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**REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND
THE COUNCIL**

**Report on the Development, Validation and Legal Acceptance of Alternative Methods to
Animal Tests in the Field of Cosmetics (2009)**

(Text with EEA relevance)

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1. INTRODUCTION

The present report is the ninth Commission report on the development, validation and legal acceptance of alternative methods to animal tests in the field of cosmetics¹. It has a twofold purpose:

- It is the yearly report in accordance with Article 9 of Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products (hereinafter "Cosmetics Directive").² In this regard it reflects the data on the number and type of experiments on animals relating to cosmetic products in 2009, as well as progress made in the development, validation and acceptance of alternative methods to animal testing in the Union and internationally.
- In addition, it informs the European Parliament and the Council that for technical reasons full replacement of the animal tests covered by the 2013 deadline will not be achieved before 11 March 2013.³ The report therefore fulfils the first part of the Commission obligation under Article 4a 2.3 of the Cosmetics Directive. This provision tasks the Commission to "inform the European Parliament and the Council" and to "put forward a legislative proposal in accordance with Article 251 of the Treaty" if the Commission analysis concludes by 2011 "that for technical reasons one or more tests referred to in paragraph 2.1 will not be developed and validated before the expiry of the period referred to in paragraph 2.1". This report does not prejudice how the Commission will respond to the second part, i.e. the decision how to address the lack of non-animal tests.

2. COMPLIANCE WITH THE TESTING AND MARKETING BAN

The Cosmetics Directive foresees a phasing-out of animal testing for cosmetics. A ban of animal *testing* of finished cosmetic products has been in force since September 2004 and a testing ban on *ingredients* or *combinations of ingredients* since March 2009. As from March 2009, it is also prohibited in the EU to *market* cosmetic products and their ingredients which

¹ It is the fifth report following the 7th Amendment of the Cosmetics Directive

² Council Directive of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products, OJ L 262, 27.9.1976, p. 169.

³ For earlier indications see already the 'Report for establishing the timetable for phasing out animal testing for the purpose of the Cosmetics Directive' http://ec.europa.eu/consumers/sectors/cosmetics/documents/animal-testing/index_en.htm

have been tested on animals, irrespective of the origin of these products. This marketing ban applies to all but the most complex human health effects to be tested to demonstrate the safety of cosmetic products (repeated-dose toxicity including skin sensitisation and carcinogenicity, reproductive toxicity and toxicokinetics), for which the legislator extended the deadline to March 2013.

2.1. Animal Testing Data

For the present report, all Member States supplied information on animal tests carried out for the safety of cosmetic products in 2009. Given that the testing ban for ingredients applies as of 11 March 2009, testing in line with the Cosmetics Directive was only possible between 1 January 2009 and 10 March 2009. In total, 344 animals were used in 2009 for tests carried out in relation to the safety of cosmetic ingredients (Table 1). In the previous years, when testing was allowed during the entire period, the figures were 1.818 for 2007 and 1.510 for 2008.

According to the information received, cosmetic ingredients have only been tested on animals in Spain and France. These Member States provided detailed information, including the testing period, the toxicological endpoint, species of animals used for experiments and number of animals used for testing (Table 2). The other 25 Member States reported that no such animal tests were performed in their territory in 2009.

Number of animals used in Member States (2009) – Table 1

	NUMBER OF ANIMALS USED	ANIMALS USED
SPAIN	42	Rabbits
FRANCE	302	Rat, rabbit, guinea-pigs
Total	344	

Number of Animals Used in Relation to Toxicological Endpoints (2009) – Table 2

TYPES OF TESTS / COUNTRIES	SPAIN	FRANCE
Skin irritation	24	12
Eye irritation	18	3
Skin sensitisation		175
Non-lethal toxicity		72
Other		40

2.2. Control and surveillance of the testing and marketing ban

The performance of animal *testing* is closely controlled in Member States and this control will be further strengthened as of 1 January 2013 by Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for

scientific purposes⁴. One case of suspected testing after the deadline of 11 March 2009 was reported, which was given the respective follow-up by the responsible authorities.

In relation to the *marketing* ban, Member States reported that they actively used the market surveillance instruments in place in order to enforce this ban. The main tool mentioned is the control of the product information file in accordance with Article 7a 1. (h) of the Cosmetics Directive. Controlling the provisions in relation to the testing and marketing ban is part of a check list agreed by Member States for the control of product files. Some Member States reported that they particularly drew the attention of the market surveillance authorities to the bans and provided training. Based on the experiences gathered so far Member States did not encounter infringements of the marketing ban.

Member States however also pointed out that ensuring strict market surveillance remains a challenge, considering the limited resources and the risk that manufacturers would include less information in product information file in order to avoid making reference to animal testing data.

3. PROGRESS IN THE DEVELOPMENT, VALIDATION AND LEGAL ACCEPTANCE OF ALTERNATIVE METHODS

3.1. In the European Union

3.1.1. Availability of alternatives for the endpoints falling under the 2009 deadline

Endpoints falling under the 2009 deadline of the marketing ban are : skin corrosivity; skin irritation; dermal absorption; mutagenicity/genotoxicity; phototoxicity; acute toxicity; and eye irritation⁵.

Full replacement alternative methods are currently available for skin corrosivity, skin irritation, dermal absorption, and phototoxicity, while eye irritation, acute toxicity and mutagenicity/genotoxicity are only covered by partial replacement methods. For these endpoints the marketing and the testing ban apply fully, thus unlike for the 2013 endpoints it is not possible to rely on data generated outside the European Union, so that industry has to rely on existing data.

Commission Regulation (EC) 440/2008 brings together all regulatory accepted test methods in relation to the 2009 endpoints. An overview of regulatory accepted test methods is available through the Tracking System for Alternative test methods Review, Validation and Approval in the Context of EU Regulations on Chemicals (TSAR)⁶. None of the relevant animal tests is specific for cosmetics and none of the alternative methods validated so far was solely applicable to cosmetic ingredients either. Annex IX of the Cosmetics Directive therefore has not been amended and does not list any specific alternative methods.

The responsible scientific committee of the European Commission, the Scientific Committee on Consumer Safety (SCCS), has recently adopted an updated version of its "Notes of

⁴ Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, OJ L 276, 20.10.2010, p. 33

⁵ See Timetable established in 2004, SEC(2004) 1210, http://ec.europa.eu/consumers/sectors/cosmetics/files/doc/antest/sec_2004_1210_en.pdf

⁶ <http://tsar.jrc.ec.europa.eu/>

Guidance"⁷, in which it also describes the use of alternative methods in the safety assessment. In June 2010, it issued an opinion setting out "Basic criteria for the *in vitro* assessment of dermal absorption of cosmetic ingredients"⁸.

3.1.1.1 mutagenicity/genotoxicity

In relation to mutagenicity/genotoxicity, the *in vitro* tests are not optimal yet as they are too sensitive and may lead to an undue limitation of ingredients. For this reason, the European Centre for the Validation of Alternative Methods of the Joint Research Centre (ECVAM) is working on improving the current battery of *in vitro* tests. The European Cosmetics Association (Colipa) is focusing on the development of genotoxicity assays based on 3D human skin models and on a human skin metabolism programme focussed on safety assessment of topically applied substances.

3.1.1.2 Eye irritation and acute toxicity

For eye irritation and acute toxicity, several assays were validated by ECVAM, however none of them taken individually can fully replace animal testing in risk assessment. Testing strategies which combine the validated assays are currently under development and evaluation. Further results are expected in 2011. For acute toxicity, a previously validated test method was evaluated with regard to its capacity to identify substances with an LD50 > 2000 mg/kg. The study is currently under peer review by the ECVAM Scientific Advisory Committee.

3.1.2. *Availability of alternatives for the endpoints falling under the 2013 implementation date*

The Commission engaged wide expertise and public input for its assessment of the availability of alternatives for the endpoints falling under the 2013 implementation date. Stakeholders (industry, non-governmental organisations), as well as EU Member States and the SCCS were invited to propose scientific experts. The selected experts analysed, under the co-ordination of ECVAM, the status and prospects of alternative methods. They were also asked to provide realistic estimates of the time required for the development of such methods (where they did not already exist) to a level approaching readiness for validation; i.e. meeting the criteria to enter pre-validation⁹. To allow broad input the Commission carried out a public consultation between 23 July and 15 October 2010¹⁰ on the draft report drawn up by the experts. The summary of the outcome of the public consultation is accessible on the Commission's website¹¹. While the majority of respondents agreed with the overall conclusions of the report, some consider that the available methods are already sufficiently

⁷ The SCCS'S Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, 7th Revision, SCCS/1416/11,

http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_004.pdf

⁸ SCCS/1358/10 http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_002.pdf

⁹ Pre-validation is a small-scale inter-laboratory study to assess the readiness of a test for inclusion in a formal large scale validation study

¹⁰ http://ec.europa.eu/consumers/sectors/cosmetics/documents/public_consultation/index_en.htm

¹¹ See: http://ec.europa.eu/consumers/sectors/cosmetics/documents/animal-testing/index_en.htm

advanced to allow for the safety assessment of cosmetics and that not enough emphasis was placed on the predictivity of the available alternative methods¹².

The result is the expert report "Alternative (Non-Animal) Methods for Cosmetics Testing: Current Status and Future Prospects – 2010" (hereinafter "the technical report"), which is available on the Commission's website¹³ and is also published in a peer reviewed journal¹⁴. This report contains a detailed overview of the alternative methods currently under development.

3.1.2.1. Repeated Dose Toxicity

Repeated dose toxicity occurs if a persistent or progressively deteriorating dysfunction of cells, organs or multiple organ systems, results from long-term repeated exposure to a chemical.

Alternative methods have so far been developed mainly with the aim of producing stand-alone methods predicting effects in specific target organs. *In vitro* models in relation to six of the most common targets for repeated dose toxicity (liver, kidney, central nervous system, lung, cardiovascular and haematopoietic system) exist. However, for the purpose of quantitative risk assessment, an integrated approach, e.g. based on the understanding of the mode of action and perturbation of biological pathways leading to toxicity, is needed.

In addition to *in vitro* techniques, initial attempts of computer-based modelling techniques have suggested the feasibility of developing models providing meaningful predictions of chronic or repeated dose toxicity. At present, a few such models are available. In addition, so-called "omics"-technologies have been developed in recent years for the purpose of understanding, and ultimately predicting toxicity.

The majority of these tests and tools are however at the research and development level. While these methods may be useful for hazard identification of target organ toxicity or for obtaining mechanistic information, none of them is currently seen as appropriate for quantitative risk assessment for repeated dose toxicity. An integrated approach needs to be developed.

To address the lack of methods replacing animal tests in the assessment of toxic effects of chronic exposure, the Commission launched a EUR 25 million research initiative entitled "Towards the replacement of repeated dose systemic toxicity testing in human safety assessment"¹⁵. As a result, 7 new research projects in this field have started in January 2011. These projects will closely cooperate to lay the scientific foundation for future safety testing methods with a higher predictive value, faster and cheaper than animal tests. They will combine the research efforts of over 70 European universities, public research institutes and companies. Colipa has committed to contribute to these projects by an additional EUR 25 million.

¹² See for example BUAV, *Meeting the Deadline of the 2013 EU Marketing Ban. A Scientific Review of Non-Animal Tests for Cosmetics*, 2011.

¹³ See http://ec.europa.eu/consumers/sectors/cosmetics/documents/animal-testing/index_en.htm

¹⁴ "Alternative (non-animal) methods for cosmetics testing: current status and future prospects—2010" in *Archives of Toxicology*: Volume 85, Issue 5 (2011), Page 367

¹⁵ FP7-Health-2010-Alternative Testing

In conclusion, it is estimated that methods for full animal replacement with regulatory accepted tests/strategies will not be available by 2013. As full replacement for repeated dose toxicity is extremely challenging the experts could not provide a clear timeline by when they expect this to be possible.

One specific endpoint to assess repeated dose toxicity, is skin sensitisation. This is the toxicological endpoint associated with chemicals that have the intrinsic ability to cause skin allergy.

Several non-animal methods are being developed for hazard identification; but data from these test methods alone will not be sufficient for risk assessment decision-making as they do not provide potency information. Full replacement of the current *in vivo* assays will not require mimicking all mechanistic steps of skin sensitisation. However, at present it is not possible to predict which combinations of assays are needed to derive potency information for individual chemicals and exposure scenarios. Consequently, a tool box covering a range of mechanistic steps has been reviewed which could provide the required information. Previous efforts by Colipa have led to the successful development of three *in vitro* test methods for the detection of potential sensitisers¹⁶. At present, there are nine ongoing research and method development projects at Colipa in this area.

In conclusion, the view of the experts is that in 2013 no full replacement of *in vivo* methods will be available. By 2017-2019 the experts expect the scientific ability to generate the necessary information for making skin sensitisation risk assessment decisions using a toolbox of non-animal test methods. Hazard identification without potency information might be possible earlier, allowing for the identification of non-sensitisers.

Another specific endpoint on repeated dose toxicity is carcinogenicity. Carcinogenesis is a complex long-term multi-factorial process, and consists of a sequence of stages. Carcinogens have conventionally been divided into two categories according to their presumed mode of action: genotoxic carcinogens that affect the integrity of the genome by interacting with DNA and/or the cellular apparatus, and non-genotoxic carcinogens that exert their carcinogenic effects through other mechanisms.

A combination of shorter-term *in vitro* and *in vivo* studies, including genotoxicity assays, is accepted to provide sufficient information for assessing the genotoxic potential of substances. Repeated dose (typically 90-day) toxicity studies are required to assess the risk of non-genotoxic chemicals.

Several *in vitro* short-term tests at different stages of development and acceptance are available. However, they will currently not be sufficient to fully replace the animal tests needed to confirm the safety of cosmetic ingredients. The current alternatives are focused on hazard evaluation only and cannot be used currently to support a risk assessment with the necessary quantitative dose-response information. However, for some chemical classes the available non-animal methods might be sufficient to rule out carcinogenic potential in a weight of evidence approach.

¹⁶ The direct peptide reactivity assay (DPRA), the human Cell Line Activation Test (h-CLAT) and the Myeloid U937 Skin Sensitisation Test (MUSST)

The experts conclude that alternatives will not be available by 2013 and they are unable to suggest a timeline for full replacement of animal tests currently needed to fully evaluate carcinogenic risks of chemicals.

3.1.2.2. Reproductive Toxicity

Reproductive toxicity refers to a wide variety of adverse effects that may occur in different phases within the reproductive cycle, as a consequence of one or more exposures to a toxic substance, including effects on fertility, sexual behaviour, embryo implantation, embryonic/foetal development, parturition, postnatal adaptation, and subsequent growth and development into sexual maturity.

Among the various stages in the reproductive cycle, embryo-foetal development is considered as one of the most critical steps. Substantial effort has been spent in the development of promising *in vitro* assays, such as the Zebrafish embryo test and pluripotent embryonic stem cell models, to allow for the detection of the teratogenic potential of substances. However, besides their current role as mechanistic support and screening tools, the role of alternative methods as part of integrated testing strategies for regulatory toxicity evaluations has to be defined further.

The complexity of mammalian reproduction requires integrated testing strategies to be able to fulfil all needs for hazard identification and risk assessment. A promising way forward is the use of recently established comprehensive databases in which toxicological information derived from standardised animal experimentations is collected.

The experts estimate that the development of a testing strategy will need more than 10 years to complete.

3.1.2.3. Toxicokinetics

Toxicokinetics informs about the penetration into and fate within the body of a toxic substance, including its absorption, distribution, metabolism (producing less toxic metabolites (detoxification) or in some cases more toxic metabolites) and excretion.

Toxicokinetics is an essential and central body of information for non animal testing strategies for systemic toxicity. A whole array of *in vitro/in silico* methods at various levels of development is available for most of the steps and mechanisms which govern the toxicokinetics of cosmetic substances. Some of these were subject of EU funded projects, such as Predict-IV. By contrast, for excretion no *in vitro/in silico* methods are available. In addition, there is a lack of experience for absorption through the lung alveoli, which calls for strengthening relevant research and development given the fact that this route of exposure is important for cosmetics.

The experts estimate that alternative methods to predict renal and biliary excretion, as well as absorption in the lungs need at least 5 to 7 years of development. However, the development of an integrated approach, linking the results from *in vitro/in silico* methods through toxicokinetics *in silico* modelling towards the full replacement of animals will take even more time.

3.2. At International Level

The Commission has put the issues of validation and regulatory acceptance of alternative methods high on its agenda of sectoral regulatory dialogues at both multilateral and bilateral level.

3.2.1. Multilateral level

The Commission continues to actively work with its counterparts from the United States, Japan and Canada in the framework of the "International Cooperation on Cosmetic Regulation" ("ICCR"). In this context, the International Cooperation on Alternative Test Methods (ICATM) that started in September 2008, was implemented in April 2009 by a Memorandum of Cooperation and has in the meantime been well established. ICATM members cooperate actively on the validation of alternatives and provide regular reporting to ICCR. Since March 2011 ICATM includes also the South Korean validation body.

In addition to these efforts, the Commission takes a leading role in promoting the development and validation of alternative test methods within the Organisation for Economic Co-operation and Development (OECD).

In 2010 the OECD adopted alternative test method guidelines and guidance document based on validation studies and evaluations by the validation bodies of ICATM in the area of dermal irritation (a new TG 439 for three in vitro test methods), genetic toxicity (a new TG 487 for the in vitro micronucleus test method), as well as reduction and refinement methods in the area of skin sensitisation and in the area of oral acute toxicity. Several international validation studies are ongoing by ICATM organizations.

3.2.2. Bilateral level

Questions of validation and regulatory acceptance of alternative methods are also at the core of the various bilateral regulatory dialogues with the main trading partners. This is in particular the case with the United States and Japan, who are also ICCR partners. Much emphasis is placed on this subject in the bilateral contacts with China.

4. CONCLUSION

The overall conclusion and outlook is positive when looking at the developments since 2003, when the current provisions were introduced. Animal testing for cosmetics purposes in the European Union is once and for all a thing of the past. The testing ban is well implemented and controlled. The number of animals used has decreased over the years to the number 344 registered for the first months of 2009, before the full testing ban entered into force.

Regarding the 2009 deadline, of the seven endpoints relevant for cosmetic products safety, replacement alternative methods are currently available for five. For mutagenicity/genotoxicity existing methods are being improved. For the two remaining endpoints, "eye irritation" and "acute toxicity", progress is being made.

Regarding the 2013 deadline, validated alternative methods will not be available for either of the three toxicological endpoints before the marketing ban enters into force. Thanks to serious efforts, a number of partial replacement methods are available. However, full replacement does not seem possible yet.

Progress has also been made in international cooperation, where the European Union is now building trust in alternative methods and joins resources with international partners in the validation of methods. A positive development is also the strengthening of the overall framework in relation to animal testing through the adoption of Directive 2010/63/EU on the protection of animals used for scientific purposes, which notably reinforced the role of validation and of ECVAM. The current report also shows that significant resources were and continue to be made available for research¹⁷ and that the cosmetics industry is taking an active and contributing role.

The Commission is currently thoroughly assessing the potential impacts of the situation set out in this report on the animal welfare, on the safety of cosmetic products available to consumers in the EU and on the social and economic context¹⁸. It is looking at all options and will make a decision based on the results of the said impact assessment as to whether or not to make a proposal to the European Parliament and the Council in relation to the implementation date 2013.

¹⁷ For an overview of research efforts in this area see: Alternative Testing Strategies – Progress Report 2010, Replacing, Reducing and refining use of animals in research (<http://axlr8.eu/axlr8-2010-progress-report.pdf>)

¹⁸ See input received from a targeted stakeholder consultation under: http://ec.europa.eu/consumers/sectors/cosmetics/documents/animal-testing/stakeholders_consultation_en.htm