried out by trained safety assessors who possess relevant knowledge in the same disciplines as mentioned above.

- The risk assessment will be carried out in a transparent and independent way, based on science. For the SCCS, the experts need, on a yearly basis, to confirm their independent status and absence of any conflict of interest. For the industry, a contract between the company and the safety assessor usually is made, which includes a statement of independence. It is very encouraging to see that in the TGSA, it is stated that the risk assessment is carried out on the

basis of existing scientific data, following the principles of science, fairness and transparency and that the independence of the safety assessment work is ensured.

From years of experience in the application of the actual EU Regulation, it is seen that scientific independence of the safety assessor, being employed either in a cosmetic company or working for a consultancy firm, is crucial for the reputation, security and liability of the people in this profession. Indeed, it is important to clearly define the responsibility of both the registrant in China (equivalent to the RP in the EU) and of the safety assessor. In the EU, the responsibility of the RP is clearly expressed in the Cosmetics Regulation (Chapter II, Art. 5). The RP is responsible for the cosmetic product in all its aspects, including its safety. Before the Cosmetic Regulation was implemented, this was a controversial issue as it was not clear who was finally responsible for the safety of the product on the market. The final responsibility of the safety assessor was depending on the content of the contract made with the company or firm involved. In the actual situation, even if the safety assessor makes a mistake, the RP stays the first responsible. Only later, a civil court case can be initiated by the RP against the safety assessor in which the mistake has then to be clearly proven. Having a clear delineation between the responsibilities of the registrant and the safety assessor significantly contributes to safe cosmetic products, based on safe and correct ingredients.

The fact that the professional academic knowledge of the safety assessor is defined in both legislative contexts is very positive (In Europe: Regulation (EC) N° 1223/2009, Art. 10.2,"… *shall be carried out by a person in possession of a diploma or other evidence of formal qualifications awarded on completion of a university course of theoretical and practical study in pharmacy, toxicology, medicine or a similar discipline, or a course recognised as equivalent by a Member State*." In China: TGSA, requirements under Art. 3: "*3.1…. major in medicine, pharmacy, chemistry or toxicology, etc.; 3.2 …. competent to look up and analyse chemistry, toxicology and other related literatures, then to analyse, assess and interpret relevant data; 3.3 analyse cosmetic safety fairly and objectively and carry out safety assessment on the basis of comprehensive analysis of all the available data and exposure condition; 3.4 …training regularly"*). It should, however, be noticed that manufacturing, quality and safety control as mentioned in the TGSA are, in our understanding, tasks for other professionals (quality and safety manager at manufacturing sites) and cannot be systematically expected as additional skills of a cosmetic safety assessor.

When mandatory safety assessment was introduced in Europe, a transition period was applied for the safety assessors who were not in the possession of one of the defined diplomas but who were capable of doing a correct safety evaluation based on their years of experience. Art. 3.1 in the TGSA, should in our understanding, be interpreted in that context. It is unlikely that immediately after introduction of the safety assessment requirement, a large enough pool of safety assessors will be available who have both, the required university qualification and 5 years of professional experience.

- Documents issued by international authorities are fully accepted as key references.

In the NoG, documents issued by international authorities are a basic requirement which is seen from the extensive references list of the NoG and its regular updates (the official

acceptance of the 11th Revision is scheduled for the SCCS plenary meeting of 30 March 2021). In the PIF, references of methodology used, need to be provided in part A on 'ingredients, references of methodology used'.

In the TGSA (Art.4.1.2), it is stated that toxicological data from tests in compliance with Chinese regulations or internationally applied methods, including non-animal data, are accepted. In Art. 5, it is further said that the Chinese regulations should be prioritised for toxicological tests, and when toxicological testing methods published by other domestic or international authoritative organisations are utilised, their source and relevance to the Chinese regulations shall be provided. Although the above points out that the Chinese Authorities accept not "only" their own 'Standards' following the Chinese regulations, in our understanding this principle could have been more convincingly expressed and aligned with the general statement of scientific progress (Art. 4.1; 6.1.3; 6.1.4; 6.1.5; ….). Not complying with these principles would imply scientifically unjustified duplication of tests that have been carried out according to international guidelines and standards. Furthermore, it would also require carrying out of animal studies in areas where internationally validated and accepted alternative methods exist.

- The use of animal-free methodology and the application of a weight of evidence approach
This brings us to a very important point for the international context of cosmetic products with particular emphasis on the European situation. In the EU, testing and marketing bans are fully implemented since 11 March 2013 and have been taken up in Regulation (EC) N° 1223/2009 since 11 March 2013. The use of animal-free methods, so called New Approach Methodologies (NAMs), form the basis of the SCCS Notes of Guidance (10th Revision). The NoG have been completely restructured when going from the 9th to the 10th Revision in order to make it clear that in the EU the risk assessment of cosmetics and their ingredients give priority to existing and validated non-animal methods. Historical animal-derived safety data obtained via oral, dermal and inhalation studies in experimental animals {*e.g.* No Observed Adverse Effect Levels (NOAEL) values, Lethal Doses in 50% of the animals (LD 50) values, *in vivo* dermal absorption data, *in vivo* carcinogenicity and reprotoxicity studies, etc.} are usually available for existing substances used as cosmetic ingredients. Also, results from refinement and reduction alternatives (*e.g.* Local Lymph Note Assay (LLNA) for sensitisation, several tests for acute toxicity, which still are animal tests), are available. These data may be used in risk assessment as long as the different cut-off dates for testing in the EU (11 March 2004, 2009 and 2013**) -** as taken up in the Cosmetic Regulation - are fully respected.

In the international context {at the 'Organisation for Cooperation and Development (OECD) level}, and regularly updated in the NoG, several officially validated NAMs, often based on more than one scientific principle, are available for the following endpoints: skin corrosion, skin irritation, eye irritation/corrosion, skin sensitisation, photo-induced toxicity, dermal absorption, mutagenicity and genotoxicity (large toolbox is available), endocrine activity, and (limited) for carcinogenicity. These NAMs are taken up in the NoG and the list is regularly updated. An overview is also yearly made available by the 'European Reference Laboratory for the Validation of Alternative Methods' (EURL ECVAM) (JRC 2019, 2020). Besides these, 'Defined Approaches' (DAs) and 'Integrated Approaches to Testing and Assessment' (IATA's),

developed at the OECD level and providing case studies, allow countries, to share and explore the use of novel methodologies. These are rapidly gaining importance. Also, a lot of high quality *in silico* methodologies became available during the last years, often with emphasis on genotoxic and non-genotoxic carcinogenicity. An extended overview of this animal-free methodology has now been added to the 11th Revision of the NoG. Plus, human data can be obtained through human biomonitoring projects. All these methodologies are, together with historical data in experimental animals, combined and decisions in risk assessment are made based on an equilibrated weight of evidence (WoE) approach.

In the TGSA, NAMs are not specifically mentioned and no priority is given to validated NAMs in the risk assessment process. Also, animal-based reduction and refinement alternative methods do not play a prominent role and have not been mentioned in the TGSA. In our understanding, actually there are only six alternative methods included in the 'Safety and Technical Standards for Cosmetics' (STSC) document. These consist of (1) the 3T3NRU (3T3 Neutral Red Uptake) test for skin phototoxicity, (2) TER (Transcutaneous Electrical Resistance) test for skin corrosion, (3) STE (Short Term Exposure) test for eye irritation, (4) DPRA (Direct Peptide Reactivity Assay) for skin sensitisation and two modifications of the Local Lymph Note Assay (LLNA) to detect skin sensitisation, developed for non-radioactive detection, including (5) LLNA:DA (DA = developed by Daicel Chemical Industries, Ltd) and (6) LLNA:BrdU-Elisa (BrdU = 5-bromo-2 deoxyuridine; Elisa = Enzyme-Linked ImmunoSorbent Assay). The 2 LLNAs are still using experimental animals and are in the 3Rs concept of Russell and Burch 'Replacement, Reduction, Refinement' only Reduction or Refinement tests, not Replacement tests (Russell *et al.,* 1959).

It is noticed that epidemiological data, population monitoring and clinical adverse effect studies are considered in the TGSA, but clinical efficacy studies also can provide interesting results for safety assessment purposes (these are not taken up).

With a vision to the future, it is strongly advised that the use of alternative animal-free methodology is brought more on the foreground as it is probably the most important determining factor for internationally successful trade results, certainly in a European context.

II.2. Hazard and risk assessment procedures

- The risk assessment procedures and calculations described in the TGSA are similar to those provided in the NoG. The safety assessment process of threshold ingredients for both the TGSA and NoG are based on 3 pillars: hazard identification, dose-response assessment, and exposure assessment. Together, these make it possible to perform risk characterisation. The Margin of Safety (MoS or Uncertainty Factor UF) is calculated using the NOAEL, the L(Low)OAEL (including a default factor of 3) and the systemic exposure dose. When the MoS is higher or equal to 100 for an ingredient, it is considered safe. This value of 100 has been proposed by the World Health Organisation (WHO) (WHO 1994). If lower than 100, more refined procedures are necessary to show safety. In this context also toxicokinetics may be considered.

- For the calculation of the MoS, it is advised that one starts from the 'Point of Departure' (PoD). The use of a PoD is generally accepted international terminology and it includes both, the NOAEL and the 'BenchMark Dose' (BMD). In the TGSA, both are mentioned and preference is, in particular, given to the use of the oral NOAEL. In the NoG, clearly preference is given to the BMD, and well-known that in most cases this value is not available for existing cosmetic ingredients and that in the actual calculation of the MoS, historical oral and also dermal NOAEL values of ingredients are used. The term PoD, however, is applied with a view to the future. When long-term *in vitro* models become available for regulatory toxicological purposes, BMD will be the preferred approach as it has a number of advantages over using NOAEL. These are indicated in the NoG. A BMD makes complete use of the available dose-response data, takes into account the shape of the dose-response curve, is less dependent on dose spacing and enables quantification of the uncertainties in the dose-response data using statistical methodology. The PoD term can also be used in the context of the 'No Expected Sensitisation Induction Level' (NESIL) and 'LifeTime Cancer Risk' (LTCR).

- For deriving a NOAEL value, some differences exit between the guidance given by the TGSA and the NoG. In the NoG, a good quality 90-day repeated dose toxicity study is generally accepted for deriving a NOAEL value. A chronic study is not mandatory. If such study already exists and is of good quality, it can of course be used, but there is no obligation to do so. This point is not clear in the TGSA. It is correctly explained that in general a 90-day study can provide the exposure levels for chronic tests. That sentence, however, could be understood as meaning that a chronic study is obligatory and is preceded by a 90-day study. While that is indeed usual practice for pesticides and other toxic chemicals, it is not a common procedure in Europe for cosmetic ingredients. Reasons are that selected safe ingredients are included in cosmetic products, that cosmetics usually have a relative short lifetime on the market as innovation stimulates the market and that consumers use a high variety of different products during their life and usually do not stick to the same products during their whole lifetime.

- **For non-threshold ingredients both the TGSA and the NoG describe the use of LTCR.** The safe value described in the TGSA is more conservative than given in the NoG as it asks for a value higher than 10^{-6}. In the NoG the range between 10^{-5} to 10^{-6} is considered. Furthermore, in the NoG, the BMD_{10} approach is also described for the lifetime risk of non-threshold ingredients and is not mentioned in the TGSA (Art 4.2.2.).

- When a dermal absorption study is not available, both the TGSA and the NoG, allow to use a default factor, but different ones. In the TGSA, 100% dermal absorption is taken into consideration in all cases where no dermal absorption test has been carried out. This was in earlier years also done by the SCCS, but after studying the dermal absorption values of all available Annex substances since 2000, it was clear that 50% is already a conservative value for intact skin. When oral intake is possible (*e.g.* lipstick, toothpaste, mouth wash) or the skin is damaged (*e.g.* baby napkin zone), only then a 100% dermal absorption is considered as default value.

- Consideration of the oral bioavailability in risk assessment is different. When no oral absorption data are available for cosmetic ingredients, which mostly is the case, the NoG

introduced a default value of 50% in order to overcome potential underestimation of the safety of an ingredient. In the TGSA, oral bioavailability has not been considered.

- For both, the TGSA and the NoG, the IFRA standards for fragrances are important, but to a different extent. In the TGSA it is indicated that fragrance ingredients need to fulfil the IFRA criteria. For the risk assessment of perfumes, according to the NoG, the same safety assessment procedure as for other ingredients is carried out. When the safety of a perfume needs to be considered for the PIF of a cosmetic product containing this perfume, it is commonly accepted that the supplier of the perfume carries out the safety assessment of the perfume. They then provide an official paper for which the responsibility is taken that perfume X in a concentration range between Y and Z can be used in the specific cosmetic product under consideration. The reason for this procedure is that the composition of a perfume is, at least in Europe, never fully disclosed by the supplier to the cosmetic manufacturer for Intellectual Property protection reasons. Therefore, it would be very difficult or even impossible to guarantee the safety of a perfume. Although this procedure is nowhere described in a binding legal text, it is a generally accepted procedure in the EU and beyond. In the same document, all information is provided that is needed by the safety assessor to be able to comply with the regulatory requirements for the PIF. In the EU, also a list of 26 fragrance substances is present in Regulation (CE) N°1223/2009 for which labelling is obligatory once a certain concentration is exceeded for rinse-off (0.01%) and leave on (0.001%) cosmetics. This is an effective protective measure for allergic consumers. This list and the protective measures are not present in the TGSA.

- The 'Threshold of Toxicological Concern' (TTC) concept is proposed as a risk assessment tool for very small amounts of ingredients. For an ingredient (deliberately added or not), present in known trace amounts and for which no systemic safety data are available, the TTC concept can be applied. This concept is taken up in both the TGSA and the NoG. It is essential that the % content and the molecular structure of the trace ingredients are known. Also, the TTC is excluded for a number of very toxic substances. The TGSA and the NoG, both include such a list of toxic substances. It should, however, be noted that the lowest values used when applying this tool are not indicated in the TGSA. It can be argued that the tool has been applied already in other fields, such as for the evaluation of chemicals, but it still would be relevant to specify here the technical requirements for TTC, rather than only provide the circumstances where it is not allowed (Art. 6.1.7). Indeed, the TTC is based on so-called Cramer classes I to III. In the EU, only the low toxicity class I (1800 µg/person/d corresponding to 30 µg/kg bw/d) and the high toxicity class III (90 µg/person/d, corresponding to 1.5 µg/kg bw/d) are used since class II is not based on solid data. The tool is in both documents present for non-genotoxic substances. In the EU, the TTC concept (0.15 µg/person/d, corresponding to 0.0025 µg/kg bw/d), is also allowed for traces of carcinogens (to be applied with care). In the TGSA document, the TTC concept is not mentioned for genotoxic compounds.

Recently, efforts have been done by different industrial partners to add a variety of chemical structures, including cosmetic ingredients such as UV filters, to the chemical space that is involved in the TTC concept. As such new values could be proposed which are more robust. This has given rise to a so-called "federated" dataset, meaning that values of 2.3 µg/kg bw/d

and 46 µg/kg bw/d were derived for Cramer Class III and I, respectively (Yang *et al.*, 2017). These values are accepted by the SCCS in the 11th Revision of the NoG (SCCS/1628/21).

- Grouping, Read Across and 'Quantitative Structure Activity Relationship' (QSAR) is possible according to both guidances. For non-functional ingredients or impurities which lack systemic toxicity data, risk assessment can be carried out referring to grouping, read across and QSAR approaches. For Read Across, the referenced chemical substances need to have either a similar chemical structure **or** to act via the same metabolic pathway and chemical/biological reactivity with the target ingredient or risk substance. The "**or**" is here crucial as this procedure is in Europe possible either for similarly structured compounds or substances with a similar mode of action and does not need to comply with both properties as written in the TGSA text. It seems that for QSAR, a similar approach is taken as for TTC, i.e. used mostly for chemical evaluation for which it needs to comply with international requirements and principles. In the TGSA no detailed requirements for QSAR are provided, rather only the circumstances where it is not applicable.

. In the 11th Revision of the SCCS NoG, a detailed part on QSAR and Read Across has been included as this field is gaining importance (SCCS/1628/21).

- The listing of physico-chemical properties of ingredients present in different sources is similar in both documents. According to the TGSA document, it seems necessary to separate the different isomers when a racemic mixture is present. In our understanding, this is not always necessary as the properties of the racemate as such can in several cases be determined, which is less labour- and resources-intensive.

- For ingredients, including natural ingredients, the historic maximum usage is proposed as a safety criterium. It will serve as a reference during the transitional period with a low weight of evidence (as listed in Appendix 4). Cosmetic products, being sold in the market, have a certain objective history which may, to some extent, prove their safety. In our understanding, this is not a first-choice parameter as effects can be different between, for example, leave on and rinse-off products *e.g.* induction of sensitisation may be experienced when topically applied in a leave on cosmetic product, whereas this side effect is not observed in rinse-off products. Furthermore, the high amounts used which are safe for rinse-off cosmetic products are not necessarily acceptable for long-time skin contact and need to be much lower. Within a product category, it is also clear that different amounts of product need to be carefully chosen for the different parts of the body (see exposure values of different cosmetic products in the NoG). Also, for children, this concept is not safe as no clear difference is made between amounts suitable for children and adults. It must, however, be added that in Appendix 4 considerations are required of the target user, applied parts and instructions for usage.

- The existence of a "special" list of cosmetic ingredients is described in both the TGSA and the NoG. In China, such a list is included in their Standards and, in Europe, it is present in the Annexes to the Cosmetic Regulation**.** The content of these lists is not entirely the same, although the underlying safety of the ingredients does not differ. Ways should be found to align the positive/negative lists between the EU and China, based on the best available science.

- **The hazard tests:** teratogenicity and developmental toxicity could be combined.

II. FINISHED COSMETIC PRODUCT: COMPARATIVE ANALYSIS OF THE TGSA WITH THE PIF - General consideration

The requirements for the composing ingredients of a cosmetic product are different in the TGSA and the PIF, which could significantly affect cosmetic trade. According to the TGSA, for each ingredient risk assessment needs to be done according to the process described in the NoG. However, the NoG criteria have been made for the Annex substances (for which concern could exist for human health), not for commonly used ingredients that have no safety concern in the cosmetic product. In the PIF, for which the content corresponds broadly with the content of the TGSA, it is not required that the NoG are followed for the risk assessment of the composing ingredients. Furthermore, it is common practice that in the risk assessment focus is particularly placed on the active substances and ingredients for which specific functions are claimed, not on those ingredients that are commonly present in similar cosmetic product categories. In several articles of the TGSA, it is mentioned that for each ingredient safety assessment needs to be done, which in principle is correct, but proportionality is here missing. This becomes evident when looking to the examples given in Appendix 2 of the TGSA. The message given in these examples could be misunderstood: for the actives and major ingredients limited information is given in the tables, whereas a lot of data are provided for commonly used ingredients that are generally recognised as safe and present at very low amounts (3 or 4 digits after the decimal point). For such trace amount substances (as in both examples), the TTC principle should be applied and if the criteria are fulfilled for TTC application as given in the TGSA, no further work nor safety information testing are necessary. The topic is further discussed under "**Safety reports on ingredients and on the finished product must be available."**

- Risk assessment of a finished cosmetic product is exposure-driven. This principle is present in both the TGSA and the PIF.

- The interpretation of patch-testing is different. In the TGSA, it is mentioned that this type of testing "*can be conducted to further eliminate adverse events of cosmetic products, on the premise of meeting ethical requirements".* In the EU, patch testing can only be ethically done for skin irritation as confirmatory testing, when the product and its ingredients have been assessed and declared to be safe. It is not meant to detect any adverse effects, but rather, to confirm the expected conclusion of safety and absence of adversity.

Patch testing for sensitisation should not be done for safety assessment and is only ethically acceptable for diagnosis purposes of patients. Indeed, patch testing may be irreversible and induce sensitisation that could cause life-long problems for the test persons involved. Furthermore, patch testing has no scientific and statistical value when small groups (<few hundred people) are involved *e.g.* when, for example, 2-3% of an ingredient or product is considered to induce sensitisation, hundreds of volunteers should be tested to get meaningful statistical results.

- Cumulative exposure is differently interpreted. In the TGSA, cumulative exposure is considered when ingredients with the same mode of action are present, as well ingredients

present in cosmetic products as substances present in other consumer products. This is not easy as exposure data for other consumer products are most often not available. In a PIF, cumulative exposure is required only for cosmetic ingredients, for example having the same preservative. Exposure to other consumer products does not need to be considered, with the exception when a significant exposure would occur. However, in case of a 'carcinogenic, mutagenic or reprotoxic' (CMR) ingredient, cumulative exposure must be carried out. Cumulative exposure is in all cases calculated and no experiments need to be carried out for this particular purpose**.** In the TGSA, CMRs have not been included, but are possibly discussed in other official documents.

- A safety assessment report is needed for every cosmetic product coming on the market. This is a similar requirement for both the TGSA and the PIF of a cosmetic product. The following point is not clear. A PIF is confidential and can be reviewed by the National Authorities at the premises indicated on the packaging (the names are underlined when more than 1 production address is present); it is, however, not sent or handed over to inspectors and Authorities. In the TGSA, the process is not described. Whether this is also the procedure in China is not indicated, but perhaps it is present in another official document.

- Post-marketing and its updating. Post-marketing surveillance is necessary for new and existing cosmetics and the information should be added to the safety dossiers of the products involved. In both, the TGSA and PIF, post-marketing is described and should be carried out for normal use of cosmetic products, not for misuse as indicated in Art. 7.4.1 of the TGSA. The latter is not complying with the general perception of cosmetics that are meant to be used in normal foreseeable conditions of use, not misuse. For post-marketing purposes, the existence of a well-structured and good, easily available complaint system is important. In the PIF, such a system is foreseen. In the TGSA, it is not included, although under Art. 7.4. that would be a welcomed paragraph. It is not clear whether this is also the procedure in China as this is not indicated in the TGSA, but perhaps it is present in another official document.

- **Physico-chemical parameters need to be determined for the finished product**. This is a similar requirement for both documents. In the PIF, the result is also used to express the stability of the product, namely for labelling of the product with a 'best before" phrase or for using the hourglass symbol when the stability is less than 30 months. When equal or longer stability than 30 months is present, the so-called 'Period After Opening' (PAO) or open jar symbol is used for labelling. It is not clear whether this is also the procedure in China as this is not indicated in the TGSA, but perhaps it is present in another official document. It would, however, be a good place to take labelling obligations here into consideration.

- Microbiological data are required for the finished product. This is a requirement for both documents. In the PIF, the result is also used to express how long the product will remain of good quality after it is opened. This PAO-labelling is done once the product is shown to be preserved for at least 30 months. It is based on the 'International Organization for Standardisation' (ISO)-standards, which are internationally accepted (ISO/TR 19838; ISO 11930; ISO 29261). A different microbiological methodology is used in China (taken up in the Safety Assessment Guidelines). For better international alignment, it would be strongly

advised to follow the internationally accepted ISO-standards and then to take these up in the TGSA.

- **Safety reports on ingredients and on the finished product must be available.** This is a requirement that is fundamentally different in the TGSA and the PIF, prepared according to Regulation (CE) N°1223/2009. In the TGSA, safety reports as well for each ingredient as for the finished product are required. In a PIF, safety information on the composing ingredients must be present, but the official safety report concerns the finished product which is based on the safety of the ingredients. No specific safety report per ingredient is requested, but all available information needs to be referred to in the PIF. MoS calculations for the major ingredients and actives must be present. At the end of the PIF, a reasoned safety report must be included stating whether the product is safe on the market, not safe or extra data are requested before it could achieve safety status.
Safety reports on ingredients are produced by the SCCS (so-called opinions) on specific Annex ingredients or substances indicated by the Member States as potentially laying at the basis of health problems. They are made by experts as a response to a specific mandate and are not linked to a commercial cosmetic product. In the PIF, which has to be generated for every commercially available cosmetic product before it may be placed on the market, no such safety reports are required, nor present. However, the safety information available in an opinion of ingredient X can be used in a PIF of a product Y containing ingredient X to show that this ingredient is safe in the concentration and application as mentioned in the opinion of that ingredient X.
Another difference in the safety reports is the request in the TGSA that all proof documents should be handed over to the Authorities. Delivering proof documents for all ingredients is not very efficient and creates a lot of confusion and mistakes. For a PIF, delivering of proof documents for ingredients is as such not required. However, it must be indicated in the PIF how and where all results are archived and stored so that they are available for inspection by the National Authorities whenever needed.

- Cosmetics for children must be safe and it should be indicated how that is done. This is a requirement for both documents. In the TGSA it is, among other measures, mentioned that nanotechnology cannot be used for cosmetics for children. The whole field of nanotechnology, however, is lacking in the TGSA, although nano-ingredients of the UV-filters ZnO and TiO_2 are at the international level specifically used in topically applied sun protection products for children. They are known to be able to deliver a high protection factor without opacity. Also, when topically used, their systemic dermal absorption is negligible. In the 11th Revision of the NoG (**SCCS/1628/21)**, a special chapter is present for the use of nanoparticles and their safety requirements. Furthermore, recently the SCCS has compiled an additional and new NoG which only deals with nanomaterials, underlining the importance for the near future of using safe nanoparticle ingredients in cosmetics (**SCCS/1611/19).**

- **Appendix 1: the safety report of cosmetic ingredients**. In appendix 1 of TGSA it is explained that "*an official safety report of a cosmetic ingredient*", signed by the safety assessor, is requested for all individual ingredients present in a

cosmetic product. If complete and if available, these reports resemble the stand-alone opinions as prepared by the SCCS. However, the latter are not specifically linked with a commercial cosmetic product. The information given in "*an official safety report of a cosmetic ingredient"* provides the same information as present for that ingredient in the PIF, but it is in the PIF linked with a commercial product and is not a stand-alone.

- **Appendix 2: the safety report of cosmetic products.** This type of report is qua content comparable with the content of a PIF with the differences as explained above. It is said that retention factors need to be mentioned in *"a safety report of cosmetic products".* However, these retention factors have not been defined nor discussed or mentioned before in the TGSA document.
- **Appendix 3: the operating procedures of a cosmetic preservative (efficacy evaluation method).** It is not clear why this method is present here. This is a testing methodology which would rather fit in the Technical Safety Standards. In any case, there is no reason to deviate from the international procedures under ISO-methodology (see also the comment given under microbiology)
- **Appendix 4: transitional safety assessment**. A simpler procedure is described which focuses mainly on the analysis of the formulation under consideration and allowes the use of so-called "*maximum historical use concentrations"* for the ingredients. These maximal concentrations are, however, no safety limits for these ingredients and are therefore only <u>of limited relevance</u> for the safety of other products using the same ingredients *e.*g. when "*the maximum historical use concentration"* is present and safe in a leave on product, it is possible that a much higher concentration could be safely used for a rinse-off product *et vice versa.*

  Where available, a safety assessment as described *in extenso* should be preferred over such "*historical maximum use concentration."*

III. ANALYSIS OF EXAMPLES

Two examples are provided. Although the intention to show examples is educative, they serve here only as examples of how to present the content of a safety report for cosmetic products, one is advised to show more relevant examples.

Formulation (1): is said to be a face cream, but it is not → a cream is either a o/w (oil in water) or w/o (water in oil) emulsion with one or more suitable emulsifiers: these are missing here. Also, the stability of a reference product should be realistic: in the example given the lipid fraction is very limited and cannot be considered as providing a stable emulsion, even when strong emulsifiers would be present. The total sum of all ingredients in a cosmetic product should be 100.00%: this is in the example given not the case. To be suitable as an educative example, it should be clearly shown that the major ingredients are much more data-rich in toxicology safety data than trace ingredients present in the cream (with respect to the

proportionality principle). This is not the case in the example given. The example would best be replaced. Functions of all ingredients should be present together with synthetic or natural origin of the different ingredients. This is not the case, although squalene used in the cream can be of natural (animal) or synthetic origin, which is important if for example one would want to present a vegan cosmetic product. The TTC concept as risk assessment tool should be applied to all ingredients which are 3 or 4 units behind the point. This is not done, although this would have been an excellent occasion to show that the TTC principle is effectively accepted and used.

Formulation (2): this is an aqueous solution, not an emulsion as indicated. In this example, the functions are given for the ingredients, but can be discussed *e.*g. use of emulsion stabiliser, but the formulation is not an emulsion. As in example (1), the major ingredients have nearly no safety data whereas the trace ingredients have. The principle of proportionality is here not present. TTC could have been applied as risk assessment tool as the trace amounts were known and also the structure of the trace ingredients.

IV. POTENTIAL GAPS

During the analysis of the TGSA document, a number of potential gaps have been identified. It should, however, be kept in mind that a number of the points mentioned here as gaps could have been taken up in other official documents. Here it is only indicated that the shortcomings mentioned are not present in the TGSA document. These are:

- No mentioning of NAMs or any description of a prioritisation strategy in favour of validated NAMs.
- Only a limited number of internationally validated 3R alternative methods is accepted, and even less validated 1R (Replacement)-methods.
- Some doubt about the general acceptance of internationally accepted test protocols / methodologies and perhaps an easier acceptance of test results that are obtained with methods according to Chinese legislation (Technical Safety Standards).
- No default factor is included in the risk assessment of cosmetics and their ingredients for oral absorption/bioavailability.
- No guidance for the use of nanomaterials and toxicological requirements is given.
- Absence of a detailed description of a complaint system in post-marketing surveillance.
- Lack of packaging information with respect to composition and impurities.
- Lack of a structure for consumers to retrieve safety information on cosmetic products.
- Lack of a description how CMRs in cosmetics should be dealt with.
- The possibility to use TTC application for genotoxic substances is not clearly present .
- No mentioning of the list of 26 allergens taken up in Regulation (CE) N° 1223/2009 for which special labelling is necessary to protect already sensitised persons.
- Lack of making the connection between the physical and microbiological tests of finished products with their stability and labelling.

- Not following the internationally accepted ISO-standards for microbiological testing of ingredients and finished products.
- No special arrangements for compounds identified as having relevant endocrine disrupting activity.
- Internationally accepted POD terminology is not used.
- Lack of adequate and educative examples of how a 'Cosmetic Ingredient Safety Report' (CISR) and a 'Cosmetic Product Safety Repo' (CPSR) should be presented.
- 'Good Manufacturing Practice' (GMP), important in the EU for making a quality PIF, has not been included in TGSA.

V. GENERAL CONSIDERATIONS

Analysis of the TGSA document and its comparison with the requested European safety assessment documents for cosmetics (NoG and PIF), result in the conclusions that there is similarity in the methodology used and mutual understanding. It is clear that the Chinese safety assessment methodology for cosmetics is becoming more and more aligned with international practice.

More explicit acceptance of internationally recognized test methods, beyond those listed in the 'Standards', is an important step forward and care should be taken that these are effectively applied and trusted. It is of key importance that these principles do not just stay nice wording, but are applied in real life situations. Gaining experience with this new way of working is important and we are ready to provide the necessary help and training.

One of the important discussion points remains the use of experimental animals and the full acceptance of the 3R-principle (Refinement, Reduction, Replacement) when performing risk assessment of cosmetics and their ingredients. Directive 2010/63/EU on the protection of animals used for scientific purposes is in Europe a horizontal 3R-legislation, which became for cosmetics a 1R-legislation in which no animals may be used anymore since March 2013 when the testing and marketing bans became fully implemented. For local toxicity and short-term testing, validated alternatives exist, but these are not yet available for systemic and long-term toxicity testing. One should, however, be aware that in an international context we come closer to animal-free and human-based methodologies {(3D-cultures with microfluidics, mini-organs, spheroids, organs-on-a-chip, human adult stem cells and induced pluripotent stem cells (hiPSC)} and that it is important to give priority to validated NAMs whenever available. Also, 'Next Generation Risk Assessment' (NGRA) is worldwide under development and is based on NAMs to come to an equilibrated WoE risk assessment without the use of experimental animals (Rogiers *et al.,* 2020).

Having reviewed the TGSA document in detail, a number of similarities and differences have been identified which have been carefully written down in this report. Also, a number of gaps were identified, although it is possible that these are taken up in other official documents than the TGSA with which the reviewer is not familiar.

Prof. Em. Vera Rogiers

Bonheiden, 30/3/ 2021

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VII. ABBREVIATIONS AND GLOSSARY OF TERMS

2D	Two-dimensional
3D	Three-dimensional
3R	Refinement, Reduction, Replacement
3T3 NRU PT	3T3 Neutral Red Uptake Phototoxicity Test
Adverse	An adverse response is defined as any treatment-related response that results in change in the morphology, physiology, growth, development or life-span of an organism, which results in an impairment of functional capacity,

	an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other environmental influences (WHO 2004)
Alternative methods	All those procedure which can completely replace the need for animal experiments, which can reduce the number of animals required, or which can reduce the amount of pain and stress to which the animal is subjected in order to meet the essential needs of humans and other animals (Rogiers *et al.,* 2000; Russell *et al.,* 1959)
AOP	Adverse outcome pathway
Art.	Article
BMD	The Benchmark Dose is proposed as an alternative for the classical NOAEL and LOAEL values. The BMD is based on a mathematical model being fitted to the experimental data within the observable range and estimates the dose that causes a low but measurable response (the benchmark response BMR) typically chosen at a 5 or 10% incidence above the control.
BMDL	The BMD lower limit refers to the corresponding lower limits of a one-sided 95% confidence interval on the BMD.
BrdU	5-bromo-2-deoxy-uridine
CISR	Cosmetic Ingredient Safety Report
CMR	Carcinogenic, Mutagenic, toxic to Reproduction
CPSR	Cosmetic Product Safety Report
CSAR	Cosmetic Supervision and Administration Regulation
DA	Defined Approach
DPRA	Direct Peptide Reactivity Assay

EC	European Commission
ECDC	European Center for Disease Prevention
ECHA	European Chemicals Agency
ECVAM	European Centre for the Validation of Alternative Methods
ED	Endocrine Disruptor
EFSA	European Food Safety Authority
ELISA	Enzyme-Linked Immunosorbent Assay
EMA/EMEA	European Medicines Agency
EU	European Union
EURL-ECVAM	European Union Reference Laboratory - European Centre for the Validation of Alternative Methods
Finished cosmetic product	The cosmetic product in its final formulation, as placed on the market and made available to the end user, or its prototype (2009/1223/EC)
GMP	Good Manufacturing Practice
hiPSC	Human induced Pluripotent Stem Cells
IATA	Integrated Approaches to Testing and Assessment
IFRA	International Fragrance Association
***In silico* methods**	Computational approaches that use (quantitative) structure-activity relationship modelling, and read-across between substances on the basis of structural or functional similarities (ICCR, 2014).

***In vitro* test method**	Biological method: using organs, tissue sections and tissue cultures, isolated cells and their cultures, cell lines and subcellular fractions Non-biological method: such as computer modelling, chemical interaction studies, receptor binding studies etc. (Based on Rogiers *et al.,* 2000)
***In vivo* test method**	Test method using living (experimental) animals [Rogiers *et al.* 2000]
ISO	International Organization for Standardisation
JRC	Joint Research Centre
LCR	Lifetime Cancer Risk
LD50	Median Lethal Dose 50%: a statistically derived single dose of a substance that can be expected to cause death in 50% of the dosed animals (expressed in mg/kg body weight)
LLNA	Local Lymph Node Assay
LLNA:DA	LLNA developed by Daicel Chemical Industries, Ltd
LLNA:BrdU	LLNA: BrdU = 5-bromo-2 deoxyuridine
LO(A)EL	The Lowest Observed (Adverse) Effect Level is the outcome of repeat-dose long-term toxicity studies, such as 28-day or 90-day tests with rats, mice, rabbits or dogs, chronic toxicity tests, carcinogenicity tests, teratogenicity tests, reproduction toxicity tests, etc. It is the lowest dose where (adverse) effects can be observed. In the calculation of the MoS, the lowest obtained LOAEL value may be used when a NOAEL is not available. The

	LOAEL should be expressed as mg/kg bw/d. (ECB, 2003)
LTCR	Life Time Cancer Risk
MoS	Margin of Safety
NAM	New Approach Methodology
Nanomaterial	An insoluble or bio-persistent an intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm. (Regulation (EC) N°1223/2009). Deviating definitions in other regulatory fields may also exist.
eNESIL	No Expected Sensitising Induction Level
NGRA	Next Generation Risk Assessment
NO(A)EL, **$NO(A)EL_{sys}$**	The No Observed (Adverse) Effect Level is the outcome of repeated dose toxicity studies, such as 28-day or 90-day tests with rats, mice, rabbits or dogs, chronic toxicity tests, carcinogenicity tests, teratogenicity tests, reproduction toxicity tests, etc. It is the highest dose for which no (adverse) effects can be observed). The NOAEL should be expressed as mg/kg bw/d. In the calculation of the MoS, the lowest obtained NOAEL value is used, in order to take into account the most sensitive species, as well as the relevant effect occurring at the lowest dose possible. Whereas the NOAEL is a dose descriptor for an external dose, the **$NOAEL_{sys}$** is a dose descriptor of the systemic exposure to a substance and is calculated from the NOAEL by use of the proportion of the substance systemically absorbed
NoG	Notes of Guidance
NR	Neutral Red
NRU	Neutral Red Uptake

OECD	Organisation for Economic Co-operation and Development
O/W	Oil in Water
PAO	Period After Opening
PIF	Product Information File
PoD	Point of Departure
QRA	Quantitative Risk Assessment
QSAR	Quantitative Structure-Activity Relationship
RP	Responsible Person
SAM	Scientific Advisory Mechanism
SCCS	Scientific Committee on Consumer Safety
SCOEL	Scientific Committee on Occupational Exposure Limits
SED	Systemic Exposure Dose
STE	Short Time Exposure
STSC	Safety and Technical Standards for Cosmetics
TER	Transcutaneous Electrical Resistance
TGSA	Technical Guidelines for Cosmetic Safety Assessment
TTC	Threshold of Toxicological Concern
UDS	Unscheduled DNA Synthesis
UF	Uncertainty Factor
UV	Ultra Violet
WHO	World Health Organisation
W/O	Water in Oil
WoE	Weight of Evidence