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REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL

on the development, validation and legal acceptance of methods alternative to animal testing in the field of cosmetics (2018)

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1. INTRODUCTION

This is the thirteenth Commission report on the development, validation and legal acceptance of methods alternative to animal testing in the field of cosmetics.

Under Article 35 of Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products[1] (the Cosmetics Regulation), each report must include information on:

- progress made in the development, validation and acceptance of methods alternative to animal testing;
- the Commission's progress on obtaining the OECD's[2] acceptance of the alternative methods validated at EU level;
- progress on third-country recognition of the results of safety tests carried out in the EU using alternative methods;
- the specific needs of small and medium-sized enterprises (SMEs).

This report also informs the European Parliament and the Council of compliance with the deadlines for the animal testing bans set out in Article 18(1) and of related technical difficulties, pursuant to Article 18(2) of the Cosmetics Regulation.

The animal testing of finished cosmetic products has been prohibited in the EU since 11 September 2004, and the testing of cosmetic ingredients since 11 March 2009 (testing ban). Since 11 March 2009, the marketing in the EU of cosmetic products and their ingredients which have been tested on animals in order to meet the requirements of Directive 76/768/EEC[3] has also been prohibited (2009 marketing ban). This marketing ban applied to all but the most complex human health effects (endpoints) that needed to be tested to demonstrate the safety of cosmetic products in the absence of alternative non-animal tests (repeated-dose toxicity, reproductive toxicity and toxicokinetics); the European Parliament and the Council decided that the ban would take effect on 11 March 2013 (2013 marketing ban). On 11 March 2013, the Commission adopted a Communication on the animal testing and marketing ban[4] and on the state of play in relation to alternative methods in the field of cosmetics. This Communication confirmed the Commission's commitment to maintaining the

[1] OJ L 342, 22.12.2009, p. 59.
[2] Organisation for Economic Co-operation and Development
[3] Council Directive of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products (76/768/EEC), OJ L 262, 27.9.1976, p. 169, repealed by the Cosmetics Regulation.
[4] Communication from the Commission to the European Parliament and the Council on the animal testing and marketing ban and on the state of play in relation to alternative methods in the field of cosmetics, 11 March 2013.

2013 deadline. Therefore, the marketing ban became fully applicable as of 11 March 2013, irrespective of the availability of alternative non-animal tests.[5]

Under Article 18(2) of the Cosmetics Regulation, the report should also cover any derogation from Article 18(1) granted in accordance with Article 18(2) of the Cosmetics Regulation. However, to date there have been no derogations granted under this provision.

The information on compliance with the testing and marketing bans and the impact of the bans in Section 2 is based on contributions from Member States, mainly covering the years 2017-2018[6]. The information on the progress made in the development, validation and legal acceptance of alternative methods in Section 3 is largely based on the 2018 status report[7] from the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) of the Commission's Joint Research Centre (JRC).

2. COMPLIANCE WITH THE TESTING AND MARKETING BANS AND THEIR IMPACT

In practice, the main way of verifying compliance with the testing and marketing bans is the cosmetic product information file (PIF). The 'responsible person'[8], who has to ensure compliance with the relevant obligations of the Cosmetics Regulation (usually the manufacturer or the importer), must keep a PIF for every cosmetic placed on the EU market. The PIF must include the cosmetic product safety report and data on any animal testing performed relating to the development or safety assessment of the cosmetic product or its ingredients[9]. The Commission Communication of 11 March 2013 provides further guidance as to what information should be included in the PIF.

2.1. Inspections and compliance

National market surveillance activities and controls monitoring compliance with the testing and marketing bans were mostly carried out in the course of regular inspections on cosmetic products, or of regular inspections on cosmetic products as part of general control activities. No inspection programmes were specifically carried out to monitor compliance with the testing and marketing bans. Compliance was usually verified through checks of PIFs conducted by competent national authorities.

Based on inspections carried out by market surveillance authorities, one Member State reported amongst the hundreds cases of control three cases of non-compliance with the marketing ban, following which the companies were asked to remedy the infringement. Some other Member States reported very few cases where the infringement was actually a lack of

[5] Judgment on the interpretation of the marketing ban as laid down in Article 18(1)(b) of the Cosmetics Regulation was issued by the Court of Justice of the European Union on 21 September 2016 (C-592/14)
[6] Some Member States reported to the Commission later than the requested deadline and also (partly) covered the year 2018.
[7] *EURL ECVAM Status Report on the Development, Validation and Regulatory Acceptance of Alternative Methods and* Approaches (2018): http://publications.jrc.ec.europa.eu/repository/bitstream/JRC113594/eurl_ecvam_status_report_2018_online.pdf
[8] See Article 4 of the Cosmetics Regulation.
[9] Article 11(2)(b) and (e) of the Cosmetics Regulation.

complete documentation to prove compliance with the bans, rather than non-compliance with the ban itself (see Section 2.2.).

2.2. Difficulties encountered with monitoring the ban and suggestions for improvement

The very large majority of the Member States who monitored compliance with the testing and marketing bans did not report any difficulties in carrying out compliance checks.

As in the previous reporting periods, the main issue raised by a few Member States was the fact that the checked PIFs were incomplete with regard to data on animal testing. This information is necessary to verify compliance with the bans. The issue of a very limited number of incomplete PIFs regarding data on animal testing was confirmed by six Member States.

The checked PIFs often contained limited toxicological data of ingredients used in the finished product. This is because suppliers of ingredients do not provide cosmetic product manufacturers with adequate toxicological information, or they only attach a declaration stating that an ingredient has not been tested on animals for the purposes of the Cosmetics Regulation. It sometimes happens that manufacturers cannot gain access even to that information since their ingredient suppliers refuse to provide them with it. When cosmetic products are imported from non-EU countries, manufacturers issue a declaration to the responsible person stating that neither the cosmetic products being imported nor their ingredients have been tested on animals in view of assessing their safety pursuant to the Cosmetics Regulation. However, they do not provide them with any information on tests carried out in accordance with other legislation.

One Member State argued that checking the PIF at the premises of a responsible person is very difficult and time consuming given the required scope, the specific training for inspectors and the need for appropriate technical equipment in place (implying increased financial costs). It is also quite challenging to ensure suitable training for responsible persons and safety assessors.

The competent authorities properly addressed all the few above-mentioned shortcomings. Manufacturers and responsible persons with PIFs that did not provide complete animal testing information were required to take corrective action. They had to provide the missing information, for instance by asking their suppliers for that information or by producing toxicological data based on alternative methods. If the information was not provided, the consequence was the withdrawal of the product(s) from the market.

2.3. Ban-related issues encountered by manufacturers, in particular SMEs, and the bans' impact on the innovativeness of the cosmetics sector

Most Member States did not report[10] any cases where a manufacturer, in particular an SME, was not able to place a cosmetic product on the market due to an inconclusive safety

[10] Among these Member States, some explicitly stated that they were unaware of such cases or they had not encountered any; the others did not specifically address this question.

assessment of the product or ingredient caused by a lack of alternatives to animal testing. However, two Member States reported that SMEs do not have sufficient knowledge about the testing and marketing bans and sufficient financial resources needed for cost-intensive toxicological tests on new ingredients. Furthermore, the cosmetic ingredients suppliers do not provide them with the required safety data voluntarily. Another problem concerns safety assessors, who are insufficient in number. At the European level there are no available lists from which responsible persons could select safety assessors to commission them to draw up a safety report. In particular SMEs therefore have problems finding a suitable safety assessor. Since they do not very often understand the specific requirements of Article 18 or of Article 11 of the Cosmetics Regulation, they assume that the safety report drawn up for them by a safety assessor is in accordance with the requirements of Annex I to the Cosmetics Regulation and do not have any doubts about its correctness.

On the question of how the testing and marketing bans have affected the innovativeness of the cosmetics sector, most Member States did not provide any information.

Two Member States reported that some SMEs face difficulties, due to the absence of alternative methods, to fully replace animal testing, and thus to compose a comprehensive safety file for a cosmetic product containing a new cosmetic ingredient, particularly with regard to skin sensitisation, repeated-dose toxicity and reproductive toxicity. Another Member State reported the concern raised by its cosmetics industry that it was not possible to perform a full safety assessment of a cosmetic ingredient in the absence of animal testing and that it was not possible to develop new ingredients used exclusively in cosmetic products e.g. new UV filters or preservatives.

One Member State emphasized the need for developing alternatives to animal testing, in particular for repeated-dose toxicity, reproductive toxicity and toxicokinetics. These are areas where complete replacement of animal testing with alternative methods is not yet possible. These shortcomings can potentially make it difficult to assess fully the safety of new cosmetic ingredients.

The absence of full replacement alternative methods for the most complex toxicological areas is indeed widely recognised. Therefore, research is ongoing to develop these methods. For the other toxicological areas, progress has been made towards the validation and regulatory acceptance of alternative methods.

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

Considerable progress was made on several fronts in the development, validation and regulatory acceptance of alternative approaches to animal testing in 2018. Research and development activities continued in areas for which replacement, reduction and refinement (3Rs) solutions are more difficult to find.

For regulatory toxicity testing, research projects focused on repeated dose and reproductive toxicity testing, on chemical mixtures and endocrine disruptors. These projects are either

based on read-across case studies or aim at developing new *in vitro* methods and integrating *in vitro* methods and *in silico* computational technologies in integrated assessment and testing strategies to translate mechanistic understanding of toxicity into risk assessment methodology.

In the area of carcinogenicity, EURL ECVAM is currently exploring how mechanistic data across toxicity endpoints (based primarily on existing *in vivo* and *in vitro* OECD test guidelines) could be best combined, instead of taking them in isolation, to waive redundant testing and, ultimately, improve carcinogenicity testing.

The well-advanced areas of topical toxicity, skin sensitisation and genotoxicity were complemented with additional *in vitro* methods or combined (*in silico* and *in vitro*) approaches which have either already been adopted or are currently being reviewed and discussed in international fora.

3.1. Progress in the EU

3.1.1. Research and development activities

Major research and development activities on methods alternative to animal testing are ongoing in the EU.

EU-ToxRisk is a European collaborative project funded by the EU Framework Programme for Research and Innovation, Horizon 2020 (H2020), to advance mechanism-based toxicity testing and risk assessment. With a budget of over EUR 30 million, it was launched in January 2016 and will last for 6 years. The project, which builds on the results of SEURAT-1[11], has developed several case studies in the complex fields of repeated dose and developmental/reproductive toxicity testing, including for endocrine disrupters. Several industries, including some cosmetics companies, are currently establishing collaborations with the project, which also closely interacts with regulatory agencies and EURL ECVAM.

The Innovative Medicine Initiative (IMI), as part of H2020, also supports various projects aiming at developing safety testing procedures without animal, namely for quality control of vaccines and safety assessment of drugs. These projects receive €35M from the European Commission plus an equal in-kind contribution from the pharmaceutical sector.

Other H2020 programmes support relevant research activities, such as the Euromix project aimed to develop an animal-free strategy for the risk assessment of mixtures of multiple chemicals, several projects related to the safety of nanomaterials, and finally numerous projects from the European Research Council (ERC) and Marie Sklodowska Curie that develop new in vitro and in silico tools that could be integrated into animal-free safety testing.

[11] The EUR 50 million SEURAT-1 research initiative, co-funded by the Commission and Cosmetics Europe (the European personal care association) was completed in 2015.

3.1.2. Validation and legal acceptance of alternative methods

EURL ECVAM is mandated under Article 48 and Annex VII of Directive 2010/63/EU[12] to validate alternative test methods at EU level and promote regulatory acceptance of these.

The European Union Network of Laboratories for the Validation of Alternative Methods (EU-NETVAL[13]) has continued to support the EURL ECVAM validation studies. The network has also helped develop guidance documents and training materials for good *in vitro* method practices.

The validation of alternative methods intended for regulatory use has progressed on a number of fronts including novel methods for predicting the skin sensitisation potential of chemicals, assessing the leaching (bioelution) of chemicals from metal alloys, and for determining acute toxicity in fish. Two EURL ECVAM validation studies deal with methods for the identification of endocrine disruptors and involve the EU-NETVAL. Several multi-stakeholder discussions on validation took place in various fora which indicate that although well-established validation principles are still relevant today, the process of validation needs to be continually adapted to keep pace with scientific and technological progress.

More details on these activities can be found in the 2018 EURL ECVAM status reports[14].

The progress of a test method from submission towards acceptance as a recognised test method for use in various sectors and its final adoption into a regulatory framework can be followed through the Tracking System for Alternative methods towards Regulatory acceptance (TSAR)[15].

3.1.3. The European Partnership for Alternative Approaches to Animal Testing

The European Partnership for Alternative Approaches to Animal Testing (EPAA) is a public-private partnership between the European Commission, eight European trade associations and 36 individual companies from the relevant business sectors[16].

The partners are committed to pooling knowledge and resources to accelerate the development, validation and acceptance of alternative approaches to animal use in regulatory testing. The overall aim is the replacement, reduction and refinement (3Rs) of animal use in regulatory testing.

In 2018, the work of EPAA included seven projects to facilitate the promotion, validation, acceptance and implementation of 3R alternatives in European regulatory testing and decision-making, and to promote international harmonisation of regulatory testing. In each of the projects the over-arching objective is to apply the 3Rs without compromising safety;

[12] 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.
[13] https://ec.europa.eu/jrc/en/eurl/ecvam/alternative-methods-toxicity-testing/eu-netval
[14] http://publications.jrc.ec.europa.eu/repository/bitstream/JRC113594/eurl_ecvam_status_report_2018_online.pdf
[15] https://tsar.jrc.ec.europa.eu/
[16] Directorates General GROW, RTD, SANTE, ENV and JRC for the European Commission; Animal Health, CEFIC, Cosmetics Europe, ECPA, EFPIA, AISE and SMEunited for the industry sectors.

indeed, several of these projects examine how human (or veterinary) safety and product quality can be assured and sometimes even improved by the use of new integrated approaches based primarily on *in vitro* methods.

In 2018, one new project started and six ongoing projects progressed well. A new project on 'Applying non-animal strategies for assessing skin sensitisation' was launched, with the main objective to organise and run a knowledge-sharing workshop. This new project builds on the continuing successful progression of the project on optimised strategies for assessing skin sensitisation. EPAA projects are good examples of the unique synergies that EPAA and its partners achieve to advance alternative methods, by bringing together the relevant industry sectors, regulators, academia and public interest, and to promote the 3Rs principle in the regulatory environment in Europe. EPAA continues to seek new opportunities for 3Rs alternatives and, following the highly successful first Partners' Forum held in 2017 on the subject of toxicokinetics and read-across, a second Forum was held in November 2018 on repeated-dose toxicity. The output of these fora, as well as information on the projects and EPAA's other activities are published on the EPAA website[17]. These activities build on existing research initiatives, identify synergies amongst sectors and seek to bridge the gap between science, innovation and regulation.

3.1.4. Dissemination of information on alternatives

The dissemination of information about alternative approaches (e.g., *in vitro* techniques and *in silico* models) and of chemical datasets contributes to the advancement and strengthening of the 3Rs knowledge. In this context, publicly accessible information systems not only can facilitate the engagement of the scientific community through the sharing and exploitation of existing data and information, but they can also inform regulators and assist educational and training activities.

The information systems and services provided and coordinated by EURL ECVAM serve this purpose, including the above-mentioned Tracking System for Alternative methods towards Regulatory acceptance (TSAR), the DB-ALM collection of *in vitro* methods, and the QSAR Model Database on *in silico* methods. In addition, EURL ECVAM has published, following the Commission Decision on the reuse of Commission documents (2011/833/EU), the results of the assessments it conducted on available 3Rs knowledge sources and related education and training activities.

EURL ECVAM has also carried out a number of awareness-raising activities regarding alternatives to animal testing, such as knowledge sharing and training.

Likewise, the EPAA actively contributed to knowledge-sharing and dissemination on 3Rs through its Annual Conference, presentation of its projects in various events and fora and its publications.

[17] https://ec.europa.eu/growth/sectors/chemicals/epaa_en

3.2. Progress at international level

3.2.1. Activities at OECD and international level

The Commission, through EURL ECVAM, plays an active role at OECD level in the regulatory acceptance of alternative methods and their international adoption. Several initiatives at the OECD are breaking new ground and delivering impact. In addition to new test guidelines and guidance documents to support non-animal approaches to assess chemical toxicity in fish, the OECD published guidance on Good *In Vitro* Method Practices (GIVIMP) to ensure the reliability and integrity of *in vitro* data intended for regulatory use. The OECD project to develop a Guideline for 'Defined Approaches' for skin sensitisation assessment which combines both *in vitro* and computational methods has made steady progress and a draft has recently undergone commenting by OECD member country experts. The Adverse Outcome Pathway (AOP) programme is growing and 2018 saw the publication of a second set of AOPs for complex endpoints that were endorsed by OECD expert groups. Further initiatives on Integrated Approaches to Testing and Assessment (IATA) included a new cycle of IATA case studies and the launch of a project to map relevant guidance documents. Incorporation of alternative approaches into regulatory frameworks has also been addressed by other international bodies such as the International Cooperation on Cosmetics Regulation (ICCR)[18] and the United Nations sub-committee on the Globally Harmonised System (GHS) of classification and labelling of chemicals.

3.2.2. Other cooperation with third countries

The Commission, through EURL ECVAM, has continued its cooperation with other members of the International Cooperation on Alternative Test Methods (ICATM)[19]. An overview of the validation status of alternative test methods validated/peer-reviewed by ICATM partners and their status of regulatory acceptance can be found in Annex 2 to the 2018 EURL ECVAM status reports. Further to the successful workshop of October 2016, EURL ECVAM, together with its ICATM partners, hosted another ICATM two-day workshop in October 2018, this time on the topic of validation of alternative methods towards internationally recognised standards for regulatory application.

Since its creation, the ICCR has focused on advancing work related to alternatives to animal testing worldwide. At the ICCR's twelfth annual meeting held in Tokyo from 10-12 July 2018, the Joint Regulators-Industry Working Group (JWG) on integrated strategies for safety assessments of cosmetic ingredients presented the report on "Integrated Strategies for Safety Assessments of Cosmetic Ingredients – Part II".

[18] The International Cooperation on Cosmetics Regulation (ICCR) is a voluntary international group of cosmetics regulatory authorities from Brazil, Canada, the European Union, Japan and the United States founded in 2007. It discusses common issues on cosmetics safety and regulation and is in dialogue with relevant cosmetics industry trade associations: https://iccr-cosmetics.org/

[19] ICATM is an international cooperation that includes governmental organisations from the EU, the United States, Japan, Canada, South Korea, Brazil and China. ICATM partners work together to promote enhanced international cooperation and coordination on the scientific development, validation and regulatory use of alternative approaches.

In brief, the Part I Report of the JWG, adopted at the ICCR eleventh annual meeting in July 2017 in Brazil summarizes major overarching principles for incorporating new approach methodologies (NAMs) into an integrated strategy for risk assessment of cosmetic ingredients (or 'Next Generation' risk assessment: NGRA), along with examples showing their usefulness to safety evaluation.

The Part II Report of the ICCR integrated strategies for safety assessments of cosmetic ingredients JWG is intended to provide some additional guidance to safety assessors on the types of NAMs that may be used in a NGRA. The report was published on the ICCR web site[20]. The ICCR Standing Committee agreed that the current JWG would continue to work on case studies as Part III of this activity.

4. CONCLUSION

Based on the contributions from Member States, three cases of non-compliance with the testing and marketing bans were reported by one Member State for 2018. The main issue encountered by a small number of Member States in their market surveillance activities related to the bans is the presence of a limited number of cases of incomplete animal testing information in PIFs. Immediate corrective measures were imposed on economic operators in all reported cases.

Despite considerable progress made in the development, validation and legal acceptance of methods alternative to animal testing, alternative test methods have not yet been accepted by the international regulatory community for the safety assessment of ingredients for some of the most complex endpoints, such as repeated dose toxicity, reproductive toxicity or carcinogenicity. Until all toxicological endpoints can be covered by alternatives, the European cosmetics industry remains limited in its ability to introduce new ingredients, apply for new uses of existing ingredients, or respond to new questions regarding the safety of existing ingredients. However, important projects, such as EU-ToxRisk, aim to address these challenges.

For more than 25 years the Commission has been fully engaged at all stages of the process to find replacements to animal testing with alternative test methods. Work is increasingly focused on developing defined approaches and integrated approaches to testing and assessment which look at all existing safety data when assessing a chemical ingredient.

The Commission has been and continues to be fully committed to encouraging the regulatory acceptance of alternative methods approved at OECD level and to promoting the EU animal testing ban in cosmetics at international level, through relevant fora and bilateral and multilateral cooperation. These activities aim not only to recognise individual alternative methods, but also to promote animal welfare and to achieve the convergence of safety assessment methods at international level.

[20] https://www.iccr-cosmetics.org/files/8315/4322/3079/ICCR_Integrated_Strategies_for_Safety_Assessment_of_Cosmetic_Ingredients_Part_2.pdf