Commission Regulation (EU) 2019/1390 of 31 July 2019 amending, for the purpose of its adaptation to technical progress, the Annex to 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) (Text with EEA relevance)

COMMISSION REGULATION (EU) 2019/1390

of 31 July 2019

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(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC[(1)], and in particular Article 13(2) thereof,

Whereas:

(1) Commission Regulation (EC) No 440/2008[(2)] contains the test methods for the purposes of the determination of the physicochemical properties, toxicity and ecotoxicity of chemicals to be applied for the purposes of Regulation (EC) No 1907/2006.

(2) The Organisation for Economic Cooperation and Development (OECD) develops harmonised and internationally agreed test guidelines for the testing of chemicals for regulatory purposes. The OECD regularly issues new and revised test guidelines, taking account of scientific progress in this area.

(3) In order to take into account technical progress and, whenever possible, to reduce the number of animals used for experimental purposes in accordance with Article 13(2) of Regulation (EC) No 1907/2006, following the adoption of relevant OECD test guidelines, two new test methods for the assessment of ecotoxicity and nine new test methods for the determination of toxicity to human health should be laid down and seven test methods should be updated. Eleven of those test methods relate to in vitro tests for skin and eye irritation/corrosion, skin sensitisation, genotoxicity and endocrine effects. Stakeholders have been consulted on the proposed amendment.

(4) Regulation (EC) No 440/2008 should therefore be amended accordingly.

Changes to legislation: *There are currently no known outstanding effects for the Commission Regulation (EU) 2019/1390. (See end of Document for details)*

(5) The measures provided for in this Regulation are in accordance with the opinion of the Committee established under Article 133 of Regulation (EC) No 1907/2006,

HAS ADOPTED THIS REGULATION:

Article 1

The Annex to Regulation (EC) No 440/2008 is amended in accordance with the Annex to this Regulation.

Article 2

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 31 July 2019.

For the Commission

The President

Jean-Claude JUNCKER

***Changes to legislation:** There are currently no known outstanding effects for the Commission Regulation (EU) 2019/1390. (See end of Document for details)*

ANNEX

The Annex to Regulation (EC) No 440/2008 is amended as follows:

(1) In part B, Chapter B.4 is replaced by the following:

B.4 ACUTE DERMAL IRRITATION/CORROSION

INTRODUCTION

1. This test method is equivalent to OECD test guideline (TG) 404 (2015). OECD guidelines for testing of Chemicals are periodically reviewed to ensure that they reflect the best available science. In the review of OECD TG 404, special attention was given to possible improvements in relation to animal welfare concerns and to the evaluation of all existing information on the test chemical in order to avoid unnecessary testing in laboratory animals. The updated version of OECD TG 404 (originally adopted in 1981, revised in 1992, 2002 and 2015) includes reference to the Guidance Document on Integrated Approaches to Testing and Assessment (IATA) for Skin Irritation/Corrosion (1), proposing a modular approach for skin irritation and skin corrosion testing. The IATA describes several modules which group information sources and analysis tools, and (i) provides guidance on how to integrate and use existing testing and non-testing data for the assessment of the skin irritation and skin corrosion potentials of chemicals and (ii) proposes an approach when further testing is needed (1). In addition, where needed, the successive, instead of simultaneous, application of the three test patches to the animal in the initial *in vivo* test is recommended in that Guideline.

2. Definitions of dermal irritation and corrosion are set out in the Appendix to this test method.

INITIAL CONSIDERATIONS

3. In the interest of both sound science and animal welfare, *in vivo* testing should not be undertaken until all available data relevant to the potential dermal corrosivity/irritation of the test chemical have been evaluated in a weight-of-the-evidence (WoE) analysis as presented in the Guidance Document on Integrated Approaches to Testing and Assessment for Skin Corrosion and Irritation, i.e. over the three Parts of this guidance and their corresponding modules (1). Briefly, under Part 1 existing data is addressed over seven modules covering human data, *in vivo* data, *in vitro* data, physico-chemical properties data (e.g. pH, in particular strong acidity or alkalinity) and non-testing methods. Under Part 2, WoE analysis is performed. If this WoE is still inconclusive, Part 3 should be conducted with additional testing, starting with *in vitro* methods, and *in vivo* testing is used as last resort. This analysis should therefore decrease the need for *in vivo* testing for dermal corrosivity/irritation of test chemicals for which sufficient evidence already exists from other studies as to those two endpoints.

PRINCIPLE OF THE IN VIVO TEST

4. The test chemical to be tested is applied in a single dose to the skin of an experimental animal; untreated skin areas of the test animal serve as the control. The degree of irritation/corrosion is read and scored at specified intervals and is further described in order to provide a complete evaluation of the effects. The duration of the study should be sufficient to evaluate the reversibility or irreversibility of the effects observed.

5. Animals showing continuing signs of severe distress and/or pain at any stage of the test should be humanely killed, and the test chemical assessed accordingly.

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Criteria for making the decision to humanely kill moribund and severely suffering animals are the subject of a separate Guidance Document (2).

PREPARATIONS FOR THE IN VIVO TEST

Selection of animal species

6. The albino rabbit is the preferable laboratory animal, and healthy young adult rabbits are used. A rationale for using other species should be provided.

Preparation of the animals

7. Approximately 24 hours before the test, fur should be removed by closely clipping the dorsal area of the trunk of the animals. Care should be taken to avoid abrading the skin, and only animals with healthy, intact skin should be used.

8. Some strains of rabbit have dense patches of hair that are more prominent at certain times of the year. Such areas of dense hair growth should not be used as test sites.

Housing and feeding conditions

9. Animals should be individually housed. The temperature of the experimental animal room should be 20 °C (± 3 °C) for rabbits. Although the relative humidity should be at least 30 % and preferably not exceed 70 %, other than during room cleaning, the aim should be 50-60 %. Lighting should be artificial, the sequence being 12 hours light, 12 hours dark. For feeding, conventional laboratory diets may be used with an unrestricted supply of drinking water

TEST PROCEDURE

Application of the test chemical

10. The test chemical should be applied to a small area (approximately 6 cm^2) of skin and covered with a gauze patch, which is held in place with non-irritating tape. In cases in which direct application is not possible (e.g. liquids or some pastes), the test chemical should first be applied to the gauze patch, which is then applied to the skin. The patch should be loosely held in contact with the skin by means of a suitable semi-occlusive dressing for the duration of the exposure period. If the test chemical is applied to the patch, it should be attached to the skin in such a manner that there is good contact and uniform distribution of the test chemical on the skin. Access by the animal to the patch and ingestion or inhalation of the test chemical should be prevented.

11. Liquid test chemicals are generally used undiluted. When testing solids (which may be pulverised, if considered necessary), the test chemical should be moistened with the smallest amount of water (or, where necessary, of another suitable vehicle) sufficient to ensure good skin contact. When vehicles other than water are used, the potential influence of the vehicle on irritation of the skin by the test chemical should be minimal, if any.

12. At the end of the exposure period, which is normally 4 hours, residual test chemical should be removed, where practicable, using water or an appropriate solvent without altering the existing response or the integrity of the epidermis.

Dose level

13. A dose of 0,5 ml of liquid or 0,5 g of solid or paste is applied to the test site.

Initial test (In vivo dermal irritation/corrosion test using one animal)

14. When a test chemical has been judged to be corrosive, irritant or non-classified on the basis of a weight of evidence analyses or of previous *in vitro* testing, further *in vivo* testing is normally not necessary. However, in the cases where additional data are felt warranted, the *in vivo* test is performed initially using one

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animal and applying the following approach. Up to three test patches are applied sequentially to the animal. The first patch is removed after three minutes. If no serious skin reaction is observed, a second patch is applied at a different site and removed after one hour. If the observations at this stage indicate that exposure can humanely be allowed to extend to four hours, a third patch is applied and removed after four hours, and the response is graded.

15. If a corrosive effect is observed after any of the three sequential exposures, the test is immediately terminated. If a corrosive effect is not observed after the last patch is removed, the animal is observed for 14 days, unless corrosion develops at an earlier time point.

16. In those cases in which the test chemical is not expected to produce corrosion but may be irritating, a single patch should be applied to one animal for four hours.

Confirmatory test (In vivo dermal irritation test with additional animals)

17. If a corrosive effect is not observed in the initial test, the irritant or negative response should be confirmed using up to two additional animals, each with one patch, for an exposure period of four hours. If an irritant effect is observed in the initial test, the confirmatory test may be conducted in a sequential manner, or by exposing two additional animals simultaneously. In the exceptional case, in which the initial test is not conducted, two or three animals may be treated with a single patch, which is removed after four hours. When two animals are used, if both exhibit the same response, no further testing is needed. Otherwise, the third animal is also tested. Equivocal responses may need to be evaluated using additional animals.

Observation period

18. The duration of the observation period should be sufficient to evaluate fully the reversibility of the effects observed. However, the experiment should be terminated at any time that the animal shows continuing signs of severe pain or distress. To determine the reversibility of effects, the animals should be observed up to 14 days after removal of the patches. If reversibility is seen before 14 days, the experiment should be terminated at that time.

Clinical observations and grading of skin reactions

19. All animals should be examined for signs of erythema and oedema, and the responses scored at 60 minutes, and then at 24, 48 and 72 hours after patch removal. For the initial test in one animal, the test site is also examined immediately after the patch has been removed. Dermal reactions are graded and recorded according to the grades in the Table below. If there is damage to skin which cannot be identified as irritation or corrosion at 72 hours, observations may be needed until day 14 to determine the reversibility of the effects. In addition to the observation of irritation, all local toxic effects, such as defatting of the skin, and any systemic adverse effects (e.g. effects on clinical signs of toxicity and body weight), should be fully described and recorded. Histopathological examination should be considered to clarify equivocal responses.

20. The grading of skin responses is necessarily subjective. To promote harmonisation in grading of skin response and to assist testing laboratories and those involved in making and interpreting the observations, the personnel performing the observations need to be adequately trained in the scoring system used (see Table below). An illustrated guide for grading skin irritation and other lesions could be helpful (3).

DATA AND REPORTING