COMMISSION OF THE EUROPEAN COMMUNITIES

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COMMISSION STAFF WORKING DOCUMENT

Timetables for the phasing-out of animal testing in the framework of the 7th Amendment to the Cosmetics Directive (Council Directive 76/768/EEC)

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1. INTRODUCTION:

The European Parliament and Council Directive 2003/15/EC, which amended for the seventh time the Council Directive 76/768/EEC concerning cosmetic products, provides that the Commission shall establish timetables for the application of provisions concerning the ban of tests on animals and of the marketing of products/ingredients tested on animals.

The new article 4a paragraphs 2 and 2.1 of the Cosmetics Directive provides that:

"2. The Commission, after consultation of the SCCNFP and of the European Centre for the Validation of Alternative Methods (ECVAM) and with due regard to the development of validation within the OECD, shall establish timetables for the implementation of the provisions under paragraph 1(a), (b) and (d), including deadlines for the phasing-out of the various tests. The timetables shall be made available to the public not later than 11 September 2004 and be sent to the European Parliament and the Council. The period for implementation shall be limited to a maximum of six years after the entry into force of Directive 2003/15/EC in relation to paragraph 1(a), (b) and (d).

(2.1) In relation to the tests concerning repeated-dose toxicity, reproductive toxicity and toxicokinetics, for which there are no alternatives yet under consideration, the period for implementation of paragraph 1(a) and (b) shall be limited to a maximum of 10 years after the entry into force of Directive 2003/15/EC".

2. CONSULTATION PROCEDURE:

In order to prepare these timetables, the Commission set up an ad hoc group of experts who drafted a report[2] in which they estimated the time necessary, including regulatory acceptance, to achieve full replacement of animal testing assuming that optimal conditions were met. The European Centre for the Validation of Alternative Methods (ECVAM) participated fully in this exercise. It must be underlined that the evaluation of the time necessary to achieve full replacement of animal tests often represents a compromise reached by the broad representation of experts rather than full agreement. The group gave recommendations and prospects which are included in the annex.

The Scientific Committee on Cosmetic Products and Non Food Products intended to consumers (SCCNFP) was requested, on the basis of this ad hoc group of experts' report, to deliver its opinion, which it did on 1st July 2004[3].

The timing estimates presented in the tables below were made assuming that optimal conditions are met. This means that all necessary resources (technical, human, financial and co-ordination) are met at all times in the process and that the studies undertaken have successful outcomes.

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[2] Report for establishing the timetable for phasing out animal testing for the purpose of the Cosmetics Directive, available on the website of the European Commission, http://pharmacos.eudra.org/F3/home.html

[3] SCCNFP/0834/04 adopted on 1 July 2004, available on the website of the European Commission, http://europa.eu.int/comm/health/ph_risk/committees/sccp/sccp_opinions_en.htm

3. TOXICOLOGICAL ENDPOINTS FOR WHICH ALTERNATIVE METHODS ARE FORESEEN BEFORE THE CUT-OFF-DATES PROVIDED BY ARTICLE 4A OF THE COSMETICS DIRECTIVE

Toxicological endpoints[4]	**Cut-off-dates provided by article 4a of the Cosmetics Directive for the *testing* ban**	**Cut-off-dates provided by article 4a of the Cosmetics Directive for the *marketing* ban**	**Estimated time to complete ECVAM validation including peer-review, of methods for replacement of animal tests, assuming that optimal conditions are met**[5]**.**	**Estimated time to achieve full replacement of animal tests with methods *adopted* at EU level**[6]**, assuming that optimal conditions are met.**
Skin corrosion	11 March 2009	11 March 2009	Already validated	Reference number : - B.40 in Annex V of Council Directive 67/548/EEC - TG 430 and TG 431 in OECD Guidelines.
UV -induced toxic effects: acute phototoxicity	11 March 2009	11 March 2009	Already validated	Reference number: - B.41 in Annex V of Council Directive, 67/548/EEC - TG 432 in OECD Guidelines
Skin irritation - for hazard identification - for risk assessment	11 March 2009	11 March 2009	2006 to 2007 >2008	2007 to 2008 >2009
Eye irritation	11 March 2009	11 March 2009	2008	2009
Skin absorption/ penetration	11 March 2009	11 March 2009	2005[7]	2006 TG 428 in OECD Guidelines
UV-induced toxic effects - Photogenotoxicity	11 March 2009	11 March 2009	2007	2008

4 Based on the SCCNFP Note of Guidance for Testing of Cosmetic Ingredients (SCCNFP/0690/03).

5 See Annex for Recommendations and Prospects from the ad hoc experts group which must be followed to respect these deadlines.

6 Currently, on average, two years are needed for adoption into Community legislation. Efforts will be made to reduce as far as possible to a delay of one year. An additional period must be foreseen in order to take account of the international aspects, in particular the *"due regard to the development of validation with OECD"*.

7 There is no validation study ongoing at ECVAM, but as OECD guideline exists, it can be assumed that method will be available by 2005.

4. TOXICOLOGICAL ENDPOINTS FOR WHICH NO ALTERNATIVE METHODS ARE FORESEEN BEFORE THE CUT-OFF-DATES PROVIDED BY ARTICLE 4A OF THE COSMETICS DIRECTIVE

For the following end-points the ad hoc experts group and the Scientific Committee on Cosmetic products and Non Food Products intended for consumers did not foresee alternative methods before the cut-off dates provided by article 4a of the Cosmetics Directive[8].

Toxicological endpoints[9]	**Cut-off-dates provided by article 4a of the Cosmetics Directive for the *testing* ban**	**Cut-off-dates provided by article 4a of the Cosmetics Directive for the *marketing* ban**
Acute toxicity	11 March 2009	11 March 2009
Skin sensitisation	11 March 2009	11 March 2013
Subacute and subchronic toxicity	11 March 2009	11 March 2013
Genotoxicity and Mutagenicity	11 March 2009	11 March 2009
UV-induced toxic effects, photo-allergy (sensitisation)	11 March 2009	11 March 2013
Toxicokinetics and metabolism	11 March 2009	11 March 2009
Carcinogenicity	11 March 2009	11 March 2013
Reproductive and developmental toxicity	11 March 2009	11 March 2013

5. ANNUAL REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL

According to the new article 9 of the Cosmetics Directive, introduced by the European Parliament and the Council Directive 2003/15/EC, the Commission has to report progress made in the development, validation and legal acceptance of alternative methods in its annual report. In this context, the Commission will report on the status and issuing of the deadlines mentioned in points 3 and 4 above.

[8] However the ad hoc experts group gave some recommendations and prospects (see Annex).

[9] Based on the SCCNFP Note of Guidance for Testing of Cosmetic Ingredients (SCCNFP/0690/03).

ANNEX

Recommendations and prospects from the ad hoc group of experts related to end-points mentioned in point 3

- Skin irritation

- For hazard identification

Prospects: Test systems and predicton models undergoing validation are tailored to the current EU classification scheme. Validation of models forGHS system would require additional studies.

- For risk assessment

Recommendations: develop tests and strategies.

Prospects: Requires further research (need to address reversibility and dose-response aspects).

- Eye irritation

Recommendations: Assess the existing data using a weight of evidence validation approach, obtain a high quality *in vivo* data set, consider differences in the regulatory classification systems, develop test strategies for hazard and risk assessment, and support the development of mechanistically-based models with a view to address reversibility or persistence of effects.

Prospects: Current activities focus on the retrospective validation of the most promising methods.

Skin absorption/penetration

Recommendations: Develop further guidance for cosmetic ingredients testing that could be useful for better standardisation of the current study protocol.

- UV -induced toxic effects

- Photogenotoxicity

Recommendations: Use 3D human skin models for photogenotoxicity testing to address at the same time toxicokinetics and the use of relevant target cells.

Prospects: It is hoped that with a sensitive test for photo clastogenicity potential plus the photo-comet test potential photocarcinogens can be detected.

Recommendations and prospects from the ad hoc group of experts related to end-points mentioned in point 4

- Acute toxicity

Recommendations: Validation of testing battery, development of prediction model(s) and development of complementary end-points to basal cytotoxicity, such as endpoints related to metabolism, toxicokinetics and target organ toxicity to potentially sensitive target organs.

Prospects: Progress will depend on the outcome of the A-Cute-Tox proposal for an Integrated Project selected for funding in the context of the EC's 6th Framework Programme. It is the first practical attempt to develop a simple and robust in vitro testing strategy for predicting human acute oral systemic toxicity with the aim to totally replace the current animal tests.

- Skin sensitisation

Recommendations: Further research in the identification of the relevant endpoints and further development-optimisation of existing in vitro tests, coordination of EU research activities on the development of predictive test methods and their incorporation in a test battery for the full replacement of the animal test and guidance for the validation of a test battery.

- Subacute and subchronic toxicity

Recommendations: Need for an integrated approach based on complementary endpoints. Efforts necessary to optimise the existing models, and to search for relevant in vitro models where fewer robust models are currently available (e.g., lung models). Need for additional basic research to better understand the pathogenesis of chronic diseases, Additional efforts necessary to estimate dose-response. Evaluation of integrated testing approaches for assessing chronic toxicity.

Prospects: The progress made will depend on adequate prioritisation, funding and coordination of efforts.

- Genotoxicity and Mutagenicity

Recommendations: Development of toxicokinetics and toxicogenomics, development of in vitro genotoxicity tests on target cell models relevant to cosmetics and leverage existing guidelines for in vivo testing to reduce current use of animals.

Prospects: The participating experts developed a new test strategy tailored for the cosmetic industry. The experts felt that reduction of animals is an important tool not sufficiently utilized at the moment. Full replacement will also depend on the progress in the field of toxicokinetics and toxicogenomics. The progress made will depend on availability of funding and mobilisation of resources.

- UV -induced toxic effects: Photo-allergy (sensitisation)

Recommendations and prospects: Once a valid in vitro approach (e.g. test battery) for skin sensitisation exists, adapt the tests to be performed with UVA-visible irradiation.

- Toxicokinetics and metabolism

[Without considering excretion]

Recommendations: If biotransformation is an issue for a specific compound this aspect should be considered in all 3 tiers of the test strategy, validation of the overall test strategy, the importance of the selection of training or validation sets of chemicals, further research efforts to investigate the pulmonary exposure to particulate compounds.

Prospects: The participating experts proposed a new tiered approach based on in vitro and in silico models. The progress made will depend on adequate prioritisation, funding and coordination of efforts.

- Carcinogenicity

Prospects: The carcinogenicity bioassays are rarely used for cosmetics but the bioassay is still needed to determine potency and target organs of a carcinogenic compound. In vitro models could detect the carcinogenic potential of a substance, however they present at present crucial limitations in order to achieve full replacement of animal tests. In vivo assays with transgenic animals might allow for a reduction/refinement in animal use.

- Reproductive and developmental toxicity

Recommendations: Development of test strategies. Series of workshops to consider the relevance of different in vitro tests currently available and their potential role in a test strategy, define gaps of non-covered areas of the mammalian cycle, and give guidance to the development of new tests that would be require.

Prospects: Progress will depend on the outcome of the workshop series and on the outcome of the ReProTect project which is an Integrated Project, in the 6th Framework Programme. With this project, the whole reproductive cycle is broken down into work packages and suitable tests were identified that now need to be evaluated, optimised, prevalidated and combined into a testing strategy. In parallel, the conceptual framework to compose and validate test strategies shall be developed.