Brussels,

SUMMARY REPORT OF THE PUBLIC CONSULTATION RESULTS

“DRAFT REPORT ON ALTERNATIVE (NON-ANIMAL) METHODS FOR COSMETICS TESTING: CURRENT STATUS AND FUTURE PROSPECTS - 2010”

I. INTRODUCTION

The Cosmetics Directive bans, as from 11 March 2009, animal testing of cosmetic ingredients being performed on the EU territory. Testing of cosmetic products themselves is already prohibited since 2004. As from March 2009, it is also prohibited to market in the EU cosmetic products containing ingredients which have been tested on animals in order to meet the requirements of the Directive. For the three most complex human health(-related) effects (repeated-dose toxicity including skin sensitisation and carcinogenicity, reproductive toxicity and toxicokinetics) the deadline is extended to March 2013.

In 2011, the Commission has to inform the European Parliament and the Council in case alternative non-animal methods will not be developed and validated before 2013 for these remaining human health(-related) effects. This information must form part of the Commission yearly report on alternatives to animal testing.

Against this background, the “Draft Report on Alternative (non-animal) methods for cosmetics testing: current status and future prospects - 2010” was prepared by experts proposed by stakeholders, under the co-ordination of the European Centre for the Validation of Alternative Methods (ECVAM), hosted by the Institute for health and Consumer Protection of the European Commission's Joint Research Centre. The report aimed at gaining a broad and objective picture of the scientific/technical issues that relate to establishing alternative test methods for the human health(-related) effects falling under the 2013 deadline for the marketing ban of the EU Cosmetics Directive. The report also contained, where possible, a science-based estimate of the time necessary to achieve full replacement of animal testing for the respective endpoints.

II. THE CONSULTATION

On 23 July 2010 the Commission launched a public consultation on the “Draft Report on Alternative (non-animal) methods for cosmetics testing: current status and future prospects - 2010”. The consultation was accessible on the Commission's "Your Voice in Europe" as
well as DG SANCO's cosmetics website\(^1\). Known stakeholders were in addition directly informed by e-mail and in stakeholder meetings.

The Commission invited factual comments, which complement the information provided in the draft report. Comments were invited on the five chapters of the draft report. A comment template form was provided. The deadline for comments was 15 October 2010.

Overall, the Commission received factual comments directly related to the content of the reports from 16 respondents. Of these, 4 were from industry, 3 from regulatory bodies, 3 from animal welfare associations (NGO's), 4 from academia, 1 from the Commission's Scientific Committee for Consumer Safety (SCCS) and 1 was not affiliated.

In 4 cases respondents made general remarks covering all chapters, in 8 cases respondents made specific remarks to all chapters and in 4 cases they made specific remarks to some chapters only. In two of the cases the Commission was informed that respondents published their comments in scientific journals.

In addition the Commission received during this consultation more than 10.000 submissions from citizens who used the consultation to express their opposition against a postponement of the 2013 implementation date and their general support for the testing and marketing ban in the Cosmetics Directive. The mails/letters/faxes followed a standard content and did not contain concrete comments on the chapters of the report. The ethical and political considerations were not subject of this consultation, but will be an important element in the Commission's decision making as to whether or not to propose a postponement of the implementation date.

Responses by Chapter

Chapter 1 - Repeated dose – including chronic, sub-chronic and sub-acute exposure

The Commission received 9 comments on Chapter 1. Out of these, 3 comments came from industry, 3 comments came from academia, 1 from a regulatory body, 1 from an animal welfare group, and 1 from the SCCS.

Chapter 2 - Skin sensitisation

The Commission received 11 comments on Chapter 2. Out of these, 3 comments came from industry, 3 came from academia, 2 from animal welfare associations, 1 from a regulatory body, 1 from the SCCS and 1 comment from a respondent with no affiliation.

Chapter 3 – Carcinogenicity

The Commission received 10 comments on Chapter 3. Out of these, 3 comments came from academia, 2 from regulatory bodies, 2 from industry, 2 from animal welfare organisations and 1 from the SCCS.

Chapter 4 - Toxicokinetics

The Commission received 8 comments on Chapter 4. Out of these, 3 comments were from academia, 2 from industry, 1 from an animal welfare organisation, 1 from a regulatory body and 1 from the SCCS.

Chapter 5 - Reproductive toxicity

The Commission received 10 comments on Chapter 5. Out of these, 4 comments were from academia, 3 from industry, 1 from a regulatory body, 1 from an animal welfare organisation and 1 from the SCCS.

III. General Comments

Industry, regulators and the scientific committee broadly supported the findings of the report as accurately describing the situation in relation to availability and outlook of alternative methods to animal testing. They made a number of suggestions in relation to the structure, the need of a summary chapter and clarifications needed in relation to timing. One industry respondent also provided reflections on the validation process as such. It was also underlined that often methods are useful for hazard identification, but not for risk evaluation.

NGO's presented a more controversial view. They underlined that there was insufficient focus in the draft chapters on the specific nature of cosmetic ingredients, their uses, their local effects and metabolism at the sites of application, and, in particular, on whether their possible absorption into the body would be likely to lead to concentrations at levels approaching thresholds of toxicological concern (TTC).

NGO's also underlined that the evaluation of the suitability of alternatives should focus on whether the alternative methods are sufficiently well developed and predictive of human responses to the same (or better) extent than animal models. They also considered that not all
aspects of the mechanism of action are needed to be covered by a model in order for it to be highly predictive (and therefore useful for regulatory purposes).

One NGO pointed out that in its view, there is no legal basis for any legislative proposal to extend the deadlines with respect to the endpoints skin sensitisation and carcinogenicity, as that these were covered by the 2009 implementation date of the marketing ban. Another NGO underlined that irrespective of the availability of alternatives, the implementation date of the marketing ban should be kept.

One respondent from academia underlined that this was a missed opportunity to come up with new ideas for the way forward and that the experts should have worked on specific proposals how the new non-animal methods may be integrated in a specific testing strategy for cosmetics.

IV. Specific Comments

1) Chapter 1 - Repeated dose – including chronic, sub-chronic and sub-acute exposure

The majority of respondents agreed with the overall content of the chapter. Respondents from academia stated that the chapter was well-written and that the provided text was important and useful.

Industry respondents underlined that the alternative models described cannot currently be used for quantitative risk assessment because there is no generally accepted approach to extrapolate the results they provide to relevant in vivo exposures and/or they are too limited in scope (e.g., they evaluate only one specific cell type or organ type or mode of action).

NGO respondents requested that the conditions which have to be met to ensure a quantitative risk assessment by alternative methods in the near future should be better presented. They also underlined that reliable QSAR models cannot only be derived for simple biological events with a common mode of action.

Several comments were received in relation to the TTC concept. While one respondent from academia did not consider it appropriate for cosmetics, industry and NGO's alike underlined its usefulness. The SCCS respondent pointed out that its use in cosmetics risk assessment was under review by the SCCS.

NGO and industry respondents remarked that the chapter was in parts very much orientated on experiences from testing of pharmaceuticals.

In particular, NGO and industry respondents added references to models they considered relevant and provided corrections and drafting suggestions.

2) Chapter 2 - Skin sensitisation

The majority of substantive comments here related to the conclusions of the chapter. While some industry and academia respondents considered the timeline in the chapter as overly optimistic, certainly for application to all types of ingredients and exposure scenarios, NGO respondents and one industry respondent considered that too much resource and effort is being spent on trying to develop in vitro models for steps that are hypothesised to contribute to determining sensitisation potency but do not need to be modelled in their point of view. In fact, in the respondents view haptenation (protein reactivity) is the key mechanism leading to skin
sensitisation and the combination of reactivity and bioavailability information would be sufficient for the characterisation of sensitising potency. They also suggest that future research activities should focus on the investigations of those chemicals for which the mechanism by which they react with proteins cannot be determined with sufficient confidence.

NGO's underlined that the chapter lacks to propose solutions to address current challenges and plans for moving skin sensitisation alternative approaches forward.

NGO respondents also suggested that reference should be made to the TTC concept as a pragmatic risk assessment tool.

The SCCS respondent provided clarification on current risk assessment requirements.

NGO, academia and the SCCS respondents pointed out that much of the cited work stemmed from the authors of the report and suggested additional references.

3) Chapter 3 – Carcinogenicity

Respondents from academia, regulators, industry and NGO's agreed with the overall conclusion that there is no possibility in the foreseeable future to completely replace animal tests to perform risk assessment for carcinogenicity for cosmetic ingredients.

A respondent from academia underlined that in relation to the genotoxic carcinogens, the balance between in vitro mammalian cell tests and in vivo tests limitations needs to be adequately presented.

Some respondents from academia and regulators clearly stated that the TTC concept is not appropriate for cosmetics ingredients, while respondents from NGO’s underlined the usefulness of the TTC concept.

It was also stated that toxicogenomic approaches reach 80-90% accuracy for predicting in vivo toxicity. However, it is important to point out that very few and only powerful carcinogens have been tested in most of these studies. Thus the capacity to identify weak or unknown carcinogens has not yet been evaluated.

NGO respondents emphasized that apparently data on the two-year cancer bioassay is rarely provided or requested by the SCCS.

Several respondents underlined the limitations of the cancer bioassay (current animal test) to predict human cancer risk.

Some academia emphasized that it is now widely felt that animal carcinogenicity data are not adequate to support the classification of a chemical as “probable human carcinogen” or “probable non-carcinogen.” What is needed is a complete rethink, with the aim of developing methods for identifying potential human carcinogens.

4) Chapter 4 - Toxicokinetics
Academia respondents, regulators and the SCCS expressed views that the chapter was heavily based on experience with pharmaceuticals and that its relevance to the Cosmetics Directive and 2013 is questionable.

NGO's underlined that overall this is a comprehensive and balanced review, which the other chapters may learn from.

However, Industry respondents considered the extensive use of PBPK modeling as a substitute for routine testing within 5 to 7 years as unrealistic.

One respondent from academia commented that several key processes that determine the extent of respiratory uptake are not directly related to cellular translocation and are difficult or impossible to study in *in vitro* cell systems. The respondent highlighted that this chapter stressed toxicokinetics as an important, if not the most important, body of information in the development of replacements to animal testing. It also underlined the usefulness of PBTK modelling in these areas. The respondent agreed fully with these messages, as well as with the arguments given.

According to the SCCS, the chapter is basically addressing pharmaceuticals and shows the complexity that is required to handle these types of compounds. Pharmaceuticals were described as per definition pharmacologically active which was not considered to be necessarily the case for cosmetic ingredients. The level of detail was described as very high making the text quite complex. It was pointed out that in actual safety dossiers of cosmetic ingredients toxicokinetics is included mainly when some uncertainty exists with respect to the safety of a compound and when that compound had a high economical value.

Regulatory body respondents agreed with the conclusion of the authors that the excretion rate of a substance and/or metabolite is difficult to predict, adding that this relates not only to excretion processes via the kidneys but may also involve exhalation of volatile and/or gaseous degradation products. The indicated estimates of 2015 – 2017 for full replacement including excretion seemed also overly optimistic.

5) Chapter 5 - Reproductive toxicity

Respondents from academia, NGO's and industry agreed in their comments that a completely new strategy for this endpoint is needed instead of trying to replace the animal tests. NGO respondents underlined the need to give more attention to *in silico* systems for predicting the uptake of cosmetic ingredients. In the respondents view enough tools should be available to develop an integrated testing strategy. One industry respondent also pointed out that the time needed is likely to be much longer, unless enough resources and collaboration models (e.g. academy, industry, authorities) are established immediately.

The SCCS pointed out that the description of existing OECD in vivo test guidelines was far too long, and provided various corrections in relation to risk assessment requirements.

V. Follow-up given to comments
All comments were submitted to the 5 Working Groups, who analyzed and discussed all comments received and, where considered appropriate, took them into account for the final report. A final plenary meeting of the Working Groups was held on 11 November 2010. The final report is made available on the Commission website\textsuperscript{2} and published in a scientific journal\textsuperscript{3}.

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