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THE INTRODUCTION OF CHINA INTERNATIONAL COOPERATION SUMMIT ON COSMETICS

INTERPRETATIONS OF THE ADMINISTRATIVE PROVISIONS OF COSMETICS REGISTRATION AND FILING MATERIALS

NON-ANIMAL APPROACHES IN SAFETY ASSESSMENTS FOR COSMETIC PRODUCTS

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Abstract

Risk-based assessment plays a vital role to ensure cosmetics are safe for Chinese consumers to use under the new Cosmetic Supervision and Administration Regulation (CSAR). Instead of using data from animal testing of cosmetic products, the CSAR allows manufacturers to take a modern risk assessment-based approach to assess the safety of cosmetic products, i.e., an exposure-driven, ingredient-based product safety evaluation. In line with the general principle and international practice where the consumer safety of cosmetics products is based on the safety of individual ingredients in a product formulation, this new framework allows the use of data from non-animal approaches and human clinical/epidemiological data, along with historical animal data on the ingredients. Such a regulatory movement is a big step forward. Whilst several toxicological testing guidelines on the use of non-animal approaches based on in vitro OCED Test Guideline (TG) methods for local effects (effects seen at the site of application) have already been included in the Safety and Technical Standards for Cosmetics (STSC) from the China National Medical Products Administration (NMPA), several other non-animal approaches exist, which are not currently in the STSC, but are now acceptable in the "Technical Guidelines for Cos-

metic Safety Assessment (draft version)" (TGCSA)[1] released recently. These include the Threshold of Toxicological Concern (TTC), Quantitative Structure Activity Relationships (QSARs) and Grouping/Read Across. Despite the recent progress in China, there are still some gaps in the acceptance of non-animal approaches. For example, some newly accepted methods lack technical guidelines or standards; some other well-recognised non-animal safety assessment approaches that have been used in practice worldwide for many years have not yet been taken for their acceptance, including History of Safety Use (HoSU)[2], the Dermal Sensitization Threshold (DST)[3], and more advanced New Approach Methodologies (NAMs)[4, 5], which use in vitro testing and computational biology to characterise the effects that increasing concentrations of an ingredient have on key biological pathways (including Adverse Outcome Pathways – AOPs) [6] as well as 'omics' techniques such as high throughput transcriptomics to define the highest dose at which an ingredient causes no biological effect.

To raise awareness of non-animal approaches and their application to cosmetic safety in China, and to encourage China to take a pioneering role in developing and applying non-animal approaches to ensure the safety of consumers using cosmetic products, we will release a series of articles in this magazine to introduce a number of widely used non-animal approaches and explain how they could be applied for risk-based safety evaluations of cosmetic ingredients or products. We hope our publications will help pave the way for the transformation of cosmetic safety science in China by helping to enhance the safety assessment capability of the Chinese community across industries, academics, and authorities.

Introduction

On 1st January 2021, the State Council of China enacted its Cosmetic Supervision and Administration Regulation (CSAR), replacing the Cosmetics Hygiene Supervision Regulations (CHSR) implemented in 1990. The notification and registration of

cosmetic products under CSAR will take place from 1st May. One of the significant achievements of this new legislation is the adoption of a modern management framework, coupled closely with state-of-the-art risk assessment methodologies to strengthen an overall supervision and administration of cosmetic products in market. This overhauled legislative framework takes an end-to-end product safety operating model to ensure that consumers are using cosmetic products safely and as intended. It focuses not only on product safety evaluations, but also addresses several essential safety components across the lifecycle of cosmetic products, covering the quality assurance of raw material or ingredients in design, Good Manufacturing Practices (GMP), and post-launch monitoring (i.e., in-market control and post-marketing vigilance). Such a holistic regulatory management scheme allows the responsibility of supervision of cosmetic safety that has relied merely on authorities in the past to be shared across broader shareholders: i.e., industries, industrial associations and other relevant third parties. Therefore, given the current regulatory and technical settings in China, how to shift the focus smoothly from the pre-market safety scrutiny of the past to this updated approach that places cosmetic risk assessment and post-marketing surveillance at the heart of this system, poses a large challenge to both cosmetic companies and Chinese authorities. For the success of these unprecedent regulatory changes in China, it is imperative to evolve corporate responsibilities in cosmetics businesses, including, but not limited to, 1) increasing manufacturing standards, 2) building up scientific capability in cosmetic risk assessments, and 3) raising awareness of self-regulation and risk management on post-marketing vigilance and adverse reaction monitoring. Meanwhile, it is also paramount for regulatory authorities (both national and local) to strengthen their capability in assessing the scientific validity of any risk-based cosmetic assessment dossiers submitted for notifications or registrations and further improve their supervision system in monitoring potential adverse effects in consumers. Above all, continuing to enhance the capability for risk-based cosmetic assessments will be key, for both regulatory authorities and for cosmetic industries, to ensure that con-

sumers continue to have access to safe cosmetic products during such a historical regulatory evolution in China.

Risk-Based Safety Assessment (RA)

As a modern safety evaluation methodology, risk-based safety assessment adopted in CSAR and described in the secondary normative document of the "The Technical Guidelines for Cosmetic Safety Assessment (draft version) (TGCSA)" [1], is one of the biggest breakthroughs of the product safety management of cosmetics in Chinese legislation history. It follows the most state-of-the-art cosmetic risk assessment principles in the world, moving away from an out-of-date hazard-based method to a risk-based approach to product safety. In the past, Chinese cosmetic safety primarily relied on pre-market safety scrutiny using a set of checklists based on animal tests on final products. Such animal-based methods entail several scientific disadvantages. For example, consumers' exposure information (habits and practice data on consumer use of different product types) has not been taken into account for assessments and results obtained from animals (e.g., rats, guinea pigs and rabbits) may not accurately predict the safety of products to human due to biological differences between species. In contrast, risk-based methodology is scientifically sound and widely used as both hazard data on all ingredients within a product as well as consumer exposure data are taken into consideration when assessing the risk a product may pose to human health. This is in line with the fundamental toxicological principle: "Solely the dose determines that a thing is not a poison", which is a famous toxicological statement from Paracelsus, "father of modern toxicology" [7]. The risk-based method with its scientific advantages has demonstrated its practical values in protecting consumers for decades in EU and USA, and is now widely used across the world. We believe the new CSAR, underpinned by risk-based safety assessment is capable of better protecting Chinese consumers and serving the Chinese cosmetics industry well to innovate with new ingredients and develop novel cosmetic products, leading to an enhanced level of competitiveness for the Chinese cosmetic industry in global markets.

Cosmetics defined in the CSAR include a wide range of product types that we use daily, including shower gels, shampoos, sunscreens, toothpastes, moisturisers, deodorants and make-up. These products contain many different ingredients that perform a variety of functions (e.g., structurants, preservatives, surfactants, moisturisers, colours, emulsifiers, and fragrances) and the safety of these ingredients should be ensured for any consumers who used them.

As stated in the TGCSA, the safety of a cosmetic product relies on the safety of all ingredients and its potential risk substances that are introduced in their raw material or from potential chemical reactions. This well recognised principle is accepted in regulations across the world. Risk assessments of an ingredient or a substance require specific information on

(1)Consumer exposure

This will include information such as the concentration of all ingredients in the formulation, product type/format (which is used to understand the potential routes of consumer exposure, including through the skin, mouth, or lungs), amount of product per use and frequency of use. Some of this information will be available from the marketing company and other information on consumer exposure is available from published surveys (e.g., Cosmetics Europe, Personal Care Products Council (PCPC), and the Scientific Committee on Consumer Safety's Note of Guidance (10th Version)8). However, country-based consumer exposure data should always be preferable for use if they are available.

(2)Toxicological hazard information on the ingredients in the product

Risk assessments must be performed for a number of human health endpoints (as outlined for example in the 'Notes for Guidance' issued by the EU Scientific Committee on Consumer Safety (SCCS)), including local effects (e.g., eye or skin irritation) and systemic effects (e.g., skin sensitisation, repeated dose toxicity, and reproductive toxicity). A large number of data sources for such information exist (e.g., SCCS,

Cosmetic Ingredient Review, PCPC, Research Institute for Fragrance Materials etc.). While most of the historic data information are historical animal experiments, increasingly, non-animal data information is now also available on ingredients from in vitro methods, computational methods, such as QSAR, read-across, as well as outcomes of Weight- of-Evidence approaches (WoE) and the Integrated Approaches to Testing and Assessment (IATA).

The overall risk assessment for a cosmetic product will combine all of this information comparing predicted Consumer Exposure Levels (CEL) with Acceptable Exposure Levels (AEL) and No Observed Adverse Effects Levels (NOAEL) for the ingredients in the product. A typical example of the overall risk assessment process for cosmetics is summarised in Fig 1.

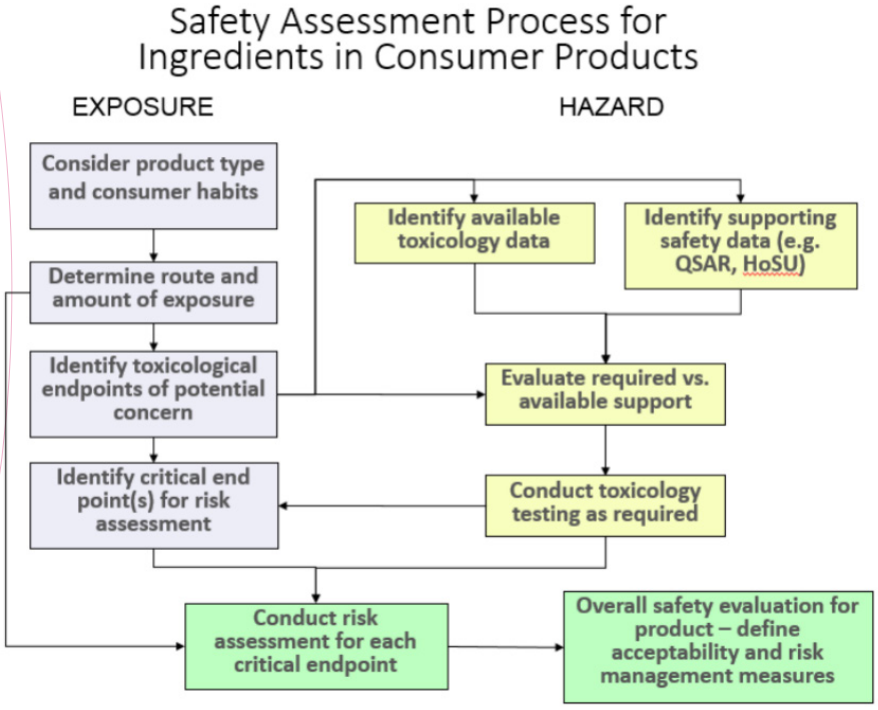

Figure 1. A typical example of safety assessment process for ingredients in consumer products

International Development of Non-Animal Approaches

The majority of historical toxicological data on cosmetic ingredients has been generated based on traditional animal models for many decades. Increasingly, non-animal approaches to chemical safety have been developed and have been used frequently over the last decade. The significant progress in non-animal approaches is driven by multiple interlinked and synergistic key forces, three of which are 1) advancements of sciences and technologies, 2) widely accepted principles of the 3Rs (Replacement, Reduction and Refinement of animal use) and 3) regulatory changes relating to animal testing bans on cosmetics and their ingredients as a global trend across a growing number of authorities.

Advancements of Sciences and Technologies:

Scientific and technological advancement has always created social and economic change. However, the past decade has shown that the speed and scale at which such change can happen is phenomenal. Chemical safety science is no exception and has been shaped significantly by the innovations and advancements in multiple disciplines from applied bioscience to information technologies (e.g., biology, chemistry, non-animal test methods, 'omics' techniques, exposure science, computational toxicology). More specifically, increased mechanistic understanding of how chemicals cause adverse health effects has led to the Adverse Outcome Pathway (AOPs) concept [6] which avoids the need to conduct animal experiments to identify and characterise toxicity. New methodologies in *in vitro* and *in silico* science and the increased uptake of 'omics' technologies have made it feasible to assess biological pathways and define a point of departure (PoD), i.e., the point established from experimental data or observational data generally corresponding to an estimated low effect level or no effect level.

The cosmetics industry has started to investigate and apply more advanced NAMs to characterise the bioactivity of ingredients, as initially described in the 2007 land-

mark publication from the US National Academies of Sciences 'Toxicity Testing in the 21st Century: A Vision and a Strategy' [8]. These ideas have been developed and extended for cosmetic risk assessment in key publications such as the International Cooperation on Cosmetics Regulation (ICCR) principles [9, 10] and the Notes of Guidance (10th Revision) from the SCCS (SCCS-NoG)[11]. Importantly, these new approaches, based on *in vitro* testing and computational biology do not look to predict the results of historical toxicity studies in rodents. Instead, they characterise the effects that increasing concentrations of an ingredient have on key biological processes or pathways (e.g., AOPs) as well as using 'omics' techniques such as high throughput transcriptomics to define the highest concentration at which the ingredient causes no biological effect. Decisions in risk assessment can be made in a scientific way by some well-developed Weight of Evidence (WoE) approaches which are capable of integrating the evidence from disparate sources, such as information from NAMs, human clinical/epidemiological data, and any available historical animal data. Similar integration strategies, such as the integrated approaches to testing and assessment (IATA), and defined approaches (DA), are also advocated with case studies for decision-making at the Organisation for Economic Co-operation and Development (OECD) level.

3Rs:

The principles of the 3Rs (Replacement, Reduction and Refinement of animal use) have been a framework for performing more humane animal research for over 50 years [12]. They have been embedded in many national and international regulations on the use of animals in scientific research and development, as well as in the policies of organisations that fund or conduct animal research. Worldwide opinion polls of public attitudes consistently show that the 3Rs being put into practice is a must for any animal research. There is no doubt that 3Rs, as an ethically sound principle, will be becoming an even stronger force in moving away from animal testing towards non-animal approaches in sciences, policies, and regulations across the world.

Regulations on animal testing ban:

The safety assessment of cosmetics and their ingredients is regulated differently around the globe. In 2009 and 2013, the Cosmetics Regulation in the EU introduced bans on animal testing for assuring the safety of ingredients in cosmetic products and finished products. To date, there are over 40 countries worldwide, which either followed the EU animal testing ban or restricted animal testing on cosmetics and cosmetic ingredients. For example, a complete ban now exists in the countries that make up the European Free Trade Association (e.g., Norway, Switzerland, Iceland and Liechtenstein), and other countries such as Israel, Turkey, India, South Korea, New Zealand, Guatemala, some states in the United States (e.g., California, Nevada, Illinois, and Virginia); Countries, such as Ukraine, Russia, Argentina, Chile, Colombia, Canada, Brazil, Japan and Australia, are in the process of phasing out animal testing of cosmetics. The European regulatory framework for cosmetic safety serves as a popular model for more and more authorities in the world to follow.

Given the above three major factors, as well as the increased scientific confidence in non-animal approaches, some chemical regulatory authorities have already given priority to existing and validated non-animal methods and evidence derived from NAMs in assessing the toxicity of industrial chemicals. For example, in Europe, the Registration, Evaluation, Authorization and restriction of Chemicals (REACh) Regulation (EC No, 1907/2006) called for the use of NAMs where suitable13, as did the SCCS-NoG. In the EU. In the United States, the recently updated Toxic Substances Control Act states that in fulfilment of the law efforts need to be made to reduce testing in vertebrate animals and implement NAMs (Lautenberg Chemical Safety Act). The followed-up strategic roadmap with its work plan sets up the 2025 and 2035 goals: to prioritize EPA's efforts to reduce animal testing including reducing mammal study requests and funding 30 percent by 2025 and eliminating them by 2035[14, 15].

The achievement of international developments of non-animal approaches were witnessed in many validated *in vitro* OCED Test Guideline (TG) methods, as results of global collaborative effects for over 30 years across many international companies, academia and several validation centres, including the European Union Reference Laboratory for alternatives to animal testing (EURL ECVAM), the Japanese Center for the Validation of Alternative Methods (JaCVAM), the South Korean Center for the Validation of Alternative Methods (KoCVAM), the Brazilian Centre for the Validation of Alternative Methods (BraCVAM), the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) in USA, etc. Most of the currently validated TG address aspects of local toxicity or short-term endpoints (e.g., mutagenicity, eye or skin irritation) and are now accepted by many worldwide regulatory authorities. Widely accepted and validated TGs for systemic and long-term toxicity as not currently available despite considerable progress in this science which has been discussed amongst the international regulatory community [16]. Thus, how to evolve traditional validation principles and apply them to the NAMs with multiple data sources poses a significant challenge to both scientific and regulatory communities.

There are several international initiatives to address the challenges both in sciences and regulations in applying non-animal approaches. Good examples of them are listed below:

- **Accelerating the Pace of Chemical Risk Assessment (APCRA)** was initiated in 2019 among many authority organisations in United States, Canada, Europe, Korea, Japan, Singapore, Australia, together with OECD [17].

- **The Animal-Free Safety Assessment (AFSA) Collaboration** [18] is another collaborative programme from Humane Society International (HSI) between industry, consultants, contract research organizations (CROs), who share the goal of accelerating a modern species-relevant approach to safety assessment globally to better protect

people and our planet, and hasten the replacement of animal testing https://www.afsacollaboration.org/. AFSA will be an ongoing source of education and training material on non-animal approaches in multiple languages.

- **The European Partnership for Alternative Approaches to Animal Testing (EPAA)** is a unique partnership between the European Commission, 37 companies, and 8 European industry federations, with an overall goal to replace animal testing by innovative, non-animal testing methods, to reduce the number of animals used and to refine procedures where no alternatives exist or are not sufficient to ensure the safety of substances (the '3R principle'). The partners are pooling knowledge and resources to accelerate the development, validation and acceptance of non-animal approaches at national, European and global levels. (https://ec.europa.eu/growth/sectors/chemicals/epaa_en).

- **The International Cooperation on Cosmetics Regulation (ICCR)** is a voluntary international group of cosmetics regulatory authorities from Brazil, Canada, Chinese Taipei, the European Union, Japan, the Republic of Korea, and the United States who meet on an annual basis to discuss cosmetics safety and regulation, as well as enter into a constructive dialogue with relevant cosmetics industry trade associations. https://www.iccr-cosmetics.org/. Last year, China joined the ICCR meeting as an observer.

- **The Long Range Science Strategy (LRSS)** is Cosmetics Europe's scientific research programme on non-animal methods. Started in 2016, LRSS was originally intended to run for five years but due to its success, it is now to continue the programme beyond 2020.

Since 2000, over €650 million in the EU and at least as much in the USA 19, have been spent on the development of NAMs through numerous scientific programmes

and projects across the world (e.g., the EU Horizon 2020 Project EUToxRisk https://www.eu-toxrisk.eu/, UK 3Rs programmes https://www.nc3rs.org.uk/, USA ToxCast & Tox21 20, 21) will hasten the watershed moment when NAMs are eventually adopted for chemical safety evaluation by global regulators.

National Development of Non-Animal Approaches in China

The beginning of national developments of non-animal approaches in China dates back to the 1990s. In 1997, four Chinese ministries (i.e., the Chinese Ministry of Science and Technology (MoST), Agriculture, Health and Food Drug) proposed the first development plan for non-animal approaches in China linked to the 3Rs principles of laboratory animal sciences [22]. Further efforts were evident in an animal welfare science policy issued by MoST in 2001 as well as the inclusion of China as an observer within a number of international programmes related to non-animal approaches (e.g., the OECD Test Guidelines Programme, International Cooperation on Alternative Test Methods, and International Cooperation on Cosmetics Regulation (ICCR), etc). The main purpose, at an early stage, was to raise the awareness of non-animal approaches and their applications within Chinese authority laboratories (e.g., China Food Drug Administration (CFDA, former of the NMPA), China Inspection and Quarantine Bureaux (CIQ), Centre for Disease Control and Prevention (CDC)).

As seen in the rest of the world, significant progress in non-animal approaches in both science and regulations in China have been made over the last decade, following many years' domestic efforts led by a few Chinese pioneer scientists in toxicology as well as rising international cooperation or collaboration from foreign governments, companies and NGOs across the globe [23]. Knowledge and capability development in the use of non-animal approaches across many authority laboratories have been greatly improved. The establishment of the two societies: the Chinese Society of Toxicological Alternatives & Translational Toxicology (TATT) un-

der the China Society of Toxicology (C-SOT) and the Society of Toxicity Testing and Alternatives (STTA) under the Chinese Environmental Mutagen Society (CEMS) has been continually shaping the Chinese landscape of non-animal approaches to a next higher level. The momentum of carrying out the developments of non-animal technologies has been further spurred by the Chinese government with increased innovation funding from both the National Natural Science foundation of China and the Key Science Programmes of MoST. A growing number of achievements have appeared across many academia, research institutes and regulatory laboratories [24, 25, 26, 27].

More specifically, a number of the OECD methods were adopted in STSC for cosmetic safety evaluations after they were successfully verified by the National Institutes for Food and Drug Control (NIFDC). Table 1 lists all in vitro methods or methods that provide 3R benefits. NMPA has a plan to continue to expand the table with other existing OECD TG in vitro methods through their rigorous verification process and shall update STSC annually with these verified[27, 28]. In parallel, cosmetic regulations on safety assessments have been gradually moved away from animal testing on finished cosmetic products. From July 2014, domestically manufactured "non-special" cosmetics, such as shampoo, shower gel, and some skin care products, could be marketed in China without product testing on animals, where safety information based on risk assessment is acceptable [29, 30]. A step change under the new CSAR will allow imported common cosmetics to be exempt from animal testing from May 1st, 2021, though the change is not applicable to special cosmetics (i.e., spot corrector/whitening, sunscreens, hair dyes, hair perms, anti-hair loss, new functional products / claims) or any types of cosmetics with new ingredients.

Table 1: Adopted OECD TG methods in “Safety and Technical Standards for Cosmetics”

Method	OECD TG	Category	Issued date
3T3 Neutral Red Uptake (NRU) Phototoxicity Test	432	Phototox	11/11/2016
in vitro skin corrosion. Transcutaneous electrical resistance test (TER)	430	Corrosive	21/8/2017
Short Time Exposure In vitro Test Method (STE)	491	Eye Irritation	22/3/2019
Local Lymph Node Assay: DA (LLNA:DA)	442A	Skin sensitisation	22/3/2019
Local Lymph Node Assay: BrdU-ELISA	442B	Skin sensitisation	22/3/2019
Direct Peptide Reactivity Assay (DPRA)	442C	Skin sensitisation	22/3/2019
Bacterial Reverse Mutation Test	471	Genetox	2007 then22/3/2019
In vitro mammalian cell gene mutation tests using the thymidine kinase assay	490	Genetox	2007
In vitro mammalian cell gene mutation tests using the Hprt and xprt genes	476	Genetox	2007
In vitro mammalian chromosomal aberration test	473	Genetox	2007
In Vitro Mammamlian Cells Micronucleus Test	487	Genetox	2021

Challenges and Outlook in China

The implementation of CSAR and its secondary guidelines will be a great millstone in Chinese cosmetic regulatory history, marking a beginning of a new era founded on a risk assessment-based safety evaluation of cosmetics under a modern supervision and management system.

Although such an approach to the safety of cosmetics has been in practice in many foreign countries for over 40 years, little hands-on experience of this approach

exists in both industries and authorities in China. There will be a number of safety assessment challenges ahead that will be faced by relevant Chinese communities linked to cosmetic products. Firstly, capability building across industries and regulators will be necessary to carry out the risk assessment-based safety evaluations on thousands of various types of cosmetic products; secondly, continuing training and education on some of the accepted non-animal approaches in the TGCSA, such as the TTC, QSARs and Grouping/Read Across, should be provided more widely in China, as they were only introduced into the Chinese toxicological community a few years ago and their application to the safety of ingredients may be relatively new to Chinese safety assessors; finally, there will be opportunities for Chinese regulators or regulatory scientists to come across to review some applications of non-animal approaches that are not explicitly mentioned in the TGCSA (e.g. HoSU, DST and NAMs for NGRA) in a submitted safety dossier for novel ingredients or formulations, where a safety conclusion may well be determined based on evidence from multiple data sources derived from non-animal approaches.

Therefore, continuing ongoing knowledge exchange of existing or novel non-animal approaches among cosmetic safety evaluation experts between China and overseas would be beneficial to ensure the safety of cosmetics and better protect consumers both in China and in the rest of the world.

To raise awareness of non-animal approaches and their application to cosmetic safety in China, and to encourage China to take a pioneering role in developing and applying non-animal approaches to ensure the safety of consumers using cosmetic products, we will release a series of articles in this magazine to introduce several widely used non-animal approaches and explain how they could be applied for risk-based safety evaluations of cosmetic ingredients or products. We hope our publications will help pave the way for the transformation of cosmetic safety science in China by helping to enhance the safety assessment capability of the Chinese community across industries, academics, and authorities.

References

1.National Medical Products Administration. Notice on Soliciting Public Opinions on the Notes of Guidance for Cosmetic Safety Evaluation (Draft) and the Rules and Catalogue for Categorization of Cosmetics (Draft). Available online: https://www.nmpa.gov.cn/xxgk/zhqyj/zhqyjhzhp/20200729175501268.html (accessed on 29 Jan 2021).

2.Neely, T et al. A multi-criteria decision analysis model to assess the safety of botanicals utilizing data on history of use. Toxicology international vol. 18, Suppl 1: S20-9. doi:10.4103/0971-6580.85882

3.Safford RJ. The Dermal Sensitisation Threshold- a TTC approach for allergic contact dermatitis. Regul Toxicol Pharmacol. 2008 Jul;51(2):195-200. doi: 10.1016/j.yrtph.2008.02.010. Epub 2008 Mar 18. PMID: 18406502.

4.Baltazar, M.T., et al. A Next-Generation Risk Assessment Case Study for Coumarin in Cosmetic Products, Toxicological Sciences, Volume 176, Issue 1, July 2020, Pages 236 252, https://doi.org/10.1093/toxsci/kfaa048

5.Thomas R. S., Bahadori T., Buckley T. J., Cowden J., Deisenroth C., Dionisio K. L., Frithsen J. B., Grulke C. M., Gwinn M. R., Harrill J. A., et al. The next generation blueprint of computational toxicology at the U.S. Environmental Protection Agency. Toxicol. Sci. 169, 317–332. (2019)

6.G.T. Ankley, et.,al, Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment, Environ Technol Chem, 29 (2010), pp. 730-741.

7.Joseph F. Borzelleca, Paracelsus: Herald of Modern Toxicology, Toxicological

Sciences, Volume 53, Issue 1, January 2000, Pages 2–4, https://doi.org/10.1093/toxsci/53.1.2

8.National Research Council. Toxicity Testing in the Twenty-first Century: A Vision and a Strategy. The National Academies Press, Washington, DC. 2007

9.Dent M, Amaral, RT, Silva PA, et al. Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients. Computational Toxicology, Volume 7, 2018:7; 20-26, https://doi.org/10.1016/j.comtox.2018.06.001.

10.REPORT FOR INTERNATIONAL COOPERATION ON COSMETICS REGULATION Regulators & Industry Joint Working Group (JWG): Integrated Strategies for Safety Assessment of Cosmetic Ingredients: Part 2

11.Scientific Committee on Consumer Safety. The SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation 10th Revision (SCCS/1602/18). Available online: https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_224.pdf (accessed on 22 March 2021).

12.Russell WMS, and Burch RL. The Principles of Humane Experimental Technique. Methuen, London, 1959.

13.European Parliament and Council of the European Union Regulation (EC) No 1907/2006 of the European parliament and of the Council of 18 December 2006 concerning the registration, evaluation, authorisation and restriction of chemicals (REACH), establishing a European chemicals agency, amending directive 1999/45/EC and repealing Council regulation (EEC) No 793/93 and commission regulation (EC) No 1488/94 as well as Council directive 76/769/EEC and commission directives

91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC http://data.europa.eu/eli/reg/2006/1907/oj (2006) (accessed on 22 March 2021)

14.USEPA. New approach methods work plan: Reducing use of animals in chemical testing. U.S. Environmental Protection Agency, Washington, DC. 2020. (EPA 615B2001)

15.Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program, June 2018. https://www.epa.gov/sites/production/files/2018-06/documents/epa_alt_strat_plan_6-20-18_clean_final.pdf (accessed on 22 March 2021)

16.Paul Friedman, Katie et al. "Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization." Toxicological sciences: an official journal of the Society of Toxicology vol. 173,1 (2020): 202-225. doi:10.1093/toxsci/kfz201

17.Gwinn M. and Friedman K. Accelerating the Pace of Chemical Risk Assessment (APCRA): An International Governmental Collaborative Initiative. Presented at CSS Science Seminar Series Webinar, Washington, DC, June 25, 2019. https://doi.org/10.23645/epacomptox.8512133

18.Report: Non-Animal Cosmetic Safety Assessment (NACSA) – Announcing a collaboration to achieve complete safety assessment of cosmetics without the use of animals – SoT launch report (2019). Available online https://tt21c.org/wp-content/uploads/2019/04/Flash-Report_NACSA-Breakfast_2019.pdf (accessed on 22 March 2021).

19.Cronin M, Doe J, Pereira M, Willett C. Re: A call for action on the development and implementation of new methodologies for safety assessment of chemical-based

products in the EU – A short communication Regulatory Toxicology and Pharmacology, 122, 2021.

20.Richard, A., R. Judson, K. Houck, C. Grulke, P. Volarath, I. Thillainadarajah, C. Yang, J. Rathman, M. Martin, J. Wambaugh, T. Knudsen, K. Mansouri, J. Kancherla, G. Tier, A. Williams, S. Little, K. Crofton, AND R. Thomas. The ToxCast Chemical Landscape - Paving the Road to 21st Century Toxicology. CHEMICAL RESEARCH IN TOXICOLOGY. American Chemical Society, Washington, DC, 29(8):1225-1251, (2016).

21.Hur J, Danes L, Hsieh JH, McGregor B, Krout D, Auerbach S. Tox21 Enricher: Web-based chemical/biological functional annotation analysis tool based on Tox21 toxicity screening platform. Mol Inform. 2018 May;37(5):1700129. doi: 10.1002/minf.201700129.

22.MoST of P. R. China, Opinions on laboratory animal science development, the Ninth Five-Year Plan on National Economy and Social Development. Policy No (1997 - No 432) (in Chinese), 1997.

23. Curren, R. and Jones, B. China is Taking Steps Toward Alternatives to Animal Testing. ATLA 40 (1): 1-2. 2012.

24.Yang Y. et al. Establishment and use of 3T3 NRU assay for assessment of phototoxic hazard of cosmetic products. AATEX 14, Special Issue, 515-518, 2009

25.Yang, Y., et al. Combined in vitro tests as an alternative to in vivo eye irritation tests. ATLA: Alternatives to Lab Animals. 38(4):303-314. 2010.

26.Yuan H, Zhang Q, Guo J, Zhang T, Zhao J, Li J, et al. A PGC-1alpha-Mediated Transcriptional Network Maintains Mitochondrial Redox and Bioenergetic Homeostasis against Doxorubicin-Induced Toxicity in Human Cardiomyocytes: Implementation of

TT21C. Toxicol Sci (2016) 150(2):400-17. doi: 10.1093/toxsci/kfw006. PubMed PMID: 26781513.

27.Luo FY, Su Z, Wu J, Zhang FL, Xing SX, Wang GL, Lu Y. The current status of alternative methods for cosmetics safety assessment in China. ALTEX. 2019;36(1):136-139. doi: 10.14573/altex.1808021. Epub 2018 Nov 19. PMID: 30456413.

28.National Medical Products Administration. Announcement of inclusion of analytical method for preservatives and other 7 testing methods to STSC (2015). 2021-No. 17, issued on 2nd March 2021 (In Chinese)

29.CFDA (2011) Note on the management and the notification process of domestic non-special use cosmetics. Record: [2011] No. 181, issued on 21st April 2011 (In Chinese)

30.CFDA (2014) A further clarification letter on the implementation issues of cosmetic registration and notification. Record: [2014] No. 70, issued on 11th April 2014 (In Chinese).

REFERENCE FOR THE INDUSTRY
WORK EXCHANGE

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CHINA HEALTH CARE ASSOCIATION