II

(Non-legislative acts)

REGULATIONS

COMMISSION REGULATION (EU) 2015/282

of 20 February 2015

amending Annexes VIII, IX and X to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards the Extended One-Generation Reproductive Toxicity Study

(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) Article 13(2) of Regulation (EC) No 1907/2006 provides that testing methods used to generate information on intrinsic properties of substances required by that Regulation are to be regularly reviewed and improved with a view to reducing testing on vertebrate animals and the number of animals involved. The principles of replacement, reduction and refinement, enshrined in Directive 2010/63/EU of the European Parliament and of the Council ([2]) should be taken into account in the design of the test methods, in particular when appropriate validated methods become available to replace, reduce or refine animal testing. Following that review, Council Regulation (EC) No 440/2008 ([3]) and the Annexes to Regulation (EC) No 1907/2006 are to be amended, if relevant, so as to replace, reduce or refine animal testing.

(2) Pursuant to Regulation (EC) No 1907/2006, a two-generation reproductive toxicity study is to be used to investigate the reproductive toxicity of chemical substances to fulfil the standard information requirements in point 8.7.3 of Annexes IX and X to that Regulation. Furthermore, column 2 of point 8.7.1 of Annex VIII to Regulation (EC) No 1907/2006 provides that the two-generation reproductive toxicity study is a possibility to assess the cases where there are serious concerns about the potential for adverse effects on fertility or development.

(3) The Extended One-Generation Reproductive Toxicity Study ([4]) (EOGRTS) is a new test method developed to assess the reproductive toxicity of chemical substances. This test method was adopted by the Organisation for Economic Cooperation and Development (OECD) in July 2011. EOGRTS is a modular test method, where breeding and assessment of a second filial (F2) generation and testing for developmental neurotoxicity (DNT) and developmental immunotoxicity (DIT) constitute distinct and independent modules.

([1]) OJ L 396, 30.12.2006, p. 1.
([2]) 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).
([3]) 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, 31.5.2008, p. 1).
([4]) OECD Test Guideline 443.

(4) EOGRTS is considered to offer a number of advantages in comparison to the two-generation reproductive toxicity study. It assesses a greater number of animals of the first filial (F1) generation and addresses additional parameters, thus improving the sensitivity and level of information that can be obtained from the test. Furthermore, as breeding of the F2 generation is not part of the basic test design, a significant reduction in the number of animals used is achieved if this design is used.

(5) EOGRTS was included in Regulation (EC) No 440/2008 by Commission Regulation (EU) No 900/2014 ([1]). Annexes IX and X to Regulation (EC) No 1907/2006 should be amended to specify how the new test method is to be used for the purposes of Regulation (EC) No 1907/2006. To this end, a sub-group of the Commission Expert Group consisting of Competent Authorities for the REACH and the classification and labelling of chemical substances Regulations (the Expert Group) was created in 2011. Based on the scientific recommendations of this Expert Group, the EOGRTS should become the preferred test method to address the standard information requirement defined in column 1 of point 8.7.3 of Annexes IX and X to Regulation (EC) No 1907/2006 instead of the two-generation reproductive toxicity study (B.35).

(6) The standard information requirement in Annexes IX and X to Regulation (EC) No 1907/2006 should be limited to the basic configuration of EOGRTS. Nevertheless, in certain specific cases, where justified, the registrant should be able to propose and the European Chemicals Agency (ECHA) should be able to request the performance of the F2 generation, as well as the DNT and DIT cohorts.

(7) It should be ensured that the reproductive toxicity study carried-out under point 8.7.3 of Annexes IX and X to Regulation (EC) No 1907/2006 will allow adequate assessment of possible effects on fertility. The premating exposure duration and dose selection should be appropriate to meet risk assessment and classification and labelling purposes as required by Regulation (EC) No 1907/2006 and Regulation (EC) No 1272/2008 of the European Parliament and of the Council ([2]).

(8) Considering that the remaining scientific concerns as regards the value of the F2 generation should be clarified on the basis of empirical data, and that substances potentially presenting the highest risk to consumers and professional users should be assessed on the basis of a conservative approach, the production and assessment of the F2 generation should be triggered for certain substances on a case-by-case basis. The Expert Group recommended that an exposure based trigger, associated with uses leading to exposures of consumers and professional users should be implemented in the relevant points of Annexes IX and X to Regulation (EC) No 1907/2006. Additional criteria, based on evidence indicating that a substance is of concern as a function of the available toxicity and toxicokinetic information, should be included to further optimise the selection of substances for which the F2 generation should be produced and subjected to testing.

(9) Developmental Neurotoxicity and developmental immunotoxicity are regarded as important and relevant developmental toxicity endpoints, which could be further investigated. However, analysing the DNT and DIT cohorts entails significant additional cost as well as technical and practical difficulties for testing laboratories. Therefore, it is considered appropriate to subject the analysis of the DIT and DNT cohorts, or only one of them, to specific concern-driven scientific triggers. Specific rules for the adaptation of the information requirement defined in point 8.7.3 of Annexes IX and X to Regulation (EC) No 1907/2006 should be introduced, so as to trigger the immunotoxicity and neurotoxicity testing. In cases where the available information on a substance indicates a particular concern on neurotoxicity or immunotoxicity, the inclusion of the DNT and the DIT cohorts, or only one of them, justified on a case-by-case basis, should be possible. Evidence supporting these concerns could originate from existing information derived from *in vivo* or non-animal approaches, from the knowledge of relevant mechanisms/modes of action of the substance itself, or from existing information on structurally related substances. Therefore, if any such particular concerns are justified, the registrant should be required to propose, and ECHA should be able to request the performance of the DNT and DIT cohorts, or only one of them.

([1]) Commission Regulation (EU) No 900/2014 of 15 July 2014 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) (OJ L 247, 21.8.2014, p. 1).

([2]) Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (OJ L 353, 31.12.2008, p. 1).

(10) Point 8.7.3 of Annex IX to Regulation (EC) No 1907/2006 requires performing a reproductive toxicity study, only if there are concerns arising from adverse effects previously detected on reproductive organs or tissues. That point provides that only 28- and 90-day repeated dose toxicity studies can be the source of such information. Given that also reproductive toxicity screening studies such as OECD Test Guideline 421 or Test Guideline 422, or other studies with repeated dose administration can provide indications on adverse effects on relevant reproductive parameters, which may justify the need to follow-up by performing an EOGRTS, column 1 of point 8.7.3 should be modified to allow such additional studies to be considered.

(11) In order to avoid imposing a disproportionate burden on the economic operators who may have already performed the tests or acquired results of two-generation reproductive toxicity study, as well as for animal welfare reasons, the robust study summaries of those studies that were initiated before the date of the entry into force of this Regulation should be considered appropriate to address the standard information requirement in point 8.7.3 of Annexes IX and X to Regulation (EC) No 1907/2006.

(12) For reasons of consistency, point 8.7.1, column 2 of Annex VIII to Regulation (EC) No 1907/2006 should be amended in order to change the cross-reference to the study required under point 8.7.3 of Annex IX to Regulation (EC) No 1907/2006 from the two-generation reproductive toxicity study to EOGRTS.

(13) ECHA, in close cooperation with Member States and stakeholders, should further develop guidance documents for the application of EOGRTS for the purposes of Regulation (EC) No 1907/2006, including on the application of the criteria for F2 and DNT/DIT cohorts. In doing so, ECHA should take full account of the work carried out in OECD, as well as in other relevant scientific and expert groups. Furthermore, when determining deadlines by which dossier updates providing results of EOGRTS are to be submitted, ECHA should take due account of the market availability of this testing service.

(14) Regulation (EC) No 1907/2006 should therefore be amended accordingly.

(15) 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

Annexes VIII, IX and X to Regulation (EC) No 1907/2006 are 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, 20 February 2015.

For the Commission

The President

Jean-Claude JUNCKER

ANNEX

Regulation (EC) No 1907/2006 is amended as follows:

(1) in Annex VIII, in the table setting out the toxicological information, in column 2 (Specific Rules for Adaptation from column 1), point 8.7.1 is replaced by the following:

	'8.7.1. This study does not need to be conducted if: — the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented, or — the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented, or — relevant human exposure can be excluded in accordance with Annex XI section 3, or — a pre-natal developmental toxicity study (Annex IX, 8.7.2) or, either an Extended One-Generation Reproductive Toxicity Study (B.56, OECD TG 443) (Annex IX, section 8.7.3) or a two-generation study (B.35, OECD TG 416), is available. If a substance is known to have an adverse effect on fertility, meeting the criteria for classification as toxic for reproduction category 1A or 1B: May damage fertility (H360F), and the available data are adequate to support a robust risk assessment, then no further testing for fertility will be necessary. However, testing for developmental toxicity must be considered. If a substance is known to cause developmental toxicity, meeting the criteria for classification as toxic for reproduction category 1A or 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary. However, testing for effects on fertility must be considered. In cases where there are serious concerns about the potential for adverse effects on fertility or development, either an Extended One-Generation Reproductive Toxicity Study (Annex IX, section 8.7.3) or a pre-natal developmental toxicity study (Annex IX, section 8.7.2) may, as appropriate, be proposed by the registrant instead of the screening study.'

(2) in Annex IX, in the table setting out the toxicological information, in column 1 (Standard Information Requirement) and column 2 (Specific Rules for Adaptation from column 1) point 8.7.3 is replaced by the following:

'8.7.3. Extended One-Generation Reproductive Toxicity Study (B.56 of the Commission Regulation on test methods as specified in Article 13(3) or OECD 443), basic test design (cohorts 1A and 1B without extension to include a F2 generation), one species, most appropriate route of administration, having regard to the likely route of human exposure, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity.	8.7.3. An Extended One-Generation Reproductive Toxicity Study with the extension of cohort 1B to include the F2 generation shall be proposed by the registrant or may be required by the Agency in accordance with Article 40 or 41, if: (a) the substance has uses leading to significant exposure of consumers or professionals, taking into account, inter alia, consumer exposure from articles, and (b) any of the following conditions are met: — the substance displays genotoxic effects in somatic cell mutagenicity tests *in vivo* which could lead to classifying it as Mutagen Category 2, or — there are indications that the internal dose for the substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure, or — there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies or non-animal approaches.

	An Extended One-Generation Reproductive Toxicity Study including cohorts 2A/2B (developmental neurotoxicity) and/or cohort 3 (developmental immunotoxicity) shall be proposed by the registrant or may be required by the Agency in accordance with Article 40 or 41, in case of particular concerns on (developmental) neurotoxicity or (developmental) immunotoxicity justified by any of the following: — existing information on the substance itself derived from relevant available *in vivo* or non-animal approaches (e.g. abnormalities of the CNS, evidence of adverse effects on the nervous or immune system in studies on adult animals or animals exposed prenatally), or — specific mechanisms/modes of action of the substance with an association to (developmental) neurotoxicity and/or (developmental) immunotoxicity (e.g. cholinesterase inhibition or relevant changes in thyroidal hormone levels associated to adverse effects), or — existing information on effects caused by substances structurally analogous to the substance being studied, suggesting such effects or mechanisms/modes of action. Other studies on developmental neurotoxicity and/or developmental immunotoxicity instead of cohorts 2A/2B (developmental neurotoxicity) and/or cohort 3 (developmental immunotoxicity) of the Extended One-Generation Reproductive Toxicity Study may be proposed by the registrant in order to clarify the concern on developmental toxicity. Two-generation reproductive toxicity studies (B.35, OECD TG 416) that were initiated before 13 March 2015 shall be considered appropriate to address this standard information requirement. The study shall be performed on one species. The need to perform a study at this tonnage level or the next on a second strain or a second species may be considered and a decision should be based on the outcome of the first test and all other relevant available data.'

(3) in Annex X, in the table setting out the toxicological information, in column 1 (Standard Information Requirement) and column 2 (Specific Rules for Adaptation from column 1) point 8.7.3 is replaced by the following:

'8.7.3. Extended One-Generation Reproductive Toxicity Study (B.56 of the Commission Regulation on test methods as specified in Article 13(3) or OECD 443), basic test design (cohorts 1A and 1B without extension to include a F2 generation), one species, most appropriate route of administration, having regard to the likely route of human exposure, unless already provided as part of Annex IX requirements.	8.7.3. An Extended One-Generation Reproductive Toxicity Study with the extension of cohort 1B to include the F2 generation shall be proposed by the registrant or may be required by the Agency in accordance with Article 40 or 41, if: (a) the substance has uses leading to significant exposure of consumers or professionals, taking into account, inter alia, consumer exposure from articles, and (b) any of the following conditions are met: — the substance displays genotoxic effects in somatic cell mutagenicity tests *in vivo* which could lead to classifying it as Mutagen Category 2, or — there are indications that the internal dose for the substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure, or — there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies or non-animal approaches.

	An Extended One-Generation Reproductive Toxicity Study including cohorts 2A/2B (developmental neurotoxicity) and/or cohort 3 (developmental immunotoxicity) shall be proposed by the registrant or may be required by the Agency in accordance with Article 40 or 41, in case of particular concerns on (developmental) neurotoxicity or (developmental) immunotoxicity justified by any of the following: — existing information on the substance itself derived from relevant available *in vivo* or non-animal approaches (e.g. abnormalities of the CNS, evidence of adverse effects on the nervous or immune system in studies on adult animals or animals exposed prenatally), or — specific mechanisms/modes of action of the substance with an association to (developmental) neurotoxicity and/or (developmental) immunotoxicity (e.g. cholinesterase inhibition or relevant changes in thyroidal hormone levels associated to adverse effects), or — existing information on effects caused by substances structurally analogous to the substance being studied, suggesting such effects or mechanisms/modes of action. Other studies on developmental neurotoxicity and/or developmental immunotoxicity instead of cohorts 2A/2B (developmental neurotoxicity) and/or cohort 3 (developmental immunotoxicity) of the Extended One-Generation Reproductive Toxicity Study may be proposed by the registrant in order to clarify the concern on developmental toxicity. Two-generation reproductive toxicity studies (B.35, OECD TG 416) that were initiated before 13 March 2015 shall be considered appropriate to address this standard information requirement.'