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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 (2008)**

(Text with EEA relevance)

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1. INTRODUCTION

The present “Report on the Development, Validation and Legal Acceptance of Alternative Methods to Animal Tests in the Field of Cosmetics” is the eighth report concerning this issue presented by the Commission. It reflects the state of play in terms of the number and type of experiments on animals relating to cosmetic products in 2007 and 2008, the current status of alternative replacement methods, and the acceptance and recognition of alternative methods at international level. The report is produced in order to comply with Article 9 of Council Directive 76/768/EEC¹ of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products (hereinafter “Cosmetics Directive”), as amended by the European Parliament and Council Directive 2003/15/EC of 27 February 2003. It is the fourth report on the basis of the 7th Amendment to the Cosmetics Directive.

This present report is the last report covering the period before the coming into force of the full testing ban for ingredients and combinations of ingredients for cosmetics and the marketing ban for all human health effects with the exception of repeated-dose toxicity, reproductive toxicity and toxicokinetics on 11 March 2009.

2. NUMBER AND TYPE OF EXPERIMENTS RELATING TO COSMETIC PRODUCTS CARRIED OUT ON ANIMALS

2.1. Legal Background

According to Article 9(a) of the Cosmetics Directive, every year the Commission shall present a report to the European Parliament and the Council on progress made in the development, validation and legal acceptance of alternative methods. The report shall contain precise data on the number and type of experiments relating to cosmetic products carried out on animals. The Member States shall be obliged to collect that information in addition to collecting statistics as laid down by Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (Experimental Animals Directive). The Experimental Animals Directive includes requirements to report at regular intervals, not exceeding three years, on the number and kinds of animals used in experiments.

The ban on the testing of finished cosmetic products has been in force since 11 September 2004, whereas the ban on testing ingredients or combinations of ingredients, applies since 11

¹ 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

March 2009, irrespective of the availability of alternative non-animal tests. The marketing ban applies since 11 March 2009, for all human health effects with the exception of repeated-dose toxicity, reproductive toxicity and toxicokinetics. For the latter endpoints the marketing ban will apply as of 11 March 2013, regardless of the availability of alternative non-animal tests. The Commission must study the progress and compliance with the deadlines, as well as possible technical difficulties in complying with the ban. By 2011 the Commission must, in particular, study whether for technical reasons one or more tests covered by the 2013 deadline will not be developed and validated before March 2013. It shall inform the European Parliament and the Council and will, if appropriate, put forward a legislative proposal.

These provisions have not been changed within the new Cosmetics Regulation².

2.2. Animal Testing Data³

For the present report, 27 Member States supplied information on animal tests carried out for the safety of cosmetic products in 2007 and 2008. According to the information submitted, cosmetic ingredients have only been tested on animals in the territories of France and Spain. 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).

In total, 1818 animals in 2007 and 1510 animals in 2008 were used in tests carried out in relation to the safety of cosmetic ingredients (Table 1). The other 25 Member States reported that no such animal tests were performed in their territory in 2007/2008 or that they cannot provide the information for the reasons explained below (see 2.3.1).

Number of animals used in Member States (2007/2008) – Table 1

| | NUMBER OF ANIMALS USED | | ANIMALS USED |
|--------|------------------------|---------|----------------------------------|
| | 2007 | 2008 | |
| SPAIN | 12 | No data | Rabbits |
| FRANCE | 1806 | 1510 | Mice, rats, guinea pigs, rabbits |
| Total | 1818 | 1510 | |

² Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products; OJ L 342, 22.12.2009, p. 59

³ See reservations on the accuracy of data under 2.3 “Evaluation of submitted data”

Number of Animals Used in Relation to Toxicological Endpoints (2007/2008) – Table 2

| TYPES OF TESTS / COUNTRIES | SPAIN | | FRANCE | |
|----------------------------|-------|---------|-------------------|------|
| | 2007 | 2008 | 2007 ⁴ | 2008 |
| Skin irritation | 12 | No data | 126 | 82 |
| Eye irritation | | | 61 | 25 |
| Skin sensitisation | | | 1154 | 1283 |
| Mutagenicity | | | 159 | 54 |
| Non-lethal toxicity | | | 266 | 66 |

The total number of animals used for testing the safety of cosmetics showed a slight increase compared to the last report's figures for 2006 (2005: 2 276, 2006: 1 329).

Nevertheless, the reported number of animals used for the testing of cosmetics or toiletries remains small compared to the total number of animals used for experimental and other scientific purposes. The Fifth Report on the Statistics on the Number of Animals used for Experimental and other Scientific Purposes in the Member States of the European Union⁵ mentioned that 8% of the total number of animals used for experimental purposes are used for toxicological and other safety evaluations, of which cosmetics represent 0.5%.

2.3. Evaluation of submitted data

In August 2008, the Commission asked Member States to send accurate data on the number and type of experiments relating to cosmetic ingredients carried out on animals in 2007 and 2008, in accordance with Article 9(a) of the Cosmetics Directive. The Commission specified that this information should also explain precisely what the figures represent and the way in which they were collated. As for the last report, the Commission annexed to this request the guidelines drawn up in order to facilitate accurate generation and collation of animal testing data relating to cosmetic products.

The Commission also requested, in view of the deadline of 11 March 2009, information regarding the way Member States intend to ensure the implementation of the marketing ban as provided by Article 4a of the Cosmetics Directive.

2.3.1. Main explanations given by Member States:

The majority of Member States replied that no animal testing in relation to cosmetic products was performed in 2007 and 2008 in their territory. The main explanations they gave to substantiate their replies were the following:

- National legislation prohibits the carrying out of animal experiments in order to test and develop cosmetic products and their ingredients.

⁴ Total figures includes 40 animals used for other tests not specified

⁵ 5.11.2007, COM(2007) 675 final

- National legislation stipulates that animal testing must be authorised in order to be lawfully performed, and therefore:
 - no authorisation was given to laboratories to test and develop cosmetic products and their ingredients;
 - there are no approved establishments for animal experiments relating to cosmetic products.
- The following do not exist on national territory:
 - testing facilities for animal testing related to human health; or
 - laboratories complying with the requirements of good laboratory practice where non-clinical studies of the health and environmental safety of substances could be carried out.
- The authorities responsible for checking cosmetic products and carrying out market surveillance do not conduct or commission animal experiments for the purposes of such checks.
- A letter and a questionnaire were sent to representatives of cosmetic product manufacturers and the answer indicated that no tests were carried out.
- Competent authorities checked the product information file which, according to Article 7a, paragraph 1(h) of the Cosmetics Directive, must also contain *data on animal testing*. They found nothing to suggest that chemical substances used as ingredients in cosmetics had been tested on animals.

2.3.2. *Details of difficulties encountered by Member States*

Some Member States elaborated on their replies by mentioning the difficulties they had in collecting the information.

As pointed out in the previous reports, chemicals are rarely tested on animals solely for their use as ingredients in cosmetics, and the majority of animal tests are conducted for multiple uses by manufacturers of chemical substances (industry assumes that approximately 80-90% of cosmetic ingredients are tested for multiple uses). Therefore, some Member States acknowledged that it is difficult to determine which testing has been carried out with a view to cosmetic purposes.

2.3.3. *Initiatives taken by Member States for the collection of data*

In view of the efforts requested of the Member States by the Commission to deliver the appropriate information, some Member States described the measures taken to improve data, such as:

- A notice was sent to all license holders authorised to carry out animal experiments specifying that they must, when submitting information on experiments in connection with cosmetics, supply information on the number and type of experiments conducted, including the purpose of the experiments and the type of cosmetic product or toiletry the substances tested were expected to be included in (skin cream, toothpaste etc.).

The notice also stated that those who had conducted experiments on animals in tests on multipurpose substances under chemicals legislation must supply information on the extent to which one of the secondary purposes of the substances could be used in cosmetics or toiletries.

- A survey based on a questionnaire involving the key laboratories most likely involved in animal testing was carried out.
- On-the-spot inspections at bodies carrying out toxicological tests on behalf of third parties were carried out and more information was requested by directly contacting laboratory managers.

2.3.4. *Measures foreseen in the light of upcoming marketing ban*

In view of the upcoming marketing ban Member States have essentially informed the Commission that they will use the market surveillance instruments in place in order to enforce the marketing ban. The main tool mentioned is the control of the information provided in the product information file in accordance with Article 7a of the Cosmetics Directive, and in particular under Article 7a (1) (h). It was also mentioned that the provisions of the new Cosmetics Regulation⁶ could facilitate this tasks as it spells out, in more detail, the content of the product information file. Some Member States gave more detailed information about the responsible market surveillance authorities, as well as plans on project-based checks. A number of Member States also planned to particularly draw the attention of market surveillance authorities to the ban through guidance notes and similar tools.

2.3.5. *Conclusion*

The Commission acknowledges that Member States have made efforts to improve the availability of data and that the overall availability has improved. However, the Commission continues to be concerned about the accuracy of the figures being reported, and this concern is shared by Member States.

The main issue relates to multiple use substances. Some Member States, when mentioning that no animal testing has been performed for cosmetic ingredients, reported that no toxicological tests were carried out for multiple or uncertain purposes where it could be

⁶ Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products; OJ L 342, 22.12.2009, p. 59

considered that the substance might be used as an ingredient in cosmetic products. Legislation stipulating that animal testing must be authorised in order to be lawfully performed appears a useful tool to determine the purpose of testing.

The Commission considers that the information held according to Article 7a (1) (h) is also a valuable source of information.

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

3.1. Legally Accepted Replacement Methods

3.1.1. Under Annex IX of the Cosmetics Directive

Annex IX of the Cosmetics Directive “lists the alternative methods validated by the European Centre on Validation of Alternative Methods (ECVAM) of the Joint Research Centre available to meet the requirements of this Directive and which are not listed in Annex V to Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances”.

The purpose of Annex IX of the Cosmetics Directive is to supplement Annex V of Council Directive 67/548/EEC. Annex IX was created in order to ensure, without delay, the regulatory acceptance of alternative methods that would not be applicable to the whole chemical sector, but only to the cosmetic sector. Considering that ECVAM did not validate alternative methods to animal testing that would not be applicable to the whole chemical sector, Annex IX was not amended in 2008 and 2009 and is still empty.

3.1.2. Council Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

Directive 2006/121/EC⁷ of the European Parliament and of the Council provided for the deletion of Annex V of Council Directive 67/548/EEC as from 1 June 2008. The Commission has adopted an implementation Regulation under Regulation 1907/2006 on REACH, which brings together, in one Regulation all the test methods contained previously in Annex V to Directive 67/548/EEC. This is Regulation 440/2008/EC⁸, which now also includes:

- B.10. Mutagenicity: *In vitro* mammalian chromosome aberration
- B.13/14. Mutagenicity: Reverse mutation test using bacteria
- B.17. Mutagenicity: *In vitro* mammalian cell gene mutation test

⁷ Directive 2006/121/EC of the European Parliament and of the Council of 18 December 2006 amending Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances in order to adapt it to Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and establishing a European Chemicals Agency, OJ L 396 of 30.12.2006.

⁸ Council Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) , OJ L 142 of 31.05.2008

- B. 40. *In vitro* skin corrosion: transcutaneous electrical resistance test (TER), equivalent to the OECD TG 430 (2004);
- B. 40 Bis. *In vitro* skin corrosion: human skin model test, equivalent to the OECD TG 431 (2004);
- B. 41. *In vitro* 3T3 NRU phototoxicity test, equivalent to OECD TG 432 (2004);
- B.42. Skin sensitisation: Local lymph node assay, equivalent to the OECD TG 429 (2002) (Note: this is not a replacement test);
- B. 45. skin absorption (skin penetration): *in vitro* Method, equivalent to the OECD TG 428 (2004);
- B.46⁹. *In vitro* skin irritation. Reconstructed human epidermis model test

3.2. Progress in Development and Validation of Alternative Approaches

3.2.1. ECVAM Technical Report

ECVAM prepared a “ECVAM Technical Report” covering the period 2008-2009¹⁰. It assesses the possibility of fully replacing animal tests before the cut-off dates set out in Article 4a of the Cosmetics Directive and provides detailed information, including an overview table, on the ECVAM activities and progress in relation to the respective endpoints.

3.2.1.1. For the end points 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 irritation. Alternative methods are currently available for all of these (see 3.1.2), with the exception of the last two, eye irritation and acute toxicity. However in relation to mutagenicity/genotoxicity, these tests are prone to an unacceptable rate of false positive results. ECVAM is working on improving the *in vitro* testing battery to address this.

For eye irritation and acute toxicity several assays were validated by ECVAM, however none of them can fully replace animal testing in risk assessment. Testing strategies which combine the validated assays are currently under development and evaluation, with the aim to completely replace the animal test for eye irritation. Further results are expected by 2011.

3.2.1.2. For the endpoints falling under the 2013 deadline

Endpoints falling under the 2013 deadline of the marketing ban are repeated-dose toxicity (including skin sensitisation and carcinogenicity), toxicokinetics and reproductive toxicology. For these no replacement alternatives are available yet and the situation is much more critical.

⁹ Included by COMMISSION REGULATION (EC) No 761/2009 of 23 July 2009 amending, for the purpose of its adaptation to technical progress, Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

¹⁰ The technical report is available on the ECVAM website <http://ecvam.jrc.ec.europa.eu/>

Toxicokinetics and metabolism in vitro and in silico test systems are of crucial importance to discard artifactual findings secondary to the in vitro environment. A collaborative effort between industry, academia, the European Commission and the three validation bodies (ECVAM¹¹, ICCVAM¹² and JACVAM¹³) was therefore set up to validate an in vitro metabolic competent test system as an important building block in integrated testing strategies for the complex endpoints.

For the endpoint on carcinogenicity, three variants of the cell transformation assay in vitro were validated according to modules 1 to 4 of the ECVAM modular approach and will shortly be submitted for ESAC peer review. In the field of skin sensitisation, three promising in vitro methods [the Direct Peptide Reactivity Assay (DPRA), the human Cell Line Activation Test (h-CLAT) and the Myeloid U939 Skin Sensitisation Test (MUSST)] were sufficiently optimised by industry and were accepted in 2009 by ECVAM for entering prevalidation.

In the area of reproductive toxicology, some promising methods, which were developed under Reprotect, an EU-funded collaborative research project in which ECVAM was also involved, may be submitted to ECVAM for (pre)validation and some in vitro methods for the identification of endocrine disruptors are currently under validation. A reduction in the number of animals used for reproductive toxicity testing is envisaged with the ongoing work that advocates a modular approach to the extended one-generation reproduction study (Moore et al., 2009).

For the endpoints falling under the 2013 deadline, the lack relevant methods to fully replace the animal tests remains a challenge.

3.2.2. *Scientific Committee on Consumer Safety (SCCS) statements*

In December 2009 the SCCS issued a Memorandum on "Alternative Test Methods in Human Health Safety Assessment of Cosmetic Ingredients in the European Union"¹⁴, in which it gives advise on the overall status of available alternative methods and their potential use in the human health risk assessment process of cosmetic ingredients and finished products.

In January 2009 the SCCP (Scientific Committee on Consumer products, now SCCS) issued a position statement on genotoxicity/mutagenicity testing of cosmetic ingredients without animal experiments¹⁵. In this statement the SCCP in particular underlines the high number of false positives (see 3.2.1.1.).

The concerns expressed in December 2007 by the SCCP¹⁶ in relation to the *in vitro* test EPISKIN™ for skin irritation testing have been taken up and the test has been included in Part B of Commission Regulation No 440/2008 as test method B.46. The SCCS however still has concerns relating to the use of this method for coloured substances.

¹¹ European Centre for the Validation of Alternative Methods

¹² Interagency Coordinating Committee on the Validation of Alternative Methods, United States

¹³ Japanese Centre for the Validation of Alternative Methods

¹⁴ SCCS/1294/10

http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_001.pdf

¹⁵ SCCP/1212/09 http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_s_08.pdf

¹⁶ SCCP/1145/07 http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_s_07.pdf

3.2.3. Support of research activities by the Commission

Developing effective and novel alternative methods has been a priority under the Framework Research Programmes of the European Union for more than 20 years. The results of the ongoing research in relation to alternative testing strategies have recently been published¹⁷. To address the lack of methods replacing animal tests in the assessment of toxic effects of chronic exposure, the Commission has launched a call with a budget of €25 million entitled “Towards the replacement of repeated dose systemic toxicity testing in human safety assessment”¹⁸. The cosmetics industry has committed to match the funding given by the European Commission, making a total of €50 million available for this research.

The Ethics Review of all research project proposals involving animal experimentation has contributed to the enforcement of EU animal welfare and experimentation standards and has strengthened the applicability of the "3 Rs" (replacement, reduction and refinement) principles when testing proposals are reviewed in the context of the evaluation procedure for the purposes of the 7th Research Framework Programme.

3.2.4. Colipa (The European Cosmetic Toiletry and Perfumery Association)

Colipa, with its research programme on Alternative Approaches to Animal Testing, plays an important role in supporting the development, validation and acceptance of alternative approaches in order to replace animal use. For eye irritation, Colipa submitted to ECVAM at the beginning of 2008 results from the optimization of the two most advanced Human Reconstructed Tissue models¹⁹. For genotoxicity and mutagenicity, Colipa is working to develop approaches to reduce the “false positive” rate of *in vitro* mammalian cell genotoxicity assays and to develop genotoxic assays in 3D human skin models. For skin allergy, Colipa aims to strengthen the understanding of how chemicals react with the skin and immune system cells to cause skin allergies. Colipa has proposed three methods to ECVAM, which are currently under prevalidation²⁰.

A major contribution is Colipa’s €25 million funding commitment in the context of the call for proposals in relation to repeated dose systemic toxicity testing (see 3.2.3.)

3.2.5. Others

The ongoing activities mentioned in the 2007 report, such as the European Partnership for Alternative Approaches to Animal Testing (EPAA)²¹ the Community Action Plan on the Protection and Welfare of Animals²² and the revision of Directive 86/609/EEC on the protection of animals used in experiments²³, were continued.

¹⁷ EUR 23886 – Alternative Testing Strategies – Progress Report 2009, Replacing, Reducing and refining use of animals in research, Genomics & Biotechnology for Health

¹⁸ FP7-Health-2010-Alternative Testing

¹⁹ SkinEthic Human Corneal Epithelium (HCE) model and the MatTek Epiocular model

²⁰ Human Cell Line Activation Test (h-CLAT), Myeloid U937 Skin Sensitisation Test (MUSST) and direct peptide reactivity assay (DPRA).

²¹ For further information see http://www.ec.europa.eu/enterprise/epaa/index_en.htm

²² COM (2006) 13 final, 23.1.2006

²³ For further information see http://ec.europa.eu/environment/chemicals/lab_animals/revision_en.htm

4. ACCEPTANCE AND RECOGNITION OF ALTERNATIVE METHODS AT INTERNATIONAL LEVEL

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

4.1. 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"). One focal point of ICCR is exploring hurdles in the international regulatory acceptance of alternative testing methods.

Important progress has been made in the international cooperation on alternative test methods with the agreement on a Framework for International Cooperation on Alternative Test Methods (ICATM) in September 2008. In April 2009 representatives from the validation bodies signed a Memorandum of Cooperation promoting enhanced international cooperation and coordination on the scientific validation of non- and reduced-animal toxicity testing methods.

In addition to these efforts, the Commission is cooperating with the OECD by regularly taking part in meetings and working groups, such as the OECD Working Group of the National Coordinators of the Test Guidelines Programme, the Endocrine Disrupters Testing and Assessment Task force and its subgroups, that deal with non-animal tests (e.g. Validation Management Group - Non-Animal), and other ad-hoc expert groups dealing with various alternative methods.

4.2. 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. In particular:

4.2.1. U.S.

Making progress on issues of validation and regulatory acceptance of alternative methods is one of the key deliverables agreed under the Transatlantic Economic Framework, and this work is closely monitored by the Transatlantic Economic Council (TEC). Alternative Methods to Animal Testing are included in the TEC work programme 2009 until 2010 and the implementation of the ICATM and continuous dialogue in view of alternative methods (possible priorities) will remain high on the agenda.

4.2.2. Japan

Alternatives to animal testing have been repeatedly raised, particularly in the framework of the regulatory reform dialogues in 2006, 2007 and 2008 and Japan stressed its support of the activities of the Japanese Center for the Validation of Alternative Methods (JACVAM).

4.2.3. *China*

Replacing animal testing for cosmetics continues to be discussed in numerous fora, and in particular at an AQSIQ²⁴-DG ENTR Working Group meeting on Cosmetics on 17 November 2008 and in meetings with the SFDA²⁵ and AQSIQ in January 2009. There is basic agreement that China must be more involved in the development of alternative methods.

5. CONCLUSION

Member States have improved their internal structure in order to provide for accurate animal testing data and effective monitoring of the application of the testing and marketing bans, as was encouraged in the guidelines annexed to the request to Member States for accurate data²⁶. Nevertheless enforcement of the testing and marketing ban continues to pose challenges in relation to multiple use substances.

Regarding the 2009 deadline, of the seven end points relevant for cosmetic products safety, replacement alternative methods are currently available for five. For the two remaining end points, “eye irritation” and “acute toxicity”, progress is being made but the deadlines for full replacement could not be met. Progress has been good and the Commission expects that the last two human health effects might be covered in the course of 2010. In the interim, industry can rely on data of tests performed before the March 2009 deadline.

Regarding the 2013 deadline, the situation is much more critical. The replacement of animal test methods by alternative methods in relation to complex toxicological endpoints remains scientifically difficult, despite the significant additional efforts that have been launched at various levels. The situation will be thoroughly analysed during the preparation of the study required under the Cosmetics Directive for 2011.

²⁴ General Administration of Quality Supervision, Inspection and Quarantine of the People's Republic of China

²⁵ State Food and Drug Administration China

²⁶ See paragraph 2.3.