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EUROPEAN CHEMICALS AGENCY

How ECHA identifies the design for the extended one-generation reproductive toxicity study (EOGRTS) under dossier evaluation

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This document is not to be considered as guidance on REACH. The identification of the extended one-generation reproductive toxicity study (EOGRTS) design is explained in detail in the ECHA *Guidance on information requirements and chemical safety assessment R.7a (version 4.1, October 2015) on reproductive toxicity (chapter R.7.6).* This document is intended to provide an overview of how ECHA evaluates and identifies the EOGRTS design in dossier evaluation. Readers are reminded that the text of the REACH Regulation is the only authentic legal reference and that the information in this document does not constitute legal advice. ECHA does not accept any liability with regard to the contents of this document.

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1. Introduction

The extended one-generation reproductive toxicity study (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) are distinct and independent modules. The appropriate study design needs to be defined, justified and documented. Specification is required for the:

- length of the premating exposure duration and dose level selection,
- need to extend Cohort 1B to include the mating of F1 animals to produce a F2 generation,
- need to include the DNT cohorts, and
- need to include the DIT cohort.

The information sources the Agency considers crucial for defining the EOGRTS design are discussed in this document in addition to aspects of triggering the study itself and its various designs.

2. The study and its various designs

Since 13 March 2015, the EOGRTS has been the new information requirement for reproductive toxicity (Annexes IX and X, Section 8.7.3.). An adequate two-generation reproductive toxicity study is only considered to meet the standard information requirement (column 1) if it was initiated before 13 March 2015.

At Annex X, the EOGRTS is a default information requirement under REACH. At Annex IX, however, it must be fulfilled only if toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation to reproductive toxicity.

A modular design of the EOGRTS has been implemented in REACH. The standard information requirement in Annexes IX and X is limited to the basic configuration of the EOGRTS (basic study design). Its study design depends on whether specific concern-driven scientific triggers are identified for the substance which is evaluated by ECHA (referred to as the "substance being evaluated" herein).

The basic study design only includes Cohorts 1A and 1B for reproductive toxicity. Based on specified conditions and concern-based criteria, the study must be expanded to include extension of Cohort 1B to include the F2 generation, the DNT Cohorts 2A and 2B, and/or the DIT Cohort 3. These criteria are described in column 2 of Section 8.7.3 of REACH Annexes IX and X and further elaborated in ECHA's *Guidance on information requirements and chemical safety assessment R.7a (version 4.1, October 2015) on reproductive toxicity (chapter R.7.6)*. Furthermore, the premating exposure duration and dose selection should be appropriate to meet risk assessment as well as classification and labelling purposes.

To support registrants in their task to select the relevant study design, the reader is referred to ECHA's *Guidance on information requirements and chemical safety assessment R.7a (version 4.1, October 2015) on reproductive toxicity (chapter R.7.6)* which contains a checklist for information that contributes to the EOGRTS design (see Appendix R.7.6–1) and further advice on triggers including examples (Appendix R.7.6–2).

3. Registrants' responsibility

Relevant information on reproductive toxicity needs to be present in the dossier as specified in the REACH annexes. The information may be a robust study summary of the respective study or an adaptation according to column 2 or Annex XI.

Registrants are responsible for collecting all available information relevant to reproductive toxicity. The available information from human, animal and non-animal studies and testing approaches need to be collected, including data from literature, which need to be evaluated and documented (see REACH Annex VI, Step 1).

If the registration dossier already contains adequate information to fulfil the EOGRTS information requirement e.g. by providing an adequate endpoint study record or adaptation justification, then there is no need to provide a testing proposal for the study.

However, if the registrants identify a need to generate further information they are obliged to provide a testing proposal for the EOGRTS with a justified specific study design according to Annex IX or X, Section 8.7.3. and ECHA's *Guidance on information requirements and chemical safety assessment R.7a (version 4.1, October 2015) on reproductive toxicity (chapter R.7.6)*.

When proposing the EOGRTS and updating the dossier with the respective study results, the registrants need to provide an adequate justification and documentation for the EOGRTS design in their registration dossiers. This is so that the Agency can understand their reasoning as to why the study is, or is not, necessary for an Annex IX registration and why the study contains, or does not contain, certain expansions. As with all testing proposals involving vertebrate animals, the registrants also have to submit their considerations for alternatives to animal testing justifying the necessity of a new animal test.

ECHA emphasises that it is in the registrants' interest to adequately justify and document the study design because their arguments are considered and addressed in dossier evaluation processes and decision making.

Thus, all relevant data should be available in the registration dossier. However, to confirm the need for the study at Annex IX and the adequate study design at Annexes IX and X, the Agency conducts an information search and evaluation as described below. In addition, third parties are invited to provide scientifically-relevant information and studies on the published testing proposals and Member State competent authorities may conduct additional searches to supplement information collected by the Agency. The approach described here below is applied to both testing proposal examinations and compliance checks.

4. Missing relevant information

As outlined above, the basic study design only includes Cohorts 1A and 1B for reproductive toxicity. Based on specified conditions and concern-based criteria, however, the study must be expanded to include the extension of Cohort 1B to include mating of F1 animals to produce the F2 generation, the DNT Cohorts 2A and 2B, and/or the DIT Cohort 3.

To be able to conclude on the study design, relevant information must be present in the registration dossier. It is emphasised that in particular the following information is relevant to conclude on the EOGRTS design:

- Uses and exposure assessment for professional workers and consumers;
- Genotoxicity;
- Bioaccumulation;

- Repeated-dose toxicity;
- Neurotoxicity;
- Immunotoxicity; and
- Endocrine effects and modes of action.

In this respect, it is emphasised that registrants are obliged to provide all physicochemical, toxicological and ecotoxicological information on the registered substance that is relevant (see Article 12(1) REACH).

If there is a data gap for an information requirement under REACH, which is crucial for evaluating the EOGRTS design, the Agency can impose sequential testing in its decision.

For example, if ECHA's dossier evaluation decision requests both a sub-chronic toxicity study (90-day) and EOGRTS, the registrants are usually only allowed to initiate the EOGRTS after submitting the results of the sub-chronic toxicity study and after the Agency has evaluated these results to verify the EOGRTS design.

In practical terms, this means that the ECHA decision sets a separate, shorter deadline for submitting the results of the sub-chronic toxicity study. Once the results of the sub-chronic toxicity study have been submitted in a dossier update, the Agency evaluates whether the originally requested EOGRTS design needs to be changed. This evaluation is based on the results of the newly submitted sub-chronic toxicity study. However, any other relevant new information can also be considered.

If the EOGRTS design needs to be changed, a new decision-making process to amend the EOGRTS design is initiated which follows the standard procedure as outlined in Articles 50 and 51 of REACH. If no change to the EOGRTS design is needed, the registrants can initiate the EOGRTS study as originally requested after a specific deadline, which is defined in the ECHA decision.

5. Routine information search and evaluation

When evaluating the EOGRTS information requirement under dossier evaluation, the Agency considers the registration dossier as it is – even if it contains data gaps for standard information requirements. The evaluation is not postponed because of a lack of data in the registration dossier of the substance being evaluated. As outlined above, however, if the missing information is relevant to conclude on the EOGRTS design, sequential testing can be imposed by the Agency to verify the study design.

In a first step – the routine information search – the Agency considers the following information:

- The registration dossier of the substance being evaluated;
- Parallel individual and joint registrations of the substance being evaluated and member dossier opt-outs;
- Available international/regulatory assessments for the substance being evaluated such as EU risk assessment reports (EU RARs) or reports from the OECD, WHO, US EPA, US FDA, NICNAS, for example; and
- Information relating to endocrine-disrupting properties of the substance being evaluated obtained from ECHA's screening activities to identify substances that matter most (see http://echa.europa.eu/addressing-chemicals-of-concern/substances-of-potential-concern/screening).

If the Agency concludes that all expansions of the EOGRTS are triggered after this routine information search and evaluation (i.e. a full-blown study is requested by extending Cohort 1B and including Cohorts 2A and 2B and Cohort 3), no further search and evaluation is usually conducted.

6. Additional information search and evaluation

An additional information search and evaluation is performed by the Agency if the full-blown EOGRTS is not triggered by the routine evaluation and if studies relevant to identify the EOGRTS design are missing or suspicions for a need to extend the Cohort 1B, include the DNT cohorts and/or DIT cohort are raised. Additional information searches may be conducted also if studies deviate from standard protocols.

In the additional information search and evaluation, information on the substance being evaluated and its structurally analogous substances from the following information sources are usually considered:

- REACH registrations (including neurotoxicity/immunotoxicity studies reported in IUCLID) and C&L notifications;
- OECD, USEPA HPVIS and NICNAS reports;
- National Toxicology Program (NTP);
- Agency for Toxic Substances and Disease Registry (ATSDR);
- Toxicity Reference Database (ToxRefDB): choline esterase inhibition;
- Hazardous Substances Database (HSDB): choline esterase inhibition, neurotoxicity and immunotoxicity;
- DEREK Nexus: neurotoxicity and immunotoxicity alerts;
- Repeated dose toxicity (HESS): neurotoxicity alerts; and
- Information relating to endocrine-disrupting properties of the structurally analogous substances obtained from ECHA's screening activities to identify substances that matter most (see the link above).

7. Triggering of the EOGRTS at Annex IX

The Agency considers that the EOGRTS at Annex IX is primarily triggered by existing information on the substance being evaluated. Information on structurally analogous substances derived from read-across approaches, which are acceptable according to Annex XI, Section 1.5 of REACH is considered as information on the substance being evaluated itself.

Therefore, information derived from such acceptable read-across approaches using structurally analogous substances can also be used for triggering the EOGRTS at Annex IX. If these read-across approaches are not acceptable, the information on these structurally analogous substances can usually not be used for triggering the EOGRTS at Annex IX. In exceptional cases, however, if there is a serious concern based on available information from structurally analogous substances, the study may be triggered although the read-across is not found acceptable by the Agency.

On the other hand, existing information on (bio)transformation products of the substance being evaluated can be used to trigger the EOGRTS at Annex IX because (bio)transformation pathways are considered an intrinsic property of the substance being evaluated, inevitably resulting in the formation of certain (bio)transformation products, which can exert relevant

effects for triggering.

It is also to be noted that in the compliance check, the Agency can only request the EOGRTS at Annex IX based on data from animal experiments with repeated dosing showing a concern. Information from other sources, such as individual (Q)SAR predictions or *in vitro* experiments may not usually form a sufficient basis to raise a concern serious enough to request the study in a compliance-check decision.

However, if there is a serious concern based on available information from non-animal approaches or structurally analogous substances, the study may be triggered. The registrants are expected to propose the study by submitting a testing proposal based on concern stemming from animals studies or other relevant information.

8. Triggering of the extension of Cohort 1B

The extension of Cohort 1B is triggered on a case-by-case basis. An exposure-based trigger, associated with uses leading to exposure of consumers and professional users, and additional criteria, based on evidence indicating that a substance is of concern as a function of the available toxicity, i.e. genotoxicity or an indication of a relevant endocrine mode of action, and/or toxicokinetic information, i.e. indication of accumulation, are included to evaluate whether the F1 generation should be mated to produce the F2 generation and subjected to testing for reproductive performance of the F1 generation.

The same principles as outlined above for triggering the study at the Annex IX level apply for triggering the extension of Cohort 1B to include the F2 generation; i.e. usually only information from the substance being evaluated, its (bio)transformation products and structurally analogous substances for which the read across has been accepted by the Agency are used for triggering.

Information from alternative methods to animal experimentation, such as results from *in vitro* studies, can also be used for triggers. A specific feature for triggering an extension of Cohort 1B is that consumer and/or professional exposure also need to be considered in addition to the toxicity-triggers as defined in Annexes IX and X to REACH.

9. Triggering of the DNT and DIT cohorts

DNT and DIT must be further investigated where the available information on a substance indicates a particular concern on (developmental) neurotoxicity or (developmental) immunotoxicity, respectively. A particular concern means that the concern should be specific to (developmental) neurotoxicity/immunotoxicity but also that the concern needs to reach a certain level of severity (see ECHA's *Guidance on information requirements and chemical safety assessment R.7a (version 4.1, October 2015) on reproductive toxicity, Appendix R.7.6–2*).

Evidence supporting these concerns could originate from existing information derived from *in vivo* or non-animal approaches, from the knowledge of relevant mechanisms or modes of action of the substance itself, or from existing information on structurally analogous substances.

For DNT and DIT cohorts, column 2 of Section 8.7.3. of Annex IX or X explicitly refers to "substances structurally analogous to the substance being evaluated". However, structurally analogous substances are not mentioned in the context of triggering the EOGRTS at Annex IX (column 1 of Section 8.7.3. of Annex IX) and for triggering the extension of Cohort 1B (column 2 of Section 8.7.3. of Annexes IX and X).

Due to this different wording of the legal text, ECHA concludes that for triggering the EOGRTS at Annex IX and toxicity-criteria to extend the Cohort 1B, usually only evidence from the substance being evaluated, its (bio)transformation products and from structurally analogous substances for which the read across has been accepted by the Agency can be used for triggering. However, in exceptional cases if there is a serious concern based on available information from structurally analogous substances, such information can also be used for triggering even if the read-across is not acceptable.

For DNT and DIT, however, a particular concern to include the Cohorts 2A, 2B and/or Cohort 3 can be based on information from structurally analogous substances independently of whether a (potential) read-across can be accepted by ECHA. Similarly, if the weight of evidence adaptation according to Annex XI, 1.2 is not acceptable, the information from structurally analogous substances may still be relevant for triggering DNT and/or DIT. A justification for the adequacy of triggers must always be provided in the registration dossier.

10. Structurally analogous substances

Existing information on structurally analogous substances can be used for triggering DNT Cohorts 2A and 2B and DIT Cohort 3. However, ECHA's *Guidance on information requirements and chemical safety assessment R.7a (version 4.1, October 2015) on reproductive toxicity (chapter R.7.6)* does not explain how to identify suitable structurally analogous substances.

In principle, the relevance and adequacy of triggers identified from existing information on structurally analogous substances should be considered and justified on a case-by-case basis.

In general, the Agency considers the following substances as structurally analogous substances of the substance being evaluated:

- Substances which are grouped together with the substance being evaluated for read-across purposes (category or analogue approach; or weight-of-evidence including read-across substances) in registration dossiers;
- Substances which are grouped together with the substance being evaluated by the OECD (OECD categories) or regulatory actors such as the US EPA (HP VIS categories) and NICNAS (NICNAS tier II human health categories); and
- Relevant (bio)transformation products of the substance being evaluated.

Other substances than those mentioned in the preceding paragraph can be used as structurally analogous substances based on case-by-case considerations.

11. Specific considerations with respect to triggering

As a general rule, information on the substance being evaluated outweighs equivalent information on a structurally analogous substance. This means, for example, that if a specific trigger is identified in a sub-chronic toxicity study on a structurally analogous substance which is not observed in an equivalent study on the substance being evaluated, then the trigger is disregarded. However, if relevant information on the structurally analogous substance covers aspects not addressed by available information on the substance being evaluated, then this information can be used for triggering (e.g. presence of a neurotoxicity study with a structurally analogous substance which has not been conducted for the substance being evaluated).

If the triggers stem from a study with lower statistical power, such as a sub-acute toxicity study according to OECD Test Guideline 407, and similar effects are not observed in a study

with higher statistical power such as a sub-chronic toxicity study according to OECD Test Guideline 408, the reason for the lack of consistency needs to be examined. Where such inconsistencies can be explained by different dose levels, routes of administration, animal species or strains, life stages tested, duration or timing of exposure, or parameters investigated, for example, the findings from the study with lower statistical power may still be considered as valid triggers. However, if the lack of consistency cannot be explained, the results from the study with higher statistical power can outweigh those from the study with lower statistical power. The consistency of findings is also discussed in ECHA's *Guidance on information requirements and chemical safety assessment R.7a (version 4.1, October 2015) on reproductive toxicity (chapter R.7.6)*.

If the findings are too weak to be used as triggers, but leave a doubt for a concern, it may be necessary to search for potentially supporting triggers. Several weak findings together may provide an adequate level of concern to be used as a trigger which is scientifically and legally justifiable.

12. Final remarks

To decide on the need for the EOGRTS at Annex IX and to identify the design of the EOGRTS at Annexes IX and X, a multitude of scientific information from numerous information sources needs to be searched and evaluated.

Existing information on a relevant aspect may be limited, ambiguous and even contradictory and the relevance of potential triggers must be assessed, for example, with respect to the question on whether they are primary or secondary effects. Therefore, expert judgement based on sound scientific reasoning is required to identify the EOGRTS design for a given substance.

The registrants are expected to clearly explain the reasons why a certain EOGRTS design has been identified as appropriate in their registration dossiers. Clear and convincing scientific reasoning should be based on the legal text and ECHA's *Guidance on information requirements and chemical safety assessment R.7a (version 4.1, October 2015) on reproductive toxicity (chapter R.7.6)*. As all the information provided in a registration dossier is taken into account and therefore directly influences the outcome of the dossier-evaluation and decision-making processes, clear and convincing scientific reasoning must be in the interest of the registrants.

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