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Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients

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ABSTRACT

Consumer safety is a prerequisite for any cosmetic product. Worldwide, there is an ever-increasing desire to bring safe products to market without animal testing, which requires a new approach to consumer safety. 'Next Generation Risk Assessment' (NGRA), defined as an exposure-led, hypothesis driven risk assessment approach that integrates *in silico*, *in chemico* and *in vitro* approaches, provides such an opportunity. The customized nature of each NGRA means that the development of a prescriptive list of tests to assure safety is not possible, or appropriate. The International Cooperation on Cosmetics Regulation (ICCR) therefore tasked a group of scientists from regulatory authorities and the Cosmetic Industry to agree on and outline the principles for incorporating these new approaches into risk assessments for cosmetic ingredients. This ICCR group determined the overall goals of NGRA (to be human-relevant, exposure-led, hypothesis-driven and designed to prevent harm); how an NGRA should be conducted (using a tiered and iterative approach, following an appropriate literature search and evaluation of the available data, and using robust and relevant methods and strategies); and how the assessment should be documented (transparent and explicit about the logic of the approach and sources of uncertainty). Those working on the risk assessment of cosmetics have a unique opportunity to lead progress in the application of novel approaches, and cosmetic risk assessors are encouraged to consider these key principles when conducting or evaluating such assessments.

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1. Introduction

Cosmetic products and ingredients should be safe for consumers for their intended use. Historically the safety assessment for some toxicological endpoints relied on animal testing. However, concern for animal welfare, regulatory action and a desire by companies to bring safe products to market without the use of animal testing using more human-relevant data has brought the need for a different approach to evaluating safety. In 2007 the US National Academies of Science (NAS) published a seminal document entitled *Toxicity Testing in the 21st Century, A Vision and a Strategy* [20,16]. This NAS report called for a transformation in toxicity testing, *"from a system based on whole-animal testing to one founded primarily on in vitro methods that evaluate changes in biological processes using cells … of human origin."* This transformation, looking at key events in toxicity pathways rather than animal organs, will require the use of new types of data that have not routinely been used in cosmetic safety evaluation. In 2017, the NAS followed up on the conceptual frameworks laid out in both the 2007 report and a 2012 report on *Exposure Science in the 21st Century* [21], with the report *Using 21st Century Science to Improve Risk-Related Evaluations* [22]. This new report discusses the advances and challenges in risk assessment related to interpreting and integrating new types (and volumes) of data, with an emphasis on exposure considerations. The momentum created by these reports has led to various initiatives, including inter-agency actions on the part of the US government, seeking to expedite and facilitate the adoption of new approaches for the risk assessment of chemicals and medicinal products [14]. In parallel, the use of data and information from new approach methodologies (NAMs) has been discussed in a broader context in Europe in a dedicated European Chemicals Agency (ECHA) Topical Scientific Workshop held in April 2016, identifying their potential and existing barriers to support regulatory decisions for the assessment of chemical substances [8].

The International Cooperation on Cosmetics Regulation (ICCR) is a voluntary international group of cosmetics regulatory authorities from Brazil, Canada, the European Union, Japan and the United States. Other countries participate by written request in an observer status. ICCR was founded in 2007, and provides a multilateral framework to maintain and enable the highest level of global consumer protection by working towards and promoting regulatory convergence, while minimizing barriers to international trade. To achieve this, ICCR has previously produced a number of recommendations relating to the safety evaluation of cosmetic ingredients and products, including principles of cosmetic product safety evaluation, and the use of alternative test methods in cosmetics safety evaluation. Given the rapid evolution in the science of toxicological safety and risk assessment, and the opportunities provided by NAMs as described in the above NAS and ECHA reports, ICCR recognized that a fundamental change in the approach to the safety evaluation of cosmetics is becoming possible. Therefore, under the auspices of the ICCR, a joint working group comprising scientists from each regulatory authority and Industry was convened to agree on and outline the principles for incorporating NAMs into an integrated strategy for risk assessment of cosmetics ingredients (or 'Next Generation' risk assessment). In this context, a Next Generation Risk Assessment (NGRA) is defined as an exposure-led, hypothesis driven risk assessment approach that incorporates one or more NAMs to ensure that use of a cosmetic product does not cause harm to consumers. This paper introduces the principles described in the ICCR report *"Integrated Strategies for Safety Assessments of Cosmetic Ingredients – Part I"*, and provides a discussion and conclusion on the implications of these principles. All previous ICCR reports and recommendations are available at http://www.iccr-cosmetics.org/topics/.

2. Principles for the Next Generation Risk Assessment of cosmetic ingredients

Here we present nine principles to ultimately help those involved in cosmetic safety assessment build integrated safety assessments without generating animal data. These principles are illustrated in Fig. 1, and further explained below. The nine principles relate to the overall goal of the risk assessment, how it should be conducted, and how it should be documented. These principles should be considered before initiating the risk assessment because, to a greater or lesser extent, all the principles inform problem formulation (which is the first step of any risk assessment).

2.1. Principle 1: the overall goal is a human safety assessment

Firstly, the safety assessment should enable a decision to be made on the safety of the ingredient/product to humans, not be designed as a prescriptive or definitive battery of tests to replicate the results of animal studies.

While there are differences in how countries regulate cosmetic products, there are also many commonalities. For example, within the ICCR, it is the responsibility of manufacturers rather than regulators to substantiate the safety of the cosmetic product.

Thus, within each ICCR region there exists the overarching principle that cosmetics must be safe when used according to directions and as customarily intended. Similarly, it is consistent across all five regions

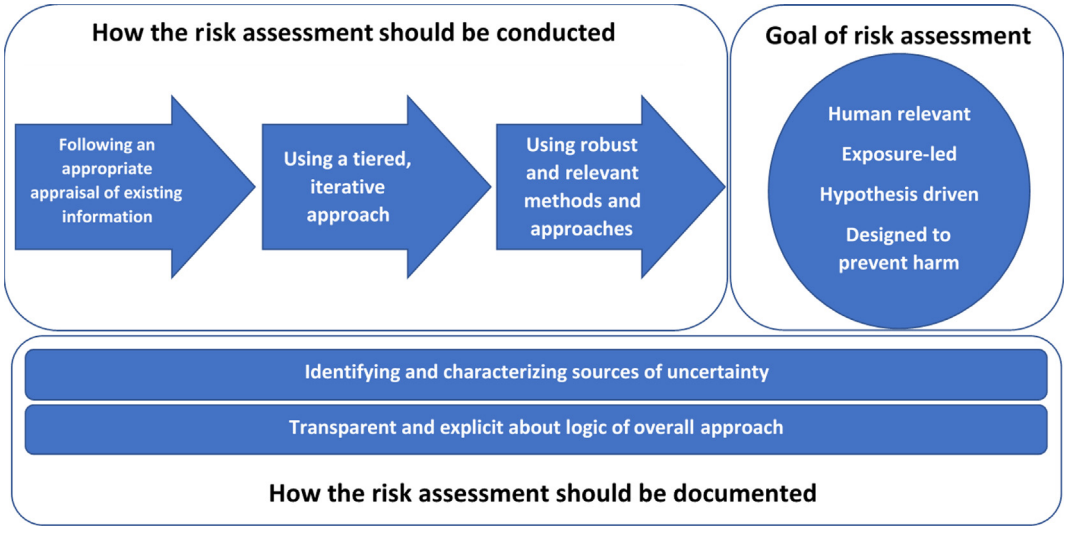

Fig. 1. Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients.