Scientific Committee on Consumer Products

SCCP

MEMORANDUM on

Actual Status of Alternative Methods on the Use of Experimental Animals in the Safety Assessment of Cosmetic Ingredients in the European Union

The SCCP adopted this opinion at its 12th plenary on 19 June 2007
About the Scientific Committees

Three 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 Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

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

SCCP

Questions concerning the safety of consumer products (non-food products intended for the consumer).

In particular, the Committee addresses questions related to the safety and allergenic properties of cosmetic products and ingredients with respect to their impact on consumer health, toys, textiles, clothing, personal care products, domestic products such as detergents and consumer services such as tattooing.

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1. INTRODUCTION

One of the mandates of the former SCCNFP (now SCCP) defined by the Commission (doc. n° XXIV/1890/98) is to act as a resource of scientific expertise to the European Commission with regard to the development of alternative methods. As such the SCCP advises the European Commission on the status of alternative methods on animal testing of cosmetics on an on-going basis.

In particular, the Commission requested the former SCCNFP to assess the possibility to replace safety data obtained on the basis of animal tests with data obtained using alternative methods and to indicate those end-points for which no alternative methods are yet available (SCCNFP/0177/99). The SCCP therefore closely follows the scientific developments of alternative methods by academia, industry and public institutions and this in a broad context in order to identify promising alternative methods that are applicable for the safety assessment of cosmetic ingredients and finished products. Also scientific meetings are organised with ECVAM**, COLIPA*** and scientists and colleagues of other scientific committees, SCHER* and SCENIHR**, and in particular the ICCG*** to keep knowledge on 3R-alternatives updated and to evaluate the results of validation studies and their applicability to the cosmetics sector.

Although important progress has been made during the last 5 years (SCCNFP/0546/02 final, SCCNFP/0834/04), the number of officially validated alternative methods, fitting into the 3Rs concept of Russell et al. (1959) and available for the practical application in regulatory testing and risk assessment of cosmetic ingredients is still limited (Rogiers and Pauwels 2005, Eskes and Zuang 2005).

As one of the scientific objectives of the EU is the development and validation of alternative methods that use fewer animals (reduction), cause less suffering (refinement) or completely avoid the use of animals (replacement), several methods in all 3R-categories have been developed and officially validated.

The problem, however, is that for cosmetics and their ingredients, the current EU legislation (Council Directive 76/768/EEC*) establishes a prohibition to test finished cosmetic products and cosmetic ingredients on animals (testing ban), and a prohibition to market in the European Community, finished cosmetic products and ingredients included in cosmetic products which were tested on animals (marketing ban). The testing ban on finished cosmetic products applies since 11 September 2004, whereas the testing ban on ingredients or combination of ingredients will apply step by step as soon as alternative methods are validated and adopted, but with a maximum cut-off date of 6 years after entry into force of the Directive, i.e., 11 March 2009, irrespective of the availability of alternative non-animal tests. The marketing ban will apply step by step as soon as alternative methods are validated and adopted in EU legislation with due regard to the OECD validation process. This marketing ban will be introduced at the latest 6 years after entry into force of the Directive, i.e., 11 March 2009, for all human health effects with the exception of repeated-dose toxicity, reproductive toxicity and toxicokinetics. For these specific health effects, a deadline of 10 years after entry into force of the Directive is foreseen, i.e., 11 March 2013, irrespective of the availability of alternative non-animal tests.

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** ECVAM = European Centre for the Validation of Alternative Methods
** COLIPA = European Cosmetic Toiletry and Perfumery Association
* SCHER = Scientific Committee on Health and Environmental Risks
** SCENIHR = Scientific Committee on Emerging and Newly Identified Health Risks
*** ICCG = Inter-Committee Coordination Group
* As amended by Directive 2003/15/EC
Memorandum on the actual status of alternative methods on the use of experimental animals in the safety assessment of cosmetic ingredients in the European Union

As summarized in the 6th Revision of the "SCCP Notes of Guidance of the testing of cosmetic ingredients and their safety evaluation" (SCCP/1005/06), the specific hazard studies, necessary for human safety assessment of cosmetic ingredients, include acute toxicity, irritation and corrosivity (skin, eye), skin sensitisation, dermal absorption, repeated dose toxicity, mutagenicity/genotoxicity, carcinogenicity, reproductive toxicity, toxicokinetic studies, photo-induced toxicity and human data (if available).

For a number of these tests, validated 3R-alternatives exist, but the list becomes short when only replacement methods are considered.

2. VALIDATED 3-R-ALTERNATIVE METHODS

Validated methods are those methods that are in compliance with the validation process, as set up in the EU by ECVAM* and its independent Advisory Committee ESAC**. This means that their relevance and reliability have been established for a particular purpose, taking into account that a prediction model was present from the start of the validation process (Balls et al. 1997, Worth et al. 2001). In the meantime, the validation process has become more flexible by introducing a modular approach (Hartung et al. 2004).

Upon compliance of a particular alternative method with all modules and after peer review by independent experts, an ESAC endorsement may follow.

Once an alternative method has passed the validation procedure, the SCCP analyses its usefulness for the safety assessment of cosmetic ingredients. It is, for example, important that a sufficient number of relevant cosmetic ingredients, taken up in the annexes of Directive 76/768/EEC, are present among the reference substances included in the validation process.

2.1 Acute toxicity

Three validated alternatives for acute oral toxicity testing exist. They are referenced in the 6th Revision of the "SCCP Notes of Guidance" (SCCP/1005/06):

- the fixed dose method (EC.B1bis, OECD 420)
- the acute toxic class method (EC B.1 tris, OECD 423)
- the up-and-down procedure (OECD 425)

They are combined refinement and reduction methods, but not replacement methods. For acute toxicity testing through the dermal and inhalation routes no validated alternatives are yet available. In the EU Research Programme, FP6*, the integrated project Acute-Tox (www.acutetox.org) has as objective to develop a replacement alternative for oral acute toxicity testing. The results are to be expected after 2010 and are not concerned with acute dermal and inhalation toxicity, which are also important for cosmetic substances.

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* ECVAM = European Centre for the Validation of Alternative Methods
** ESAC = ECVAM Scientific Advisory Committee
* FP6 = FrameWork Programme 6
2.2 Irritation and corrosivity of the skin

For skin corrosion, 3 validated alternatives exist. They are referenced in the 6th Revision of the SCCP Notes of Guidance (SCCP/1005/06):

- the TER test (rat skin transcutaneous electrical resistance test) (EC B.40, OECD 430)
- EpiSkin™ (EC B.40, OECD 431)
- EpiDerm™ (EC B.40, OECD 431)

The last two tests are commercialised reconstructed human epidermal equivalents. The 3 tests are replacement tests that are mainly useful outside the cosmetic field.

For skin irritation, the EpiSkin™ model passed ESAC as a validated alternative method (April 2007). It is proposed as a stand-alone test that could replace the in vivo skin irritation test for the purpose of distinguishing between R38 (irritating to skin) skin irritating and non-irritating substances. The endpoint used is MTT [3-(4,5)-dimethyl-2-thiazolyl-2,5-dimethyl-2H-tetrazolium bromide] reduction. To obtain better sensitivity, while maintaining similar specificity, a second endpoint can be determined: interleukin-1α (IL-1α) production (http://ecvam.jrc.it/index.htm) (31 May 2007). The relevance of the test for safety testing of cosmetic ingredients present in the annexes of Directive 76/768/EEC, is actually examined by the SCCP and appropriate recommendations will be made.

2.3 Eye irritation

No validated alternative method for eye irritation exists. Screening methods for hazard identification (not risk assessment) to eliminate severe eye irritants are the BCOP (Bovine Cornea Opacity Permeability) and ICE (Isolated Chicken Eye) tests. Both tests use tissues from slaughterhouses. The tests replace the use of experimental animals to identify severe irritants, but animal testing is still required for mild and non irritants as in the case of cosmetic ingredients (http://ecvam.jrc.it/index.htm; consulted 31 May 2007). This was agreed at the ESAC meeting of April 2007 based on supporting results from ICCVAM**. Both tests plus two other screening tests, IRE (Isolated Rabbit Eye) and HET-CAM (Hen’s Egg Test-Chorio Allantoic Membrane) are already taken up in the ECB Manual of Decisions for Implementation of the 6th and 7th Amendments to Directive 67/548/EEC, but can, as such, not be used for cosmetic ingredient safety assessment. However, they are useful within REACH*** (Regulation (EC) No 1907/2006) for labelling and transport purposes.

ECVAM has a validation programme on alternative eye irritation testing using eight models. It is generally believed that a battery of in vitro tests will be required to assess the multiple mechanisms involved in eye irritation in vivo.

2.4 Skin sensitisation

The LLNA (Local Lymph Node Assay) (EC B.42, OECD Guideline 429), endorsed in 2000, is a reduction and refinement animal test (referred to in the 6th Version of the SCCP’s Notes of Guidance). Since an allergic response does not occur after a single contact with a substance and at least a second exposure is necessary, the SCCP considers that the LLNA is a "repeated dose toxicity test".

** ICCVAM = Interagency Coordinating Committee on the Validation of Alternative Methods.
*** REACH = Registration, Evaluation, Authorisation and restriction of Chemicals
A reduced LLNA (rLLNA) has been approved by ESAC. A retrospective analysis of published data obtained with the LLNA (Kimber et al. 2006) has taken place. It was concluded that within a tiered testing strategy in the context of REACH a reduced version of the LLNA, using only a negative control group and the equivalent of the high-dose group from the full LLNA, can be used as a screening test to distinguish between sensitisers and non-sensitisers. When compared with the full LLNA, the rLLNA may produce a few false negatives (3/169 in the reference document, reducing to 2/169 when negative results obtained with concentrations of <10% are considered invalid). The rLLNA does not allow the determination of the potency of a sensitising chemical (http://ecvam.jrc.it/index.htm) (31 May 2007). Therefore, the rLLNA, although useful for hazard identification, is not adequate for risk assessment of cosmetic ingredients.

In the on-going FP6 EU Research Programme, the integrated project Sens-it-iv (www.sens-it-iv.eu) is investigating the skin sensitisation process and the development of a replacement alternative. Results are expected after 2010.

2.5 Dermal absorption

In vitro dermal absorption is described in OECD Guideline 428. The SCCNFP adopted a set of basic criteria (SCCNFP/0167/99) which have been updated twice (SCCNFP/0750/03, SCCP/0970/06). OECD 428 addresses dermal absorption from a much broader point of view than the more stringent requirements for cosmetics. Therefore, the SCCP considers that it essential that for cosmetic ingredients not only OECD Guideline 428 but also the SCC(NF)P additions on the basic criteria are applied. The in vitro dermal absorption methodology is a replacement strategy.

Absorption of a substance through the inhalation and oral routes are also of importance for cosmetic ingredients (e.g. in sprays, aerosols, lipsticks and tooth paste). For both, no validated in vitro alternatives are available. In the FP6 Research Programme, the in vitro project LIINTOP (http://www.liintop.cnr.it) just started and considers further optimisation of in vitro intestinal models for in vitro oral absorption.

2.6 Repeated Dose Toxicity

At present, no alternative methods to replace in vivo repeated dose toxicity testing on experimental animals have been proposed nor validated. The SCCP is of the opinion that evaluation of the systemic risk via repeated dose toxicity testing is a key element in evaluating the safety of new and existing cosmetic ingredients. In the FP6 Research Programme, no relevant projects in this field exist, with the exception of the Predictomics project (http://www.predictomics.com) (3 June 2007) which only addresses a limited part of the problems posed (e.g. suitable liver- and kidney-derived test systems to early predict common chronic liver and kidney damage).

In the context of REACH, combined efforts by ECVAM/NICEATM* are done to predict the starting dose by cytotoxicity measurements. Human toxicity seems to be better predicted than animal toxicity. In any case, the outcome is expected not earlier than 2008.

* NICEATM = National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods
2.7 Mutagenicity/genotoxicity

Several *in vitro* mutagenicity/genotoxicity tests are available. They are present in the ECB Manual of Decisions for Implementation of the 6th and 7th Amendments to Directive 67/548/EEC and/or as OECD guidelines. An updated overview is given in the 6th Revision of the SCCP Notes of Guidance. Essentially, the SCCP recommends 3 *in vitro* assays (SCCNFP/0755/03), being

- Bacterial Reverse Mutation Test (EC B.13/14, OECD 471)
- *In Vitro* Mammalian Cell Gene Mutation Test (EC B.17, OECD 476)

The *in Vitro* Micronucleus test was recently validated based on a compilation of existing data. No new studies are necessary (http://ecvam.jrc.it/index.htm).

In case of clear negative results a relevant mutagenic potential of the test compound can be excluded with sufficient certainty. However, when mutagenic activity is indicated, additional *in vitro* and/or *in vivo* testing is usually required. Decisions are taken on a case by case basis and before any *in vivo* testing is considered, a complete scientific analysis of all available data is essential. A recent analysis by Kirkland et al. (2007) demonstrated an extremely high false positive rate in *in vitro* genotoxicity tests when compared with carcinogenicity in rodents. When no *in vivo* rodent carcinogenicity data are available, as often is the case, the usual way to determine whether a positive *in vitro* genotoxicity result is relevant for humans is to develop weight of evidence or mode of action arguments. These can be partly based on *in vitro* investigations, but usually rely heavily on *in vivo* assays (Kirkland et al, 2006).

For hair dyes and hair dye components a specific stepwise *in vitro* testing strategy has been proposed by the SCCP (SCCP/0971/06), in principle consisting of the 3 tests mentioned, extended by:

- an UDS* test in mammalian cells *in vitro* (EC B.18, OECD 482)
- an *in vitro* SHE** cell transformation assay (OECD 495).

However, there is no evidence that increasing the number of *in vitro* assays would result in any increase in the ability to detect a relevant mutagenic potential but is likely to further decrease the specificity.

With the currently available *in vitro* assays performed in accordance with the actual international guidelines it will not be possible to appropriately evaluate a mutagenic potential in many cases. New *in vitro* methods and test strategies are needed. On-going validation work is concerned with *in vitro* cell transformation assays, the comet assay and skin models for genotoxicity testing. However, it is not known at present when these methods will be available as routine tests and whether they can actually enable reliable genotoxicity/mutagenicity testing without *in vivo* testing.

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* UDS = unscheduled DNA synthesis.
** SHE = Syrian hamster embryo.
2.8 Carcinogenicity

For genotoxic as well as for non-genotoxic carcinogens, no validated alternative methods are available or are under development. Recently, an in vitro "omics" project was initiated in the FP6 Research Programme Carcinogenomics (http://www.carcinogenomics.eu/), to detect early markers for geno- and non-genotoxic carcinogens in different types of cell cultures representing liver, kidney and lung.

2.9 Reproductive Toxicity

Validated alternative methods or strategies, covering the large field of reproductive toxicity do not yet exist. Three alternative methods, restricted to embryotoxicity (representing a limited part of the reproductive cycle) have been approved by ESAC (ESAC 2001). They consist of:

- the Whole Embryo Culture (WEC) test
- the MicroMass (MM) test
- the Embryotoxic Stem Cell Test (EST).

The Whole Embryo Culture (WEC) test is still an animal test since pregnant animals are needed as a source of embryos.

These 3 tests have not been taken up in regulatory testing (not in the ECB Manual of Decisions for Implementation of the 6th and 7th Amendments to Directive 67/548/EEC nor in OECD Guidelines) and need further investigation.

At this moment, it is unclear how the above-mentioned methods will be used in general risk assessment procedures. A first requirement is that their relevance is proven for the application area of the compound under question. A suitable alternative method for chemicals is not necessarily relevant for testing of pharmaceutical actives used at low concentrations or for testing of cosmetic ingredients present on the annexes with certain restrictions. In the FP6 Research Programme, the integrated ReProTect project (http://www.reprotect.eu/) is entering its last year, but probably an extension will be necessary.

In the context of REACH, there are efforts to validate an in vivo one-generation study to replace the traditional in vivo two-generation study (EC B.35, OECD 416).

2.10 Toxicokinetic Studies

No validated alternative methods that cover completely the field of ADME (absorption, distribution, metabolism, excretion) exist. Some in vitro models are suitable to study the absorption of substances from the gastro-intestinal tract (e.g. caco-3 cell cultures) or the biotransformation of substances (e.g. isolated hepatocytes and their cultures), but none of the many existing models have been validated (Eskes and Zuan 2005). Although toxicokinetic data for cosmetic ingredients are only requested in certain circumstances, their relevance is high for extrapolating both in vivo and in vitro data to the human situation.

2.11 Photo-induced Toxicity

The 3T3 Neutral Red Uptake Phototoxicity Test (3T3 NRU PT) is a validated replacement test (EC B.41, OECD 432). Besides its validation with a wide variety of chemical substances, it has also been successfully validated using some current UV-filters (Spielmann et al. 1998).
3. FURTHER CONSIDERATIONS

In recent years, progress has been made in the development and validation of alternative methods for regulatory testing of chemical substances in general, but also in the specialist field of cosmetic ingredients (Rogiers and Pauwels 2005). These tests are primarily used for hazard identification and are not suitable for risk characterisation.

Most successes in the development of alternative methods are in local toxicity and short-term testing; they are often reduction/refinement methods. The methodologies consuming the highest number of animals, however, are in long-term testing and systemic toxicity; in these fields validated alternatives and in particular validated replacement alternatives are lacking.

As experience shows the timing of test development, pre-validation, validation, regulatory acceptance and use of alternative methods (Eskes and Zuang 2005), it is unlikely that the deadlines of 2009 and 2013 can be met and concern has been expressed by the SCCNFP (SCCNFP/0834/04), jointly by the CSTEE and SCCNFP (CSTEE 2004), by SCCP, SCHER and SCENIHR together (ICCG/1/06) and recently by ECVAM (ECVAM 2007).

The implementation of REACH in 2007 has accelerated the efforts and initiatives by the Commission and individual parties to develop new alternative methods and validate existing ones. Examples are the creation of epaa* (http://ec.europa.eu/enterprise/epaa/conf.htm, consulted July 2007), the epaa Annual Conferences "Europe goes alternative", ecopa**’s initiatives around REACH (http://www.ecopa.eu) (3 June 2007), the test strategy development for REACH by ECVAM (May 2007), and many other initiatives. However, the question arises how REACH, encouraging the use of the 3Rs strategy and the application of "suitable" and "sufficiently well developed" alternatives (REACH Regulation (EC) No 1907/2006), will affect cosmetic testing strategies. The SCCP considers that the methods proposed for REACH may not be suitable for risk assessment of cosmetic ingredients.

Nanomaterials as cosmetic ingredients (eg. UV-filters nano- ZnO and TiO₂) pose a new challenge for safety testing. As for all validated tests, nanoparticle materials have never been included in the reference compounds during the validation process. This field is not yet developed and needs special attention.

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* epaa = European Partnership for Alternative Approaches to Animal Testing  
** ecopa = European Consensus Platform on 3R-Alternatives
4. CONCLUSION

The actual status for alternative methods suitable for cosmetic hazard testing is summarized in the following table:

<table>
<thead>
<tr>
<th>Validated replacement alternatives available</th>
<th>Validated reduction/refinement alternatives available</th>
<th>No validated alternatives available</th>
</tr>
</thead>
<tbody>
<tr>
<td>- skin corrosivity/irritation*</td>
<td>- acute toxicity</td>
<td>- eye irritation</td>
</tr>
<tr>
<td>- dermal absorption</td>
<td>- skin sensitisation</td>
<td>- repeated dose toxicity</td>
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<tr>
<td>- mutagenicity/genotoxicity</td>
<td></td>
<td>- carcinogenicity</td>
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<tr>
<td>- phototoxicity</td>
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<td>- reproductive toxicity</td>
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<td></td>
<td></td>
<td>- toxicokinetics</td>
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</tbody>
</table>

* skin irritation currently under study by the SCCP

Therefore the SCCP concludes that for 4 endpoints validated replacement alternatives are available, for 2 endpoints validated reduction/refinement alternatives exist; and for 5 endpoints no validated alternative methods are yet available.

The majority of alternative methods is only suitable for hazard identification of cosmetic ingredients, but not for their risk characterisation.

5. REFERENCES

- Balls M. and Fentem J.H. Progress toward the validation of alternative tests. ATLA 25, 33-43, 1997
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ESAC Statement on the scientific validity of the Embryonic Stem Cell Test (EST), the Micromass Test and the Postimplantation Rat Whole-Embryo Culture Assay - in vitro tests for embryotoxicity. Adopted by the ECVAM Scientific Advisory Committee (ESAC) at its 17th Meeting of 16-17 October 2001 at ECVAM, Ispra, Italy (2001).


ICCG/1/06 - Inter Committee Coordination Group of Scientific Committees (ICCG) Position Statement "Alternatives to animal tests". Adopted by the ICCG during the ICCG meeting of 3 July 2006 after consultation of each of the non-food Scientific Committees.


Kirkland D.J., Aardema M., Banduhn N., Carmichael P., Fautz R., Meunier J.-R and Pfuhler S. In vitro approaches to develop weight of evidence and mode of action discussions with positive genotoxicity results. Mutagenesis 22, 161-175, 2007


Rogiers V. and Pauwels M. Good science must be the key factor in the development and use of alternative methods for safety assessment of cosmetics. ALTEX 23 (Special Issue 2006):346-352


SCCNFP/0177/99 - Opinion concerning present development and validation of adequate alternative methodologies to the use of animals in safety testing of cosmetics, adopted by the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers during the plenary of 23 June 1999.

SCCNFP/0245/99, Final: Opinion concerning basic criteria of the protocols for the skin compatibility testing of potentially cutaneous irritant cosmetic ingredients or mixtures of ingredients on human volunteers, adopted by the SCCNFP during the plenary session of 8 December 1999.

SCCNFP/0546/02, Final: Memorandum concerning the actual status of alternative methods to the use of animals in the safety testing of cosmetic ingredients, adopted by the SCCNFP during the 20th plenary meeting of 4 June 2002.


SCCNFP/0834/04 final - Opinion concerning "Report for establishing the timetable for phasing out animal testing for the purpose of the cosmetics directive" issued by ECVAM (30/04/2004), adopted by the SCCNFP on 1 July 2004 by means of the written procedure.

SCCP/0970/06: Opinion on basic criteria for the in vitro assessment of dermal absorption of cosmetic ingredients - updated February 2006, adopted by the SCCP during the 7th plenary meeting of 28 March 2006.

SCCP/0971/06: Updated recommended strategy for testing oxidative hair dye substances for their potential mutagenicity/genotoxicity, adopted by the SCCP during the 7th plenary meeting of 28 March 2006.

SCCP/1005/06: The SCCP's Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, adopted by the SCCP during the 10th plenary meeting of 19 December 2006.


Worth A.P. and Balls M. The importance of the prediction model in the development and validation of alternative tests. ATLA 29, 135-143, 2001