MEMORANDUM ON THE USE OF IN SILICO METHODS FOR ASSESSMENT OF CHEMICAL HAZARD

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Scientific Committee on Consumer Safety

SCCS

MEMORANDUM ON THE USE OF *IN SILICO* METHODS FOR ASSESSMENT OF CHEMICAL HAZARD

The SCCS adopted this Memorandum at its plenary meeting

on 6 October 2016

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Two independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) The Scientific Committees review and evaluate relevant scientific data and assess potential risks. Each Committee has top independent scientists from all over the world who are committed to work in the public interest.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee, on request of Commission services, provides Opinions on questions concerning health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (e.g. cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (e.g.: tattooing, artificial sun tanning, etc.).

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http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm

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1. BACKGROUND

The European Commission's Independent Scientific Committee on Consumer Safety (SCCS) provides scientific opinions on health and safety risks of non-food consumer products (e.g. cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products) and services (e.g. tattooing, artificial sun tanning).
Testing cosmetic ingredients and products on animals, and marketing of new cosmetic ingredients/products tested on animals, is now banned in Europe under the EU Cosmetics Regulation (Regulation (EC) No 1223/2009). This has brought the focus on alternative non-animal methods to derive safety data for cosmetic ingredients. The alternative methods include *in silico* (computational) models and systems that are based on (quantitative) structure-activity relationship, and/or read-across between structurally/functionally similar substances. This Memorandum is intended to provide a general perspective on the current status of *in silico* methods in risk assessment of cosmetic ingredients in Europe.

2. The SCCS Position on Alternative Methods

The SCCS position on the use of alternative methods for obtaining chemical safety data is clarified in the SCCS Notes of Guidance [[1]] as follows:
On page 2 'For the safety evaluation of cosmetic substances, all available scientific data are considered, including the physical and chemical properties of the compounds under investigation, *in silico* data such as results obtained from (Q)SAR ((quantitative) structure activity relationship) calculations, chemical categories, grouping, read-across, physiologically-based pharmacokinetics (PBPK) /toxicokinetics (PBTK) modelling, *in vitro* experiments and data obtained from animal studies (*in vivo*).'
On page 24 'The 3Rs alternatives comprise *in chemico*/*in silico* methods, *in vitro* methods and increasing use of combinations thereof, to obtain a sufficient evidence to allow reliable assessment of safety. Up to now only *in vitro* methods have been validated as predictive tools for local toxicity and mutagenicity/genotoxicity. It is generally acknowledged that before any testing (*in vitro*/*in vivo*) is carried out in the context of risk assessment, all possible information on the substance under consideration should be gathered from different available means. In this regard, *in silico* methodologies have gained importance. Several *in silico* methods are now available that cover different toxicological endpoints (e.g. genotoxicity, skin sensitisation). The predictive computational models are based on either (quantitative) structure-activity relationship ((Q)SAR), expert systems (rule-based models), or grouping/read-across from experimental data on analogous chemicals. Besides guidance documents on grouping/read-across (OECD 2014a), the OECD QSAR Tool Box 1 may be used for a systematic approach to the formation of chemical categories and other chemical analogies and predicting toxicological effects (OECD 2009a). The use of a combination of different approaches in an *in silico* battery usually increases confidence of the derived predictions. However, regardless of the *in silico* models used, the compounds under consideration should fall within the applicability domain of the respective model. Despite such developments, a recent report from the International Cooperation on Cosmetics Regulation (ICCR, 2014) concluded that the current use of *in silico* approaches is largely limited to internal decision making both at the industry and at the regulatory levels in most ICCR jurisdictions, and has not yet been fully adopted as a mainstream alternative to other testing methods for the safety assessment of cosmetic ingredients. Whilst recognising the need for appropriate choice of *in silico* tools and the expertise required for the use and interpretation of the results, and acknowledging certain limitations of the methods, the SCCS is of the opinion that *in silico* methodologies may be best used in a weight of evidence

[1] The SCCS Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation, 9th revision, SCCS/1564/15 (Revised version of 25 April 2016), available at http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_190.pdf

(WoE) approach to the risk assessment of a compound under consideration. This implies that for all the methodologies described in this section, *in chemico* (i.e. grouping and other chemical analogy approaches) and *in silico* (i.e. QSAR) methods should be applied, whenever possible, to derive estimates on toxicity before any experimental testing is considered.'

3. Other observations

In the following a few pointers are provided as a general perspective on the use of *in silico* methods in chemical risk assessment. However, these should not be seen as to represent the official position of the European Commission or any of its Scientific Committees:

1. To scope the prospects and limitations of *in silico* approaches for safety assessment of cosmetics, experts from the SCCS participated in a working group of the International Cooperation on Cosmetics Regulation (ICCR), which is a platform of regulators and industry from the EU, the US, Japan, Canada, and Brazil, and is aimed at developing a common understanding of safety assessment of cosmetics across the different jurisdictions. The ICCR report [2] provides a detailed account of the current status, prospects and limitations of *in silico* methods for safety assessment of cosmetics. The report highlights that, despite a lot of advancement in this field and the need for alternative methods, the use of *in silico* models/systems has not yet been adopted as a mainstream method for safety assessment of cosmetic ingredients in any of the ICCR's jurisdictions. The current use of these methods is largely limited to internal decision making both at the industry and the regulatory levels.
2. The main barrier to the adoption of *in silico* methods seems to stem from the fact that the assessors rely on data from 'validated' methods for regulatory assessments. They may also consider data from 'valid' methods but only as a part of supporting evidence. Whilst several validated *in vitro* methods are currently available and are used in safety assessments, virtually none of the currently available *in silico* model/system carries such a 'validation' tag. Any agreed basis on which an *in silico* model/system can be regarded 'validated', and hence fit for use in a regulatory setting, is currently not in place. A few models/systems, developed under the stringent quality and testing criteria (e.g. according to the OECD principles) are available, but they can at best be regarded as 'valid'.
3. Different models/systems may be built on different datasets and using different algorithm(s). They may therefore process the information in different ways and may yield differing or even contradicting results. Because of the differences in the underlying datasets, each model/system may also have a different applicability domain within which the predicted estimates of toxicity can be considered reliable. In this context, it is not clear how the results from two or more models/systems should be interpreted where the estimates are widely different or contradicting.
4. The usefulness of the commonly available *in silico* models/systems in assessing sterio-isomers of bioactive compounds is doubtful.
5. Each model/system reflects a different level of uncertainty and variability associated with the data used in developing it. Further uncertainty could be added during the modelling process and may be further compounded in the case of integrated models/systems. The *in silico* models/systems should therefore not only provide estimates, but also a measure of uncertainty in the results.

[2] ICCR [International Cooperation on Cosmetics Regulation] (2014) *In silico* Approaches for Safety Assessment of Cosmetic Ingredients, A report for the International Cooperation on Cosmetics Regulation, available at: www.iccrnet.org/files/5314/1407/7607/2014-07_In-silico_Approaches_for_Cosmetic_Product_Safety_Assessments.pdf

6. There is a need for robust frameworks for establishing quality and validity of a given *in silico* model/system, and a systematic way of how more than one model/system can be used to overcome some of the limitations. As the ICCR report has recommended, further work in this area is needed in relation to the development of a uniform and standardised approach that allows the selection and use of appropriate *in silico* system(s), interpretation of the results, and integration of different approaches in a consistent scheme to collate sufficient weight of evidence for use in safety assessment of cosmetic ingredients.

7. The use of *in silico* models/systems and the interpretation of results for chemical safety assessment requires a certain level of expertise in (bio)chemistry and toxicology. It is also a relatively new field for the safety assessors. There is therefore a need for training the safety assessors using a systematic framework that enables them to select and use the right models/systems, interpret the results, and gather sufficient 'weight of evidence' from different *in silico* methods to reliably use in safety assessment in a regulatory perspective.